Eur J Clin Pharmacol (2005) 61: 873–880
DOI 10.1007/s00228-005-0043-5

PHARMACODYNAMICS

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Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939—an oral, direct Factor Xa inhibitor—after multiple dosing in healthy male subjects

Received: 1 July 2005 / Accepted: 26 September 2005 / Published online: 17 November 2005

Abstract *Objectives:* There is a clinical need for safe new oral anticoagulants. The safety, tolerability, pharmacodynamics, and pharmacokinetics of BAY 59-7939—a novel, oral, direct Factor Xa (FXa) inhibitor—were investigated in this single-center, placebo-controlled, single-blind, parallel-group, multiple-dose escalation study. *Methods:* Healthy male subjects (aged 20–45 years, body mass index 18.6–31.4 kg/m^2) received oral BAY 59-7939 (n=8 per dose regimen) or placebo (n=4 per dose regimen) on days 0 and 3–7. Dosing regimens were 5 mg once, twice (bid), or three times daily, and 10 mg, 20 mg, or 30 mg bid. *Results:* There were no clinically relevant changes in bleeding time or other safety variables across all doses and regimens. There was no dose-related increase in the frequency or severity of adverse events with BAY 59-7939. Maximum inhibition of FXa activity occurred after approximately 3 h, and inhibition was maintained for at least 12 h for all doses. Prothrombin time, activated partial thromboplastin time, and HepTest were prolonged to a similar extent to inhibition of FXa activity for all doses. Dose-proportional pharmacokinetics ($AUC_{\tau,norm}$ and $C_{max,norm}$) were observed at steady state (day 7). Maximum plasma concentrations were achieved after 3–4 h. The terminal half-life of BAY 59-7939 was 5.7–9.2 h at steady state. There was no relevant accumulation at any dose. *Conclusions:* BAY 59-7939 was safe and well tolerated across the wide dose range studied, with predictable, dose-proportional pharmacokinetics and pharmacodynamics and no relevant accumulation beyond steady state. These results support further investigation of BAY 59-7939 in phase II clinical trials.

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Introduction

BAY 59-7939 is a novel, oral anticoagulant undergoing clinical evaluation for the prevention and treatment of thromboembolic disorders [1]. Current clinical guidelines recommend the routine use of anticoagulant drugs, such as the indirect Factor Xa (FXa) inhibitors—the low molecular weight heparins (LMWHs) and the synthetic pentasaccharide fondaparinux—or the vitamin K antagonists (warfarin), in a wide range of indications. These include high-risk surgery, trauma, atrial fibrillation, and acute coronary syndromes [2]. LMWHs and fondaparinux are well established for short- and medium-term prophylaxis and treatment, but they require subcutaneous administration [3]. Vitamin K antagonists are currently the only anticoagulants indicated for long-term prevention of thromboembolic events in high-risk patients and are administrated orally; however, these drugs require frequent patient monitoring because of their unpredictable pharmacokinetics, narrow therapeutic window, and multiple food and drug interactions [4].

Direct inhibition of clotting factors, such as thrombin or FXa, with small, specific molecules is becoming an increasingly attractive antithrombotic strategy. These inhibitors, such as the direct thrombin inhibitors ximelagatran and dabigatran, tend to have predictable pharmacodynamics and a low propensity for food and drug interactions and are, theoretically, less likely to require monitoring than vitamin K antagonists [5]. However, as yet, no new drug has been able to replace the vitamin K antagonists, and there remains a need for oral anticoagulants that are not only effective and safe for long-term use but also do not require routine monitoring [3].

The results of in vitro studies have shown that BAY 59-7939 is a direct FXa inhibitor and is more than 10,000-fold more selective for FXa than for other related serine proteases [1]. In contrast to the indirect FXa inhibitors (LMWHs and fondaparinux), BAY 59-7939 does not require the cofactor antithrombin [6, 7]. Studies in animals have shown that BAY 59-7939 inhibits both free FXa and FXa within the prothrombinase complex, has in vivo antithrombotic activity [1] and high bioavailability (60–80%), and is rapidly excreted via both renal and fecal routes [8].

BAY 59-7939 has been shown to be safe and well tolerated across a wide dose range (1.25–80 mg) in a single-dose study of over 100 healthy male subjects, with predictable, dose-dependent pharmacokinetics that correlated closely with pharmacodynamic parameters [7]. Bleeding is a well-acknowledged risk with anticoagulant drugs, and it is important to note that there was no increased risk of bleeding with BAY 59-7939, even across the 64-fold dose range studied. A phase IIb dose-ranging study of BAY 59-7939 for the prevention of venous thromboembolism in patients undergoing elective knee replacement surgery showed that BAY 59-7939 at doses of 2.5–10 mg twice daily had similar safety and efficacy to standard regimens of enoxaparin [9]. Further large-scale studies are ongoing.

