Preclinical and Clinical Characteristics of Rivaroxaban: A Novel, Oral, Direct Factor Xa Inhibitor

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ABSTRACT

There are several novel anticoagulants in development that target factor (F) Xa—the pivotal point of the coagulation cascade. One promising agent is rivaroxaban (a highly selective, oral, direct FXa inhibitor), which is in advanced clinical development for the prevention and treatment of thromboembolic disorders. Oral rivaroxaban may be given in fixed once-daily doses, with the potential for no coagulation monitoring. These properties, along with results from preclinical and clinical studies, suggest that rivaroxaban may have advantages over current treatments. Studies in arterial and venous animal models demonstrated that rivaroxaban has potent antithrombotic effects, without prolonging bleeding times. In healthy subjects, rivaroxaban was well tolerated, with a predictable pharmacological profile and a low propensity for clinically relevant drug–drug interactions. Phase II studies of rivaroxaban for the prevention of venous thromboembolism (VTE) after major orthopedic surgery support these findings. The results also suggested that a total daily dose range of 5 to 20 mg rivaroxaban had similar efficacy and safety to enoxaparin, and that 10 mg rivaroxaban once daily was the optimal dose. This review assesses the preclinical and clinical characteristics of rivaroxaban, and discusses phase II findings with rivaroxaban for the prevention of VTE after major orthopedic surgery.

KEYWORDS: Rivaroxaban, BAY 597939, factor Xa inhibitor, oral anticoagulants, venous thromboembolism

Rivaroxaban (BAY 597939) is a novel, oral, direct factor (F) Xa inhibitor in advanced clinical development for the prevention and treatment of thromboembolic diseases.¹ The efficacy and safety of rivaroxaban are currently being investigated in several indications: prevention of venous thromboembolism (VTE) after major orthopedic surgery, the treatment and secondary prevention of VTE, the prevention of stroke in patients with atrial fibrillation, and the secondary prevention of acute coronary syndromes. This article describes the preclinical and clinical pharmacologic data of this new anticoagulant compound, and describes results from the phase II studies of rivaroxaban for the prevention of VTE after major orthopedic surgery.

KEY FINDINGS FROM PRECLINICAL STUDIES

Rivaroxaban binds directly to human FXa (Fig. 1),² the protease at the pivotal point of the coagulation cascade.

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The x-ray crystal structure of rivaroxaban bound to FXa reveals an L-shaped structure in which the central oxazolidinone ring of rivaroxaban is connected to the chlorothiophene and morpholinone moieties, which bind to the S1- and S4-pockets of FXa, respectively. This structure allows rivaroxaban to be highly selective for FXa; indeed, at concentrations up to 20 μM, rivaroxaban does not interact with other related serine proteases. Rivaroxaban inhibits free FXa (with an inhibition constant Q, 0.4 ± 0.02 nM), prothrombinase activity, and clot-associated FXa. Rivaroxaban is an effective anticoagulant; in human plasma, it inhibits endogenous FXa activity (concentration that inhibits 50% [IC50], 21 nM), and doubles prothrombin time (PT) and activated partial thromboplastin time (aPTT) at 230 nM and 690 nM, respectively. Rivaroxaban also potently inhibits thrombin generation, activated by tissue factor, in human platelet-rich plasma (IC50, 25 nM); complete inhibition of thrombin generation can be achieved at a concentration of ~80 nM.

The antithrombotic effect of rivaroxaban has been evaluated in several arterial and venous thrombosis animal models. In a rat arteriovenous (AV) -shunt model, oral administration of rivaroxaban inhibited arterial thrombosis, with a median effective dose (ED50) of 5 mg/kg. In a rat venous stasis model, intravenous administration of rivaroxaban reduced the development of venous thrombosis, with a ED50 of 0.1 mg/kg. Following oral administration of rivaroxaban to rabbits, rivaroxaban was effective for the treatment of venous thrombosis, and inhibited arterial thrombosis in an AV-shunt model, with a ED50 of 0.6 mg/kg. Antithrombotic-effective doses in rats and rabbits, rivaroxaban did not prolong bleeding times significantly. These findings, and other studies, suggest that, by directly inhibiting FXa activity, rivaroxaban may be an effective oral anticoagulant for the prevention and treatment of arterial and venous thrombosis.

