Background—An effective and safe oral anticoagulant that needs no monitoring for dose adjustment is urgently needed for the treatment of diseases that require long-term anticoagulation. Rivaroxaban (BAY 59-7939) is an oral direct factor Xa inhibitor currently under clinical development.

Methods and Results—This randomized, parallel-group phase II trial in patients with proximal deep-vein thrombosis explored the efficacy and safety of rivaroxaban 10, 20, or 30 mg BID or 40 mg once daily compared with enoxaparin 1 mg/kg BID followed by vitamin K antagonist. Each treatment was administered for 12 weeks. The primary efficacy end point was an improvement in thrombotic burden at day 21 (assessed by quantitative compression ultrasonography; ≥4-point improvement in thrombus score) without recurrent symptomatic venous thromboembolism or venous thromboembolism–related death. The primary safety end point was major bleeding during 12 weeks of treatment. Outcomes were adjudicated centrally without knowledge of treatment allocation. The primary efficacy end point was achieved in 53 (53.0%) of 100, 58 (59.2%) of 98, 62 (56.9%) of 109, and 49 (43.8%) of 112 patients receiving rivaroxaban 10, 20, or 30 mg BID or 40 mg once daily, respectively, compared with 50 (45.9%) of 109 patients treated with enoxaparin/vitamin K antagonist. There was no significant trend in the dose–response relationship between rivaroxaban BID and the primary efficacy end point (P=0.67). Major bleeding was observed in 1.7%, 1.7%, 3.3%, and 1.7% of patients receiving rivaroxaban 10, 20, or 30 mg BID or 40 mg once daily, respectively. There were no major bleeding events with enoxaparin/vitamin K antagonist.

Conclusions—Results of this proof-of-concept and dose-finding study support phase III evaluation of the orally active direct factor Xa inhibitor rivaroxaban, because efficacy and safety were apparent in the treatment of proximal deep-vein thrombosis across a 3-fold range of fixed daily dosing. (Circulation. 2007;116:180-187.)

Key Words: thrombosis ■ thromboembolism ■ deep-vein thrombosis ■ factor Xa ■ anticoagulants
fold selectivity than for other related serine proteases, and also inhibits prothrombinase activity and clot-associated FXa activity. Rivaroxaban has predictable pharmacokinetics and pharmacodynamics in healthy subjects and those undergoing orthopedic surgery. The relative bioavailability of rivaroxaban is high (≈80%); it has a dual mode of excretion, primarily via the renal route (66%) and also by the fecal/biliary route; and it is excreted primarily as unchanged drug. Maximum plasma concentrations are reached in 2 to 4 hours in healthy subjects, and it has a half-life of ≈9 hours in young healthy subjects and 12 hours in healthy elderly subjects (aged >75 years). Rivaroxaban should not require routine laboratory monitoring and can be given as a fixed dose.

The aim of this phase II dose-finding study was to explore the efficacy and safety of rivaroxaban, relative to standard therapy, for the treatment of acute proximal deep-vein thrombosis (DVT). This proof-of-concept study was planned to assess the ability of rivaroxaban to treat existing clots, because previous studies have shown that short-term anticoagulation with rivaroxaban, for up to 10 days, can prevent VTE after major orthopedic surgery. This is the first study to evaluate an orally active FXa inhibitor for the treatment of a disease that requires long-term anticoagulation.

Methods

Study Patients

Patients with symptomatic acute thrombosis of the popliteal or more proximal veins, confirmed by complete compression ultrasound (CCUS) were considered for enrollment in the present study if they were aged 18 years or over, had no symptoms of pulmonary embolism (PE), had not received a VKA, and had received no more than 36 hours of treatment with unfractionated heparin or a low–molecular-weight heparin (3 doses 12 hours apart or 2 doses 24 hours apart).