The objective of this study was to further investigate the safety, tolerability, pharmacodynamics, and pharmacokinetics of BAY 59-7939 when administered as multiple doses to healthy male subjects.

Methods

Study design

This was a single-center, placebo-controlled, single-blind, parallel-group, dose-escalation study. The protocol was approved by the Ethics Committee of the North Rhine Medical Council, and the study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and German drug law [10, 11]. All subjects gave written informed consent to participate in the study.

Healthy Caucasian male subjects, 20–45 years of age (body mass index 18.6–31.4 kg/m^2), were randomly assigned to receive either oral BAY 59-7939 (n=8 per dose regimen) or matching placebo (n=4 per dose regimen). Subjects remained on-site from day −1 to day 12 and were randomized to receive one of six BAY 59-7939 dosing regimens—5 mg once (od), twice (bid), or three times daily (tid); 10 mg bid; 20 mg bid; or 30 mg bid—or matching placebo on days 0 and 3–7. In addition, a full medical examination was performed at follow-up, no more than 14 days after the last study dose.

Each BAY 59-7939 dose step was initiated when the results of the previous dose step were available and if there were no unacceptable adverse effects. All study medication was taken with water at mealtimes, within 5 min of finishing a standard meal. The next meal was eaten 4 h later.

Safety and tolerability

Occurrence and severity of adverse events, bleeding time, laboratory values, blood pressure, heart rate, and electrocardiogram (ECG) were assessed daily until day 12 and at follow-up.

Pharmacodynamic parameters

FXa activity and the global clotting tests—prothrombin time (PT), activated partial thromboplastin time (aPTT), and HepTest—were assessed daily until day 12. PT and aPTT examine the effects of drugs on coagulation stimulated by the extrinsic and intrinsic clotting pathways, respectively. HepTest is used to monitor anticoagulation with LMWHs, and it measures FXa activity indirectly. All three tests are routinely performed to monitor patients receiving anticoagulants; PT, in particular, is widely used in anticoagulation clinics to monitor the effects of vitamin K antagonists.

Pharmacokinetic parameters

The following pharmacokinetic parameters were calculated for BAY 59-7939 using model-independent (noncompartmental) methods: area under the plasma concentration-time curve (AUC); AUC during a dosage interval at steady state (AUC_{τ}); AUC during a dosing interval divided by dose per kg body weight ($AUC_{\tau,norm}$); maximum plasma concentration (C_{max}); C_{max} divided by dose per kg body weight ($C_{max,norm}$); half-life associated with the terminal slope ($t_{1/2}$); time to reach maximum drug concentration in plasma (t_{max}); and the accumulation ratio R_{A4} (AUC_{τ} divided by AUC).

Sample analysis

Blood samples were collected for pharmacodynamic and pharmacokinetic analysis before administration of the study drug and at regular intervals thereafter. Plasma samples were obtained by centrifugation and were frozen and stored below −15°C until analysis at the laboratories at Bayer HealthCare AG (Germany).

After sample dilution, FXa activity was determined by a photometric assay. Briefly, FXa activity was determined by a two-step process: Total FX in plasma was activated to FXa using Russell's viper venom in the presence of calcium ions; subsequently, the chromogenic substrate ZD-Arg-Gly-Arg-pNA (S-2765, Chromogenix, Milan, Italy) was hydrolyzed by FXa, releasing the chromogenic group pNA (p-nitroanilin). The amount of pNA released is proportional to FXa activity and was determined by spectrophotometry at 405 nm. All standards and controls were prepared from the 3rd International Standard Coagulation Factors II and X Concentrate, Human 98/590 (NIBSC, Potters Bar, UK). Concentrations above 0.1 IU/ml (the lower limit of quantification; LLOQ) were determined with a precision of 9.5–14% and an accuracy of 99.5–114%; baseline values of FXa activity prior to study drug administration were set as 0% inhibition. PT [assessed using freeze-dried thromboplastin from rabbit brain with an international sensitivity index (ISI) of 1.2 (Neoplastin Plus; Roche Diagnostics, Mannheim, Germany)], aPTT [assessed using a kaolin-activated test (Roche Diagnostics)], and HepTest

Table 1 The incidence (*n*) of drug-related, treatment-emergent adverse events (TEAEs) after administration of BAY 59-7939 and placebo; includes events occurring in more than one subject (*ALT* alanine aminotransferase, *GLDH* glutamate dehydrogenase)