Positive findings from the preclinical studies of rivaroxaban led to the initiation of the clinical development program for this anticoagulant compound.

**CLINICAL PHARMACOLOGY OF RIVAROXABAN**

Phase I clinical studies were conducted to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of rivaroxaban in healthy subjects after oral administration of single and multiple doses. Interaction studies were also performed to determine the propensity of rivaroxaban to interact with other drugs.

**Pharmacokinetics**

A single-ascending-dose study investigating rivaroxaban doses between 1.25 and 80 mg, and a multiple-ascending-dose study investigating doses of 5 to 30 mg twice daily (bid), were undertaken in healthy male subjects. In these studies, rivaroxaban had predictable pharmacokinetics: it had a rapid onset of action, with maximum plasma concentrations (Cmax) observed within 2.5 to 4 hours of administration (Fig. 2A). In addition, after multiple rivaroxaban doses, dose-proportional increases in area under the plasma concentration–time curve were observed, and no substantial accumulation of rivaroxaban at steady state (day 7) was detected. The terminal half-life of rivaroxaban was 5.7 to 9.2 hours at steady state.

Rivaroxaban is excreted via two major routes: primarily via the renal route (66%) but also via the
fecal/biliary route (28%). Approximately 36% of a rivaroxaban dose is excreted unchanged in the urine.

**Pharmacodynamics**

In both the single- and multiple-dose studies, the pharmacodynamic effects of rivaroxaban closely followed its pharmacokinetic profile. Rivaroxaban dose-dependently inhibited FXa activity (Fig. 2B) and prolonged the global clotting tests PT, aPTT, and HepTest\(^Q5\), with maximum inhibitory effects occurring 1 to 4 hours after administration. Maximum inhibition of FXa activity ranged from 22% to 68% between the lowest and highest doses, and inhibition was maintained for ~12 hours with doses greater than 5 mg. There were no major differences in inhibition of FXa activity at steady state compared with the first day of dosing, although trough levels of inhibition increased with higher doses.\(^9\)

In the single-dose study, rivaroxaban was shown to have no effect on ecarin-induced thrombin activity, demonstrating that rivaroxaban has no direct effect on thrombin.\(^8\) However, an additional study conducted in healthy subjects demonstrated that, via its inhibitory effect on FXa activity, rivaroxaban inhibited thrombin generation effectively and dose dependently in platelet-rich plasma after activation by tissue factor or collagen.\(^11\) The study also demonstrated that inhibition of thrombin generation was maintained in some assays for up to 24 hours after administration of rivaroxaban. Results from in vitro studies using human plasma have shown that rivaroxaban has no direct effect on agonist-induced platelet aggregation,\(^12,13\) and this was confirmed in studies conducted in healthy human

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**Figure 2** (A) Rivaroxaban plasma concentrations (displayed as geometric means), and (B) median inhibition of factor Xa activity in healthy male subjects receiving rivaroxaban twice daily. (From Kubitza D, Becka M, Wensing G, et al. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939—an oral, direct factor Xa inhibitor—after multiple dosing in healthy male subjects. Eur J Clin Pharmacol 2005;61:873–880.)
Collectively, these findings demonstrate that rivaroxaban is an effective anticoagulant, with no direct effect on platelet aggregation.

**Correlation between the Pharmacokinetics and Pharmacodynamics of Rivaroxaban**

Inhibition of FXa activity and PT both correlated strongly with rivaroxaban plasma concentrations (Fig. 3). Inhibition of FXa activity correlated with rivaroxaban plasma concentrations following an $E_{\text{max}}$ model, whereas a direct linear relationship was observed between rivaroxaban plasma concentrations and PT. Inhibition of thrombin generation also correlated closely with rivaroxaban plasma concentrations, in accordance with an $E_{\text{max}}$ model. These findings confirmed the predictability of the pharmacokinetics and pharmacodynamics for rivaroxaban.