The main exclusion criteria were related to bleeding risk: cerebral ischemia; intracerebral bleeding or gastrointestinal bleeding within the past 6 months; neurosurgery within the past 4 weeks or other surgery within the past 10 days; an active peptic ulcer; a known bleeding disorder; prolonged international normalized ratio (INR) or activated partial thromboplastin time; and a platelet count below 100 × 10^9/L. Other exclusion criteria included known brain metastasis; cytotoxic chemotherapy; life expectancy <6 months; body weight <45 kg; severe heart failure (New York Heart Association class III to IV); uncontrolled severe hypertension (>200/100 mm Hg); a derived creatinine clearance of <30 ml/min or serum creatinine >1.5× the upper limit of normal (ULN); impaired liver function (transaminases >2×ULN); a likelihood of reduced oral drug absorption (severe inflammatory bowel disease, short gut syndrome); and child-bearing potential without effective contraception. Patients were also excluded if they required thrombolytic therapy or treatment with antiplatelet agents, nonsteroidal anti-inflammatory drugs with a half-life >17 hours, or potent CYP3A4 inhibitors, such as ketoconazole. Short-term analgesia with acetylsalicylic acid, 500 mg/d, was permitted before and during the study.

Study Design

The ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis) study was a multinational, multicenter, partially blinded, parallel-group study in which patients were randomized by central computer, within 36 hours of confirmed diagnosis of symptomatic proximal DVT, to receive 1 of 4 double-blinded dose regimens of rivaroxaban or open-label standard anticoagulant therapy for 12 weeks (Figure 1). Patients in the oral rivaroxaban treatment groups received double-blinded doses of 10, 20, or 30 mg twice daily (BID) or 40 mg once daily, with food, for 12 weeks. Pharmacokinetic and pharmacodynamic data and phase II DVT prevention trials suggested these doses were likely to be effective and safe. Patients in the open-label, standard-anticoagulant group received enoxaparin 1 mg/kg BID by subcutaneous injection and a VKA (warfarin, phenprocoumon, or acenocoumarol, as agreed in participating countries). Enoxaparin was given for at least 5 days and until the INR had reached 2 to 3 for 2 consecutive days; the VKA was continued for 12 weeks. Clinical follow-up continued until 30 days after the last dose of study medication. Anticoagulant therapy after 12 weeks was at the investigators’ discretion.

The study complied with the Declaration of Helsinki and Good Clinical Practice guidelines, was approved by local Institutional Review Boards, and required written and informed consent before patients were enrolled. Study results were reviewed regularly by an expert Independent Data Safety Monitoring Board.

Study Procedures

Proximal DVT at baseline was confirmed by CCUS examination. A baseline perfusion lung scan was undertaken within 72 hours of the CCUS and within 36 hours of starting study drug. The CCUS examination and perfusion lung scan were repeated on mean day 21 (range, 18 to 26); an additional CCUS examination was performed on day 84±14 days.

To ensure a high quality of standardized CCUS, all sonographers received CCUS training, and study centers were certified by the Central Adjudicating Laboratory before subjects were recruited. In addition, investigators were advised that asymptomatic perfusion defects are frequent findings when patients with proximal DVT have routine lung scans and should not alter clinical management.

The protocol required patients to continue with study medications after mean day 21 (range, 18 to 26) if local review of the CCUS and lung scan results found no deterioration. However, continued study treatment was subject to the investigator’s clinical judgment if local adjudication suggested asymptomatic deterioration.
Efficacy and Safety Outcomes
The primary efficacy outcome was an improvement in thrombotic burden at mean day 21 (range, 18 to 26; defined as a ≥4-point reduction in the thrombus score as measured by CCUS examination) without confirmed symptomatic extension or recurrence of DVT, confirmed symptomatic PE, or VTE-related death. Secondary efficacy outcomes included an improvement in thrombus score of ≥4 points as measured by CCUS examination and/or an improved perfusion lung scan on day 21, without deterioration in the other and without symptomatic recurrence of VTE; an improvement in CCUS examination score at 3 months (84±14 days); and the incidence of symptomatic and confirmed PE or DVT (recurrence or extension) during the 3 months of study therapy.

Clinically suspected extension or recurrence of DVT was investigated by CCUS examination, and suspected PE by lung scanning and/or spiral computerized tomography and/or angiography. If investigations were negative, study treatment was continued and the planned CCUS and lung scan examinations were undertaken. Study treatment was stopped upon confirmation of VTE or significant bleeding, which was managed according to usual clinical practice.