Disorder	Placebo (*n*=21)	BAY 59-7939					
		5 mg od (*n*=7)	5 mg bid (*n*=7)	5 mg tid (*n*=7)	10 mg bid (*n*=7)	20 mg bid (*n*=7)	30 mg bid (*n*=8)
Any drug-related TEAE	6	3	0	4	0	3	4
Headache	4	2	–	2	–	3	2
Diarrhea	2	–	–	1	–	–	1
Fatigue	2	–	–	2	–	–	–
Dyspepsia	–	–	–	1	–	–	1
Flatulence	1	1	–	–	–	–	–
Increase in ALT and GLDH more than three times upper limit of normal	–	–	–	–	–	–	1
Dizziness	–	–	–	–	–	–	1
Altered taste	–	–	–	–	–	–	1
Exanthema	1	–	–	–	–	–	–
Feeling hot	–	–	–	–	–	–	1
Hyperacidity	–	1	–	–	–	–	–
Pressure in ear/tinnitus	–	–	–	1	–	–	–

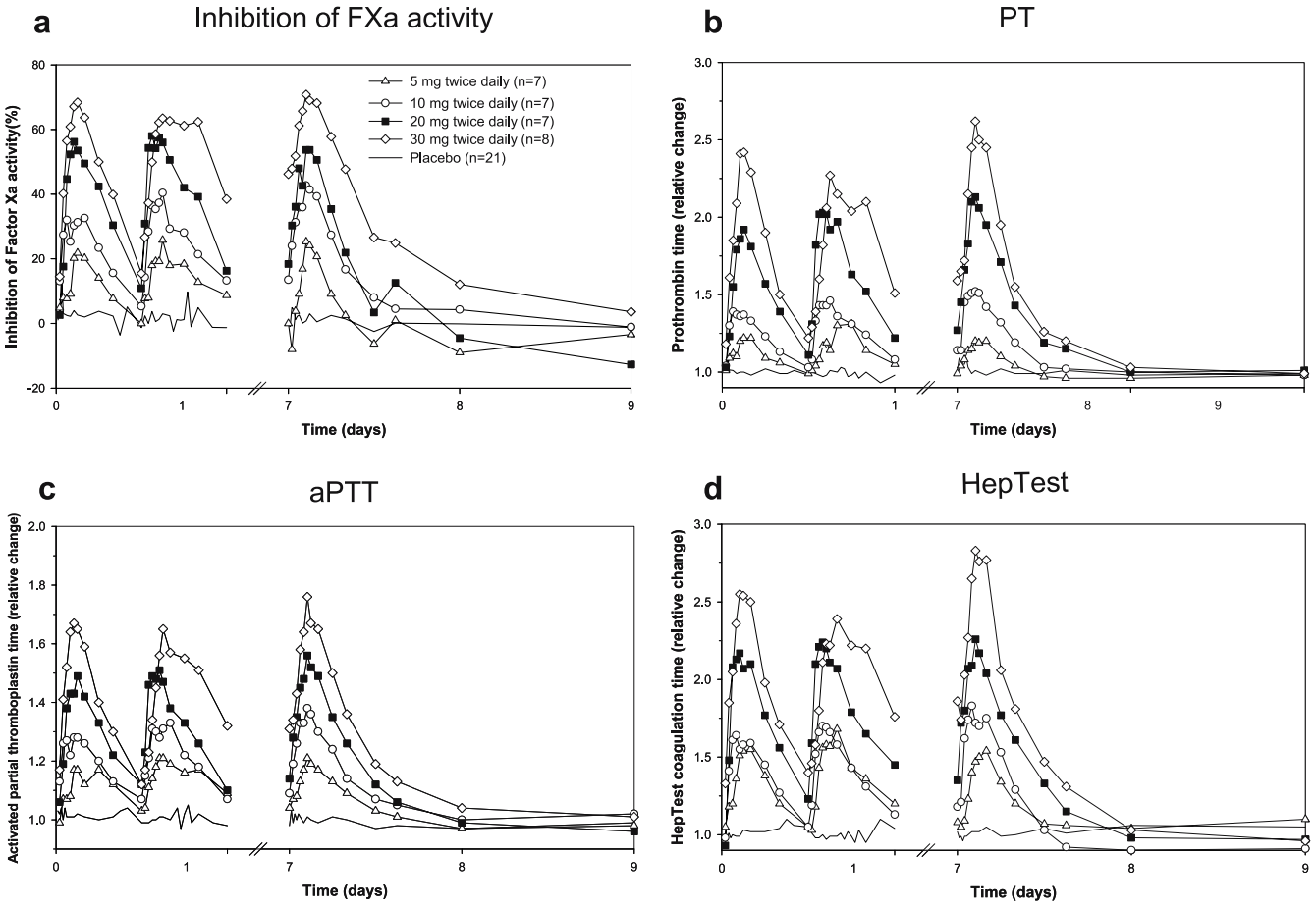

Fig. 1 FXa activity (median percentage inhibition compared with baseline) after administration of BAY 59-7939 5 mg, 10 mg, 20 mg, or 30 mg twice daily. **a** Median prolongation of prothrombin time **b**, activated partial thromboplastin time **c**, and HepTest **d**. Subjects received study drug on day 0 and days 3–7