**Safety and Tolerability of Rivaroxaban in Healthy Subjects**

Rivaroxaban was well tolerated in healthy subjects; the incidence of adverse events was similar for rivaroxaban and placebo after single doses up to 80 mg, and slightly higher with rivaroxaban than placebo after multiple doses.
doses up to 30 mg bid. The most common adverse event reported was headache, and few adverse events were deemed related to rivaroxaban. Transient increases in plasma levels of liver enzymes, such as alanine aminotransferase, were observed in a small number of subjects receiving rivaroxaban, but similar increases were also observed in those receiving placebo. No clinically relevant changes in bleeding time were observed after multiple doses of rivaroxaban, and there were no clinically relevant changes in blood pressure, heart rate, electrocardiogram, changes in safety laboratory parameters (except clotting tests), or vital signs.

In a thorough study conducted in healthy male and female subjects (n = 54) age ≥ 50 years, and performed in accordance with ICH E14 guidelines, rivaroxaban did not prolong the QTc interval.

Numerous interaction studies have been conducted with rivaroxaban. In healthy male subjects, there were no clinically relevant mechanistic interactions between rivaroxaban and aspirin, naproxen, or di-goxin. Furthermore, only a limited additive effect on anti-FXa activity was observed when rivaroxaban and enoxaparin were coadministered. Therefore, concomitant use of these drugs with rivaroxaban may be possible in clinical practice, although this will require confirmation in large-scale clinical studies in patients with diverse demographic characteristics, and numerous comorbidities and comediations.

**CLINICAL STUDIES: PREVENTION OF VTE AFTER MAJOR ORTHOPEDIC SURGERY**

There is a serious risk of VTE, manifesting as deep vein thrombosis (DVT) or pulmonary embolism (PE), after surgical procedures such as major orthopedic surgery, and alternatives to the currently available oral therapies are needed.

Furthermore, VTE prevention after major orthopedic surgery is an excellent model in which to demonstrate the efficacy and safety of novel anticoagulants, because of the high event rate (a small number of patients is required to show an effect), short treatment duration (typically 5 to 10 days), and the ability to quantify and control bleeding in a hospital environment. As a result, four phase II studies were performed to assess the efficacy and safety of rivaroxaban for VTE prevention after major orthopedic surgery.

An open-label, phase IIa, proof-of-principle study of rivaroxaban was conducted in patients undergoing total hip replacement (THR). The efficacy and safety of oral rivaroxaban (2.5 to 30 mg bid and 30 mg once daily [od] initiated postoperatively) were compared with subcutaneous enoxaparin (40 mg od, initiated before surgery). Patients received study drugs for 5 to 9 days when mandatory, standardized bilateral venography was performed. The main endpoints in this study were the composite of any DVT, PE, and all-cause mortality (primary efficacy endpoint); the composite of proximal DVT, PE, and VTE-related death (major VTE; secondary efficacy endpoint); and major postoperative bleeding (primary safety endpoint). Rivaroxaban reduced the incidence of the primary efficacy endpoint, and there was a dose trend with increasing rivaroxaban doses (p = 0.0504); furthermore, the incidence of major VTE decreased dose dependently with rivaroxaban (p = 0.0108). As would be expected with an anticoagulant, the incidence of major postoperative bleeding increased dose dependently with rivaroxaban (p = 0.0008). Results with the rivaroxaban 30 mg od dose were in line with the dose–response relationships with the bid doses for all endpoints, suggesting that od rivaroxaban dosing could be feasible. In this study, the efficacy of rivaroxaban relative to enoxaparin, and the dose-dependent increase in major bleeding, demonstrated proof of principle for rivaroxaban in this indication.

Given that the favorable results with the bid rivaroxaban doses in the phase IIa study, two separate, double-blind, phase IIb studies of rivaroxaban with bid rivaroxaban dosing were conducted. These large, randomized, double-blind, active comparator-controlled (versus enoxaparin), parallel-group, dose-ranging studies investigated a 12-fold dose range of rivaroxaban (total daily doses 5 to 60 mg) administered bid in patients undergoing primary THR (N = 722) or total knee replacement (N = 621) in Europe and North America, respectively. These studies used the same endpoints as the proof-of-principle study.