The primary safety outcome was the incidence of major bleeding with onset no later than 2 days after the last dose of study drug. Secondary safety measures included the incidence of minor bleeding events. Bleeding was considered major if it was fatal, affected a critical organ (retroperitoneal, intracranial, intraocular, or intraarticular), or was clinically overt and led to treatment cessation, a fall in blood hemoglobin ≥2 g/dL, or transfusion of 2 or more units of packed red blood cells or whole blood; all other overt bleeding events were considered minor.16

All clinically suspected VTE, bleeding events, deaths, and paired perfusion lung scans (see below) were adjudicated, without knowledge of the treatment group, by an independent central adjudication committee at the Henderson Research Centre, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada.

Scoring of CCUS and Perfusion Lung Scan Examinations
Video recordings of CCUS examinations and copies of perfusion lung scans were adjudicated centrally without the knowledge of the treatment group (CCUS Adjudication Committee, University Hospital Carl Gustav Carus, Dresden, Germany). A score reflecting the burden of leg vein thrombus was defined a priori and was analogous to the venography score described by Marder et al.17 It included all affected proximal and distal vein segments and took into account the thrombus diameter. It was derived from central adjudication of video recordings and/or spiral computerized tomography and/or angiography. If investigations were negative, study treatment was continued and the planned CCUS and lung scan examinations were undertaken. Study treatment was stopped upon confirmation of VTE or significant bleeding, which was managed according to usual clinical practice.

The ultrasound scoring system used in the present study was shown to have very low interobserver variability. For the purposes of this study, an improvement in thrombotic burden between patients would be randomized.

1.4 mg once daily and the active comparator, so that a total of 600 patients would be available for efficacy analysis. This sample size was calculated with nQuery Advisor, version 4, statistical software. Statistical analyses were performed with the assumption of a linear dose effect, a positive outcome relative to the primary efficacy end point in 32%, 43%, and 54% of patients receiving 10, 20, and 30 mg BID, respectively, and that 75% of patients would be available for efficacy analysis. This sample size would yield a 2-sided type I error rate of 0.05 for the trend test and a type II error rate of 0.15, corresponding to a power of 85%. It was planned that a similar number of patients would be given rivaroxaban 40 mg once daily and the active comparator, so that a total of 600 patients would be randomized.

The primary efficacy analysis (to determine the dose-response relationship between twice-daily rivaroxaban and the primary effi-

Figure 2. Method for calculating thrombus burden score. If a venous segment was not compressible, points were accumulated as indicated above. The segment score was increased 1.5-fold if its compressed diameter was ≥1.5 times the arterial diameter and reduced 0.5-fold if this was ≤0.5 times the arterial diameter.

Laboratory Assessments
Blood samples were collected for central laboratory analysis of clinical chemistry, blood cell counts, and blood coagulation before randomization and on treatment days 1, 7±2, 21±2, 56±4, 84±4, and 114±4 (clinical chemistry only). Blood coagulation results were withheld from investigators, who managed VKA by monitoring INR locally. Electrocardiography was performed on days 1, 21±2, and 84±4.

In patients whose liver function tests became abnormal, the decision to stop blinded rivaroxaban therapy or continue under close laboratory supervision was based on a predetermined algorithm. Treatment was discontinued if the derived creatinine clearance fell below 30 mL/min (confirmed by 2 consecutive readings).

Statistical Analyses
The projected sample of 120 patients per twice-daily rivaroxaban treatment group was derived with nQuery Advisor, version 4, module PGT 1-1 (Statistical Solutions Ltd, Cork, Ireland), with the assumptions of a linear dose effect, a positive outcome relative to the primary efficacy end point in 32%, 43%, and 54% of patients receiving 10, 20, and 30 mg BID, respectively, and that 75% of patients would be available for efficacy analysis. This sample size would yield a 2-sided type I error rate of 0.05 for the trend test and a type II error rate of 0.15, corresponding to a power of 85%. It was planned that a similar number of patients would be given rivaroxaban 40 mg once daily and the active comparator, so that a total of 600 patients would be randomized.