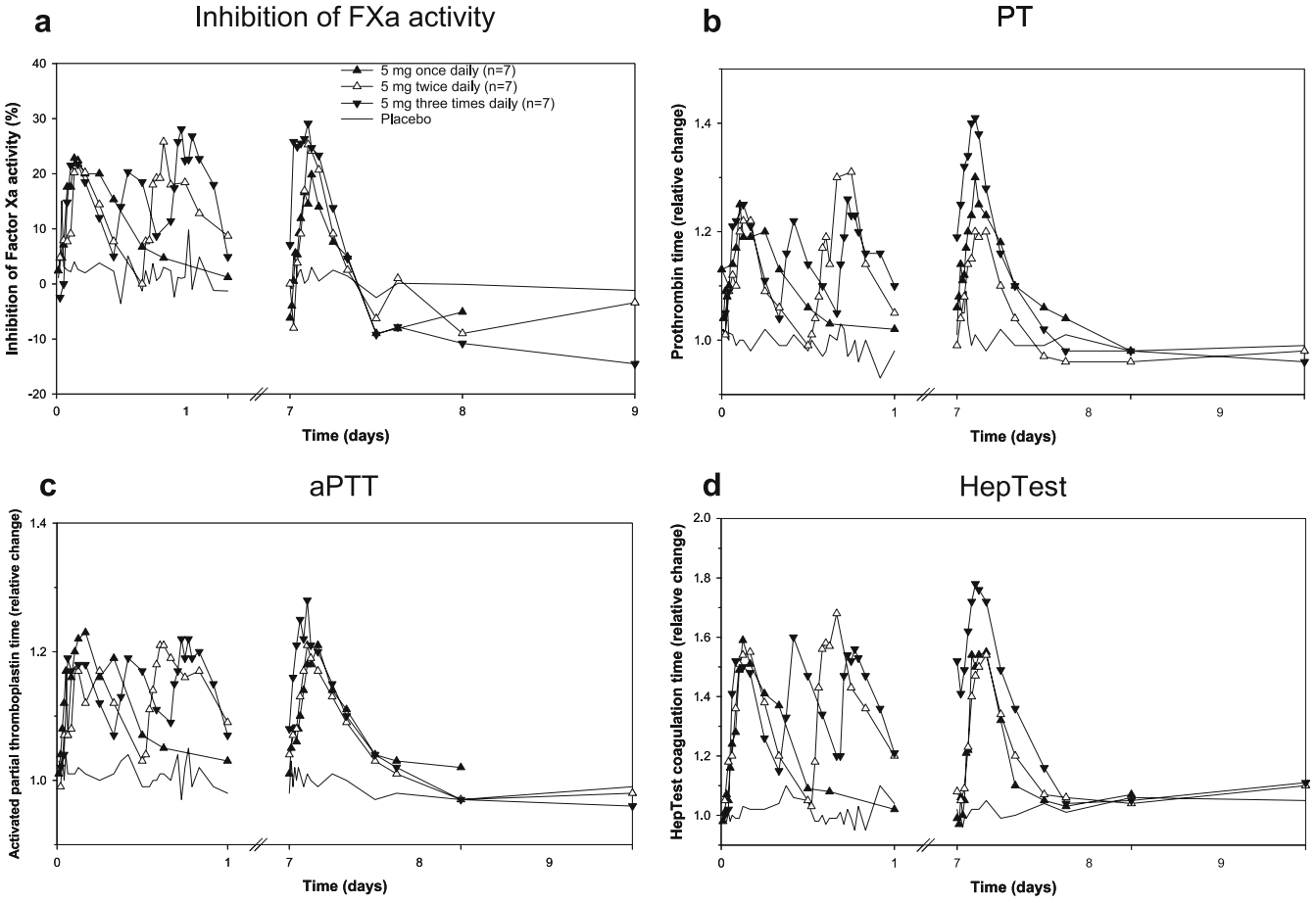

Fig. 2 FXa activity (median percentage inhibition compared with baseline) after administration of BAY 59-7939 5 mg once, twice, or three times daily. **a** Median prolongation of prothrombin time **b**, activated partial thromboplastin time **c**, and HepTest **d**. Subjects received study drug on day 0 and days 3–7

(Haemachem, St. Louis, MO, USA) were measured with a ball coagulometer KC 10 (Amelung, Germany) using standard methods according to the manufacturer's instructions. Values for PT, aPTT, and HepTest prior to study drug administration were defined as baseline (1.0); results are presented as relative change from baseline following treatment.