In both studies, the observed incidence of the primary efficacy endpoint was similar to that of enoxaparin across the 12-fold dose range of rivaroxaban; the incidence of major VTE was also similar to that of enoxaparin (Table 1). No deaths were reported in either study. There was a significant dose–response relationship between rivaroxaban and major postoperative bleeding in both studies (p < 0.05); however, there were no significant differences between any rivaroxaban dose group and enoxaparin. The observed incidence of major postoperative bleeding was similar to enoxaparin in the rivaroxaban 5- to 20-mg dose groups.

These studies were designed to allow a pooled analysis of the results, which confirmed that, when both efficacy and safety were considered, the optimal dose range of rivaroxaban was total daily doses of 5 to 20 mg.

**Once-Daily Rivaroxaban for Prevention of VTE after Major Orthopedic Surgery**

While the two phase II bid studies were taking place, additional evidence became available to suggest that an od regimen of rivaroxaban may be appropriate. In addition to the efficacy and safety of od rivaroxaban in
the proof-of-principle study, clinical pharmacology studies suggested that the pharmacodynamic effects of rivaroxaban persist for 24 hours after od dosing. Furthermore, a clinical pharmacology study investigating potential interactions between rivaroxaban and the low molecular weight heparin enoxaparin showed that rivaroxaban 10 mg had similar pharmacodynamic effects to those of 40 mg enoxaparin, with measurable effects at 24 hours. The half-life of enoxaparin, measured using the pharmacodynamic anti-FXa assay, is short: 4.1 hours. Nevertheless, od dosing of enoxaparin has been shown to be highly effective for the prevention of VTE after major orthopedic surgery. The results of these studies led to the initiation of a phase IIb dose-finding study to investigate the efficacy and safety of od rivaroxaban for the prevention of VTE after major orthopedic surgery. This was a large, randomized, double-blind, active-comparator-controlled (versus enoxaparin), parallel-group, dose-ranging study in patients undergoing THR, which used a similar methodological approach to the bid studies, and the same clinical endpoints.

Rivaroxaban, administered od, demonstrated similar efficacy to enoxaparin in patients who had undergone elective, primary THR. The observed incidence of the primary efficacy endpoint (any DVT, PE, and all-cause mortality) across the 8-fold dose range evaluated in this study was lower with rivaroxaban than with enoxaparin (5.7 to 13.5% versus 25.2%, respectively). Although the tendency toward a dose–response relationship between rivaroxaban and the primary efficacy endpoint was not statistically significant (p = 0.0825; Fig. 4), there was a significant dose–response relationship between rivaroxaban and major VTE (p = 0.0072). The observed incidence of major VTE was lower with all rivaroxaban doses (0.9 to 2.7%) than with enoxaparin (2.8%), except for the 5-mg dose (the lowest effective dose), in which the incidence of major VTE was 8.5%.

There was a significant dose–response relationship between rivaroxaban and major postoperative bleeding (p = 0.039; Fig. 4); however, there were no significant differences between any rivaroxaban dose and enoxaparin (although the study was not powered to show the differences between individual doses). The two lowest doses of rivaroxaban (5 and 10 mg od) had similar rates of major bleeding to enoxaparin (2.3 and 0.7 versus 1.9%, respectively). Importantly, all major postoperative bleeding events were confined to the surgical site, and there were no cases of fatal bleeding or bleeding into a critical organ.

No treatment arm was stopped because of safety concerns or lack of efficacy, and when safety and efficacy were considered together, rivaroxaban 10 mg od was defined as the optimal dose—a dose within the range identified in the bid studies.