The primary efficacy analysis (to determine the dose-response relationship between twice-daily rivaroxaban and the primary effi-
Figure 3. Flow of patients through the ODIXa-DVT study. ITT indicates intention-to-treat; PP, per-protocol.

cacy end point) was performed in the per-protocol population. A logistic regression model with total daily dose of rivaroxaban as a covariate was used to test the hypothesis that the effect of the covariate was zero. Patients qualified for the primary efficacy analysis if they had a CCUS assessment between days 18 and 26 or if they had symptomatic and confirmed DVT extension or recurrence, PE, or VTE-related death up to day 26 and had no major protocol violations (eg, prohibited medications or <80% compliance with study drug). Outcomes were eligible for efficacy analyses if they occurred within 3 calendar days of stopping study drugs. A supportive analysis was performed in the intention-to-treat population.

Patients qualified for safety analyses if they received at least 1 dose of study medication and had relevant safety assessments. Outcomes were eligible for safety analyses if they occurred within 2 calendar days of stopping study drugs. Logistic regression analysis was also used to test for a dose-response relationship between twice-daily rivaroxaban doses and the primary safety outcome (major bleeding). The statistical analysis was performed by the sponsor of the study.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Between March 2004 and June 2005, 636 patients were enrolled in the study, and 613 were randomized; 23 were not randomized because of protocol violation (n = 21) or adverse events (n = 2; Figure 3). An additional 9 patients, all randomized to rivaroxaban, did not receive study medication because of protocol violation (n = 6) or withdrawn consent (n = 3).

The baseline characteristics of the 604 randomized patients who received study treatment (safety population) are shown in Table 1. The treatment groups were similar. Seventy-six patients were not eligible for efficacy analysis at day 21 for the following reasons: baseline or day 21 CCUS not evaluable (n = 50); insufficient compliance (n = 12); CCUS examination fell outside the prespecified time window (n = 10); study medication ceased too early relative to CCUS (n = 3); and DVT not detected at baseline (n = 1). Thus, 528 patients were included in the per-protocol analysis of the primary efficacy end point. A total of 530 patients (87.7%) continued treatment until 84 days.

Of all patients randomized to receive rivaroxaban, 73 discontinued treatment for the following reasons: adverse event (n = 41), consent withdrawn (n = 10), death (n = 2), insufficient therapeutic effect (n = 1), noncompliance with study drug (n = 2), protocol violation (n = 16), and lost to follow-up (n = 1). Ten patients in the enoxaparin/VKA group discontinued study drug for the following reasons: adverse event (n = 1), consent withdrawn (n = 7), death (n = 1), and protocol violation (n = 1). In patients treated with a VKA, the average proportion of time within the target INR range of 2.0 to 3.0 was \( \approx 60.0\% \).

Efficacy Outcomes

The proportion of patients who met primary outcome criteria for efficacy was similar among all 4 rivaroxaban dose groups and the enoxaparin/VKA group. The primary efficacy end point (improvement of \( \geq 4 \) points in thrombus score in the absence of recurrent VTE and VTE-related death) was observed in 53 (53.0%) of 100, 58 (59.2%) of 98, 62 (56.9%) of 109, and 49 (43.8%) of 112 patients receiving rivaroxaban 10, 20, or 30 mg BID or 40 mg once daily, respectively, compared with 50 (45.9%) of 109 of those treated with enoxaparin/VKA (Table 2). No significant trend was observed in the dose-response relationship between twice-daily rivaroxaban and the primary efficacy end point (P = 0.67).

During the initial 21-day treatment period, 2 symptomatic, confirmed, recurrent VTE events occurred in patients receiving rivaroxaban (1 proximal DVT in each of the 10- and 20-mg BID groups [per-protocol population]). A nonfatal PE occurred in the rivaroxaban 30-mg BID group in the intention-to-treat population.

At 3 months, the efficacy end point was observed in 71 (71.0%) of 100, 70 (71.4% of 98), 80 (73.4%) of 109, and 77 (68.8%) of 112 of patients receiving rivaroxaban 10, 20, or 30

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics According to Treatment Groups: Safety Population (n=604)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Sex, % male</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Weight, kg</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>Height, cm</td>
</tr>
</tbody>
</table>

OD indicates once daily; BMI, body mass index.
Values are mean ± SD.
mg BID or 40 mg once daily, respectively, compared with 78 (71.6%) of 109 of those treated with enoxaparin/VKA. Values are given for those patients with valid measurements at 3 months.