Samples for pharmacokinetic analysis were analyzed by a fully validated high-performance liquid chromatography (HPLC)/mass spectrometry (MS)/MS method (Hewlett–Packard system 1100 coupled with tandem mass spectrometry API 3000; MDS Sciex) after solid/liquid extraction. Concentrations above the LLOQ (0.5 μg/l) were determined with a precision of 3.8–5.3% and an accuracy of 96.3–104.5%.

Statistical methods

To investigate whether BAY 59-7939 exhibited dose-proportional pharmacokinetics, $AUC_{\tau,norm}$ and $C_{max,norm}$ were analyzed assuming the data were log-normally

Table 2 Pharmacokinetic parameters of BAY 59-7939 in plasma on day 7 (steady state; *n*=41). Values are given as geometric mean (geometric coefficient of variation)

Parameter	5 mg od (*n*=7)	5 mg bid (*n*=7)	5 mg tid (*n*=6)	10 mg bid (*n*=7)	20 mg bid (n=7)	30 mg bid (*n*=7)
AUC_τ (μg·h/l)	505.5 (19.7)	458.5 (13.1)	557.3 (20.4)	863.8 (18.6)	1,903.0 (24.5)	2,728.0 (14.6)
C_{max} (μg/l)	76.4 (18.3)	85.3 (17.7)	123.8 (19.7)	158.0 (18.8)	318.1 (18.7)	451.9 (10.5)
$t_{½}$ (h)	8.4 (32.6)	7.0 (27.8)	5.8 (35.5)	7.6 (26.7)	8.0 (40.7)	9.2 (64.1)
t_{max}[a] (h)	3.00	3.00	2.00	2.98	2.50	3.02
R_{A4} (%)	98.8 (10.1)	85.3 (17.2)	113.6 (8.2)	105.8 (14.6)	95.4 (13.8)	110.3 (21.4)

[a]Median
Accumulation ratio R_{A4} is AUC_τ divided by AUC

Table 3 Point estimates (least-squares means) and two-sided confidence intervals (CI) for pairwise BAY 59-7939 treatment comparisons (expressed as ratios) of the primary parameters $AUC_{\tau,norm}$ and $C_{max,norm}$ at steady state on day 7 (ANOVA; n=41)

Reference	Test	Steady state	
		$AUC_{\tau,norm}$ (day 7) Ratio (90% CI)	$C_{max,norm}$ (day 7) Ratio (90% CI)
5 mg (bid)	10 mg bid	1.09 (0.90, 1.33)	1.11 (0.94, 1.32)
	20 mg bid	0.95 (0.78, 1.16)	1.06 (0.89, 1.26)
	30 mg bid	1.02 (0.84, 1.24)	1.15 (0.97, 1.37)
10 mg (bid)	20 mg bid	0.87 (0.72, 1.06)	0.95 (0.80, 1.13)
	30 mg bid	0.94 (0.77, 1.14)	1.03 (0.87, 1.23)
20 mg (bid)	30 mg bid	1.07 (0.88, 1.31)	1.09 (0.91, 1.29)

distributed. No assumptions were made about the relationship between dose and pharmacokinetic parameters, and an exploratory analysis of variance (ANOVA; including the "factor groups") was carried out using the log-transformed values of $AUC_{\tau,norm}$ and $C_{max,norm}$.

Results

Baseline demographics for all subjects were similar across all treatment groups. Mean age was 32.5 years (range 20–45 years). Mean weight and height were 81.6 kg (range 59–104 kg) and 180.3 cm (range 163–200 cm), respectively. Mean body mass index was 25.1 kg/m^2 (range 18.6–31.4 kg/m^2).

Safety and tolerability

Of the 68 subjects enrolled, four were excluded before treatment (laboratory values outside the accepted range); therefore, safety evaluations were available for 64 subjects. There were no clinically relevant changes in bleeding time in any subject receiving BAY 59-7939, independent of dose and dosing frequency.

There was no evidence of a relationship between dose or dosing frequency and the incidence of adverse events (Table 1), and there were no serious adverse events. There were no drug-related, treatment-emergent adverse events in the BAY 59-7939 5-mg-bid and 10-mg-bid groups; the incidences of drug-related, treatment-emergent adverse events were slightly higher in the other BAY 59-7939 dose groups compared with placebo. Headache was the most frequent adverse event, affecting 9/43 (21%) BAY 59-7939 subjects and 4/21 (19%) placebo recipients. One subject in the 5-mg-tid group discontinued treatment prematurely because of an adverse event that was judged by study personnel to be possibly drug related: pressure in the ear after the first administration of BAY 59-7939, leading to tinnitus lasting approximately 1 h.