### Safety and Tolerability

In the phase IIb studies investigating the use of rivaroxaban for the prevention of VTE after major orthopedic surgery, rivaroxaban was well tolerated, with a safety profile similar to that of enoxaparin. The incidence of increased liver enzymes with rivaroxaban generally was lower than that observed in the enoxaparin

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**Table 1 Incidences (%) of Any DVT, PE, and All-Cause Mortality; Major VTE; and Major Postoperative Bleeding in the Two Phase IIb Twice-Daily Studies of Rivaroxaban (ODIXa-HIP2 and ODIXa-KNEE), the Pooled Analysis of Those Studies, and the Phase IIb Study of Rivaroxaban Administered Once Daily (ODIXa-HIP od)**

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<td>Any DVT, PE, and all-cause mortality</td>
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<td>ODIXa-HIP2</td>
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<td>ODIXa-KNEE</td>
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<td>ODIXa-HIP od</td>
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<td>Major bleeding</td>
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<td>ODIXa-HIP od</td>
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Results for the pooled analysis are shown after adjustment for age, gender, and study. DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; od, once daily.
groups in the postsurgical setting after short-term use. Rivaroxaban had no effect on electrocardiographic or laboratory parameters (except clotting tests), and only a low incidence of nausea and vomiting was reported with early postoperative administration of rivaroxaban.

All patients received fixed doses of rivaroxaban, irrespective of age, gender, body weight, renal and hepatic impairment (patients with severe renal impairment, defined as a creatinine clearance of less than 30 mL/min, were excluded from the studies), and regular monitoring of rivaroxaban levels was not undertaken (at a local level) in these studies, nor was it required.

PHARMACOKINETICS AND PHARMACODYNAMICS IN PHASE II STUDIES

The pharmacokinetics and pharmacodynamics of od and bid rivaroxaban (5, 10, and 20 mg total daily doses) were compared in the two phase IIb studies in patients undergoing THR. This analysis demonstrated that rivaroxaban $C_{\text{max}}$ was higher and the minimum plasma concentration ($C_{\text{trough}}$) was lower with od dosing compared with bid dosing, as would be expected when the same total daily dose of a drug with predictable pharmacokinetics is administered in one rather than two doses. However, the confidence intervals of the $C_{\text{max}}$ and $C_{\text{trough}}$ values overlapped significantly, suggesting that od dosing should not expose patients to an increased risk of bleeding or VTE.

The pharmacokinetics of rivaroxaban was affected by the following patient demographic and clinical characteristics: age and renal function influenced the clearance of rivaroxaban, and body weight influenced its volume of distribution. The effects of these demographic factors were only moderate, and were as expected from the results of numerous dedicated phase I studies conducted in otherwise healthy elderly subjects, subjects with renal impairment, or subjects with extreme body weight.

As observed in healthy subjects, the pharmacodynamic effects of rivaroxaban correlated closely with its pharmacokinetics, and a linear correlation was observed for PT. This finding suggested that this commonly available coagulation test may be suitable for assessing rivaroxaban exposure, if this was necessary, in special cases.

SUMMARY AND CONCLUSIONS

The results of preclinical and clinical studies of rivaroxaban indicate that direct inhibition of FXa with a small-molecule inhibitor is a feasible and promising approach for the prevention and treatment of thromboembolic disorders.
Rivaroxaban is a novel, oral, direct FXa inhibitor, which selectively inhibits FXa. By inhibiting FXa, rivaroxaban prolongs clotting times (as shown by numerous global clotting tests) and reduces thrombin generation. Early studies in animal thrombosis models demonstrated the ability of rivaroxaban to prevent and treat venous thrombosis, and to prevent arterial thrombosis. Phase I studies in healthy subjects then showed its predictable pharmacologic profile, by elucidating the close correlation between its pharmacokinetic and pharmacodynamic effects. These studies also demonstrated a low propensity for interactions with commonly used medications, including aspirin, non-steroidal anti-inflammatory drugs, and digoxin, and showed that fixed doses of rivaroxaban can be administered to patients irrespective of age, gender, body weight, and renal impairment.

Phase II studies investigating rivaroxaban for the prevention of VTE after major orthopedic surgery have suggested that it has similar efficacy and safety to enoxaparin, and can be given in a convenient fixed dose. A od oral anticoagulant such as rivaroxaban, which can be administered as a fixed dose without coagulation monitoring for the prevention of VTE, could be an attractive alternative to currently available therapies.

REFERENCES


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