During the extended treatment period (between days 21 and 84), an additional 7 VTE-related events occurred in the per-protocol population: 2 fatal PEs (1 in the rivaroxaban 10-mg BID group and 1 in the rivaroxaban 40-mg once-daily group); 2 nonfatal PEs (1 in the rivaroxaban 20-mg BID group and 1 in the rivaroxaban 40-mg once-daily group); and 3 proximal DVTs (1 in the rivaroxaban 30-mg BID group, 1 in the 40-mg once-daily group, and 1 in the enoxaparin/VKA group). The same events were observed in the intention-to-treat population, and an additional proximal DVT was observed in the safety population in a patient receiving enoxaparin/VKA, as well as 3 deaths not related to VTE (1 in the rivaroxaban 10-mg group and 2 in the rivaroxaban 20-mg group). Table 3 summarizes the incidence of symptomatic recurrent VTE events throughout the entire treatment period.

Safety Outcomes

Major bleeding in 1.7%, 1.7%, 3.3%, and 1.7% of patients receiving rivaroxaban 10, 20, or 30 mg BID or 40 mg once daily, respectively (Table 4). Two events occurred in each of the 10- and 20-mg BID and 40-mg once-daily groups, and 4 events occurred in the 30-mg BID group. No major bleeding events occurred in the enoxaparin/VKA group. No significant trend was observed in the dose-response relationship for rivaroxaban BID and major bleeding (P = 0.39). The incidence of minor bleeding events is shown in Table 4.

Fourteen patients died: 13 (2.7%) of 478 given rivaroxaban and 1 (0.8%) of 126 in the enoxaparin/VKA group (relative risk 3.4, 95% confidence interval [CI] 0.56 to 33.07). No deaths reported during the study were considered drug related. Two deaths in the rivaroxaban groups were attributed to PE (see above). One rivaroxaban patient died of liver failure (see below).

Most of the remaining deaths were attributed to malignancies, including metastatic cancer and lung cancer. Other causes of death included septicemia, disseminated intravascular coagulation, and pneumonia.

Other Observations

The incidence of treatment-emergent alanine aminotransferase (ALT) elevations >3×ULN in the rivaroxaban groups ranged from 1.9% to 4.3% compared with 21.6% in the enoxaparin/VKA-treated group, and this was not dose-dependent. Approximately half of the ALT elevations in the rivaroxaban-treated patients occurred during the first 3 weeks of treatment (Table 5). In the enoxaparin/VKA-treated patients, the majority of ALT elevations occurred during the first 2 weeks of treatment (Table 5). Beyond 21 days, the proportions of rivaroxaban- or VKA-treated patients with ALT elevations >3×ULN were similar (1.9% versus 0.9%) with similar 95% CIs (Table 5). The overall median time to elevation of ALT >3×ULN was 10.5 days in the 4 rivaroxaban treatment groups and 7 days in the enoxaparin/VKA group. One patient had ALT >3×ULN in combination with bilirubin ≥2×ULN; this patient died of acute liver failure (details below).

Rivaroxaban was stopped prematurely in 3 patients because of elevated liver enzyme levels. Two had early elevations of liver aminotransferases. In 1, ALT and aspartate aminotransferase began to increase on the day after the initiation of treatment, which was stopped after 5 days; ALT and aspartate aminotransferase levels returned to below the ULN. In the other, ALT and aspartate aminotransferase were elevated on the day of study drug initiation before first intake of study drug, when treatment was stopped immediately. This patient died 2.5 weeks later of carcinoma with liver metastases.