One subject receiving BAY 59-7939 30 mg bid had increased levels of alanine aminotransferase [ALT; maximum 3.3 times the upper limit of normal (ULN)] and glutamate dehydrogenase (GLDH; maximum 5.4 times the ULN); these changes were attributed to BAY 59-7939. The levels of serum enzymes in this subject decreased by day 12 and subsequently returned to baseline. Similarly transient increases in ALT and GLDH were observed in subjects receiving placebo (ALT increases to 2.1 times the ULN in one subject, returning to baseline by day 8, and GLDH increases to 2.8 times the ULN in five subjects, returning to baseline by day 12). A transient increase in GLDH to two times the ULN was also observed in one subject receiving BAY 59-7939 10 mg bid. BAY 59-7939 was not associated with clinically relevant changes in blood pressure, heart rate, or ECG.

Pharmacodynamics

Results from 64 subjects were valid for analysis of pharmacodynamic parameters.

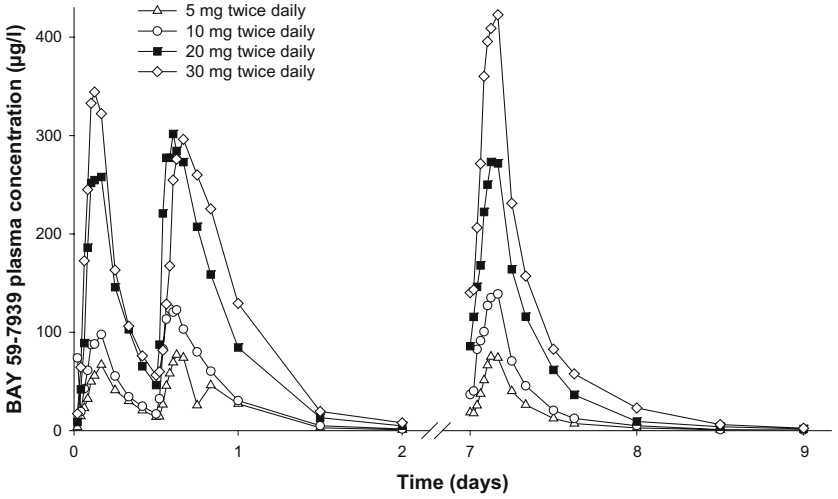

Fig. 3 Plasma concentrations of BAY 59-7939 after twice-daily dosing, displayed as geometric means

Twice-daily dosing (BAY 59-7939 5–30 mg bid)

BAY 59-7939 inhibited FXa activity in a dose-dependent manner; FXa activity was unaffected in the placebo group (Fig. 1a). Maximum inhibition of FXa activity occurred approximately 3 h after BAY 59-7939 dosing. Following the first dose of BAY 59-7939, maximum inhibition of FXa activity was 22% after 5 mg, 33% after 10 mg, 56% after 20 mg, and 68% after 30 mg, and inhibition was maintained for 8–12 h after 5 mg and for approximately 12 h after the 10-mg, 20-mg, and 30-mg doses. There were no major differences in maximum inhibition of FXa activity between the first and second daily doses, or on day 7 compared with day 0, although trough levels were increased with the 20-mg and 30-mg bid doses.

Median PT, aPTT, and HepTest were prolonged in a dose-dependent manner (Fig. 1b–d). Maximum prolongations were reached 1–4 h after administration of BAY 59-7939. On day 7, maximum PT values were similar to those measured after the first dose on day 0. Trough values for PT and aPTT after administration of BAY 59-7939 10 mg, 20 mg, and 30 mg bid on day 7 were still elevated after 12 h compared with baseline.

BAY 59-7939 5 mg od, bid, and tid dosing

Maximum inhibition of FXa activity on day 0 was similar after 5 mg given od, bid, and tid (Fig. 2a), and there were no relevant differences in maximum inhibition of FXa activity on day 7 compared with day 0 for the three regimens. FXa activity was inhibited for up to 12 h after 5-mg od dosing and beyond 24 h after bid and tid dosing in some subjects. On day 7, PT and aPTT were prolonged dose dependently (Fig. 2b,c). Prolongation of HepTest followed the same pattern as inhibition of FXa activity over the three dosing regimens (Fig. 2d). Minimum inhibition of FXa activity and clotting time prolongation was greater with bid and tid dosing compared with od dosing.

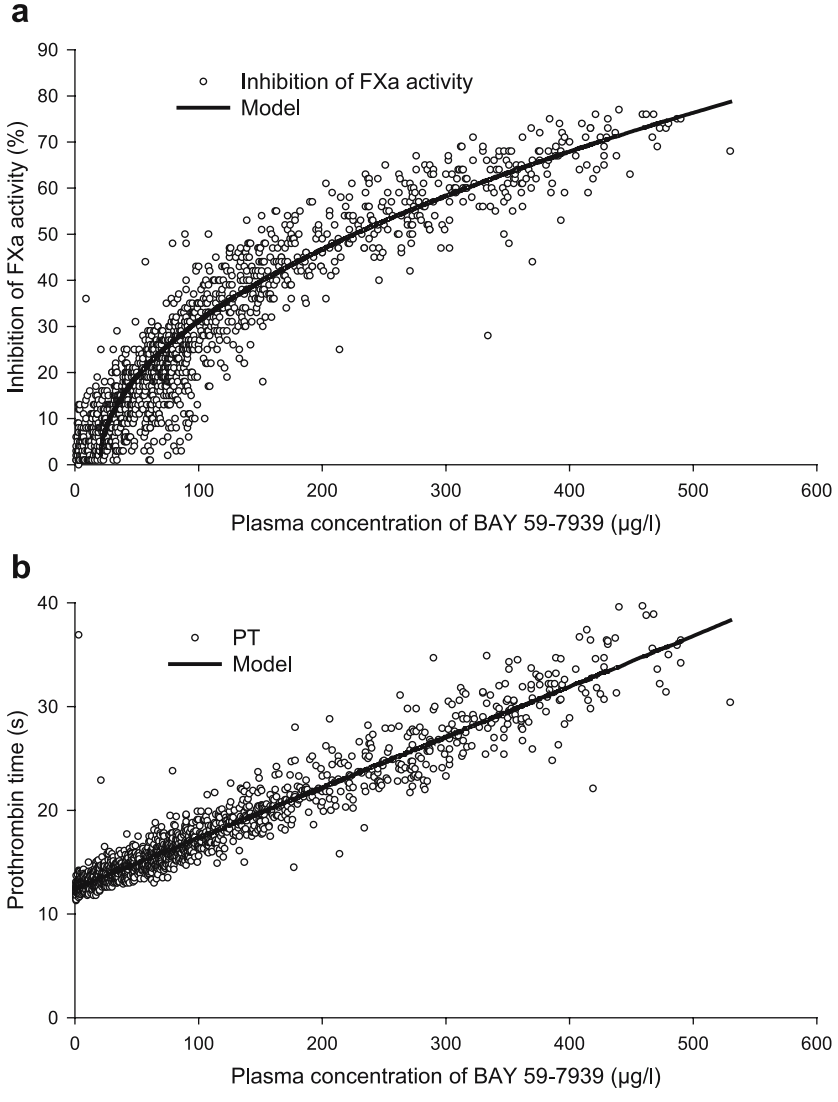

Fig. 4 **a** Correlation between inhibition of FXa activity and plasma concentration of BAY 59-7939 (*n*=1,200). **b** Correlation between PT and plasma concentrations of BAY 59-7939 (*n*=1,592)

Pharmacokinetics

Results from 61 subjects were valid for pharmacokinetic analysis (Table 2). Exposure to BAY 59-7939, in terms of AUC and C_{max}, was dose proportional for all doses (5 mg, 10 mg, 20 mg, and 30 mg bid) after day 0 and day 7, according to statistical analyses (Table 3). Maximum plasma concentrations of BAY 59-7939 were reached approximately 3–4 h after initial administration for all doses and all regimens (Fig. 3). The $t_{1/2}$ for BAY 59-7939, determined after day 0, was 3.7–5.8 h. It was prolonged on day 7 to 5.8–9.2 h (Table 2), which could be due to the longer measurement period on day 7 (up to 96 h after dosing) compared with day 0 (12 h after dosing). The accumulation ratio R_{A4}, which relates $AUC_{\tau,ss}$ to AUC after a single dose, was close to 100% for all dose regimens investigated (range 85–113%).

Pharmacokinetic and pharmacodynamic correlation

Plasma concentrations of BAY 59-7939 were linked to inhibition of FXa activity, using an E_{max} model (Fig. 4a), and to PT by a direct linear relationship (Fig. 4b), with Pearson's correlation coefficients of 0.950 and 0.958, respectively.

Discussion

The results of this study showed that multiple doses of BAY 59-7939, an oral, direct FXa inhibitor, were well tolerated across a wide range of doses, with predictable pharmacodynamics and pharmacokinetics.

BAY 59-7939 showed no clinically relevant effects on bleeding time after initial drug administration and, importantly, at steady state on day 7, irrespective of dose or dosing frequency. Overall, adverse events were not dependent on dose or dosing frequency, and no drug-related, treatment-emergent adverse events were observed with the 5-mg-bid or 10-mg-bid dose regimens. Although headache was the most frequently occurring drug-related, treatment-emergent adverse event, its incidence was similar with both BAY 59-7939 and placebo (21% vs. 19%, respectively). Transient increases in the liver enzymes ALT and/or GLDH were observed in two subjects receiving BAY 59-7939 (10 mg bid and 30 mg bid), as well as six subjects receiving placebo; all increased levels returned to baseline without intervention. Rosenzweig et al. published a meta-analysis that showed that up to 7.5% of subjects receiving placebo in phase I studies had increases in liver enzymes more than two times the ULN; this was attributed to maintained caloric intake and lack of physical activity [12]. In addition, up to 25% of subjects receiving placebo had ALT more than three times the ULN in individual studies with a small sample size [12]. In a phase II clinical study of BAY 59-7939 (doses between 2.5 mg bid and 30 mg bid) for the prevention of venous thromboembolism after major orthopedic surgery, mild transient increases in aspartate transaminase and ALT were observed in all treatment groups, including patients receiving the comparator drug enoxaparin, with no dose-response relationship observed in the BAY 59-7939 groups [9]. In this phase I study, BAY 59-7939 had no clinically significant effects on vital signs or ECG. Overall, these results confirm the findings of an earlier study in healthy subjects, which showed that BAY 59-7939 is well tolerated and safe across a 64-fold range of single doses [7].

The onset of inhibition of FXa activity with BAY 59-7939 was rapid, with maximum effect occurring within 2–3 h of dosing in all dosing groups. In addition, the inhibition of FXa activity was dose dependent across all dosing regimens, and maximum inhibition of FXa activity did not differ significantly between initial drug administration and steady state. Furthermore, FXa activity was still partially inhibited at the end of the dosing interval for all doses and dosing frequencies, except at 5 mg od. The minimum level of inhibition of FXa activity was higher with increasing dose and dosing frequency. The clinical relevance of these effects at the end of the dosing interval will be determined in clinical trials. However, LMWHs have almost negligible anti-FXa activity after 12 h, yet demonstrate anticoagulant effects with once-daily dosing [13]. Similar efficacy to the LMWH enoxaparin was observed with all of the BAY 59-7939 doses tested (2.5–30 mg bid) in a recent clinical study of BAY 59-7939 for the prevention of venous thromboembolism following major orthopedic surgery [9]. The current study showed that all of these clinically effective doses (5–60 mg total daily dose) had relevant pharmacodynamic effects.

With regard to global clotting tests, the maximum prolongations of PT, aPTT, and HepTest were dose dependent with bid dosing and were reached within 1–4 h, confirming the predictability and fast onset of the anticoagulant effect of BAY 59-7939 previously observed in the single-dose study [7]. Peak prolongation of these clotting tests generally occurred at the same time as maximum inhibition of FXa activity, and peak prolongation of PT was similar at steady state to initial drug administration. As well as the routinely performed, well-established clotting tests used in this study, BAY 59-7939 has also been shown to prolong the specific thrombin generation assays platelet-induced thrombin generation time (PITT) and prothrombinase-induced clotting time (PiCT) [14]. Because of the position of FXa at the convergence point of the intrinsic and extrinsic clotting pathways, inhibition of FXa activity by BAY 59-7939 can be monitored using assays that measure clotting resulting from the activation of either of these two pathways, by FXa itself, or by thrombin generation.

BAY 59-7939 did not show undue accumulation beyond steady state. This was confirmed by the accumulation ratio R_{A4}, which relates AUC_{τ} at steady state to AUC after a single dose, and was approximately 100% for all doses. At steady state, $AUC_{\tau,norm}$ and $C_{max,norm}$ showed that exposure to BAY 59-7939 was dose proportional. The $t_{1/2}$ was between 5.8 and 9.2 h, and the dosing regimen (od, bid, or tid) had little impact on C_{max} values.

Pharmacodynamic and pharmacokinetic parameters correlated closely. There was a direct, linear relationship

between plasma BAY 59–7939 concentration and PT. This suggests that PT, a routinely used coagulation test, could be used clinically to monitor the anticoagulant effect of BAY 59-7939 if necessary. The ISI of the PT reagent used in this study was 1.2. Reagents with different ISI values could potentially alter the slope of the correlation curve between plasma BAY 59-7939 concentrations and PT, and this should be assessed in future studies; however, the linearity of the correlation would not be expected to be affected. This suggests that PT would be a viable monitoring test of the anticoagulant effect of BAY 59-7939, whatever the ISI of the reagent used, if such monitoring were necessary in individual patients. Plasma BAY 59-7939 concentrations and inhibition of FXa activity also correlated closely. These correlations are similar to those observed in the single-dose escalation study, in which doses of BAY 59-7939 up to 80 mg were administered, and reinforce the predictability of the pharmacodynamics and pharmacokinetics of BAY 59-7939 [7].

In conclusion, the results of this study confirmed that BAY 59-7939, an oral, direct FXa inhibitor, was well tolerated and was not associated with an increased risk of bleeding in healthy subjects. BAY 59-7939 has predictable, dose-proportional pharmacokinetics and pharmacodynamics, with no relevant accumulation beyond steady state. These attributes, in addition to its oral administration route, highlight the clinical promise of BAY 59-7939 in future anticoagulant therapy.

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