In the third patient, rivaroxaban 40 mg once daily was stopped after 23 days owing to a diagnosis of hepatitis B with raised liver aminotransferases; viral serology showed acute

TABLE 2. Incidence of Primary Efficacy End Point (Thrombus Regression at Day 21 [Days 18–26]) Without Recurrent Symptomatic VTE or VTE-Related Death: Per-Protocol Population (n=528)

<table>
<thead>
<tr>
<th>Rivaroxaban</th>
<th>10 mg BID (n=100)</th>
<th>20 mg BID (n=98)</th>
<th>30 mg BID (n=109)</th>
<th>40 mg OD (n=112)</th>
<th>Enoxaparin/VKA (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved, n (%)</td>
<td>53 (53.0)</td>
<td>58 (59.2)</td>
<td>62 (56.9)</td>
<td>49 (43.8)</td>
<td>50 (45.9)</td>
</tr>
<tr>
<td>95% CI, %</td>
<td>42.8–63.1</td>
<td>48.8–69.0</td>
<td>47.0–66.3</td>
<td>34.4–53.4</td>
<td>36.3–55.7</td>
</tr>
<tr>
<td>Deteriorated, n (%)</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

OD indicates once daily.

Values are given for those patients with valid measurements.

TABLE 3. Incidence of Recurrent DVT, PE, or VTE-Related Death up to Day 84 (+14): Intention-to-Treat Population (n=543)

<table>
<thead>
<tr>
<th>Rivaroxaban</th>
<th>10 mg BID (n=106)</th>
<th>20 mg BID (n=100)</th>
<th>30 mg BID (n=111)</th>
<th>40 mg OD (n=114)</th>
<th>Enoxaparin/VKA (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>2 (1.9)</td>
<td>2 (2.0)</td>
<td>2 (1.8)</td>
<td>3 (2.6)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Death (VTE-related)</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>PE, nonfatal</td>
<td>0 (0.0)</td>
<td>1 (1.0)</td>
<td>1 (0.9)</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>1 (0.9)</td>
<td>1 (1.0)</td>
<td>1 (0.9)</td>
<td>1 (0.9)</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

OD indicates once daily.

Values are n (%).
TABLE 4. Incidence of Bleeding Events Occurring ≤2 Days After Last Dose of Study Drug: Safety Population (n=604)

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Rivaroxaban* (All Doses)</th>
<th>Enoxaparin/VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;14 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>6/446 (1.3)</td>
<td>22/116 (19)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.5–2.9</td>
<td>12.3–27.3</td>
</tr>
<tr>
<td>14–21 d</td>
<td>2/266 (0.7)</td>
<td>2/70 (2.9)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.1–2.5</td>
<td>0.4–9.9</td>
</tr>
<tr>
<td>&gt;21 d</td>
<td>8/429 (1.9)</td>
<td>1/115 (0.9)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.8–3.6</td>
<td>0.0–4.8</td>
</tr>
</tbody>
</table>

Values collected before or on the same day that study medication was initiated were considered baseline.

*No dose-response relationship was shown; therefore, dosing groups were pooled.

Table 4 includes the incidence of bleeding events occurring ≤2 days after the last dose of study drug, showing safety data for Rivaroxaban and Enoxaparin/VKA. The table highlights the number of bleeding events across different time points, with 95% CI for each category. The data indicates a general trend of fewer bleeding events with Rivaroxaban compared to Enoxaparin/VKA, emphasizing the safety profile of the drug.

Discussion

In this dose-finding study, 4 fixed-dose regimens of rivaroxaban spanning a 3-fold daily dosing range were evaluated for the treatment of proximal DVT. Thrombus burden after 3 and 12 weeks of treatment was consistently reduced with each rivaroxaban dose, to a similar extent as with enoxaparin/VKA therapy. Recurrent VTE events and major bleeding events were uncommon in all treatment groups.

TABLE 5. Incidence of Treatment-Emergent ALT Elevations >3×ULN

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Rivaroxaban* (All Doses)</th>
<th>Enoxaparin/VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;14 d</td>
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</tr>
</tbody>
</table>

Values collected before or on the same day that study medication was initiated were considered baseline.

*No dose-response relationship was shown; therefore, dosing groups were pooled.

Table 5 presents the incidence of treatment-emergent ALT elevations >3×ULN for Rivaroxaban and Enoxaparin/VKA. The data shows a general trend of fewer ALT elevations with Rivaroxaban compared to Enoxaparin/VKA, indicating a favorable safety profile for the drug.

hepatitis B with seroconversion during the study period, and the patient died of acute liver failure 48 days after starting treatment. One month before inclusion in the study, this patient received 2 transfusions because of anemia during palliative chemotherapy for metastatic uterine sarcoma. Liver histology, taken at autopsy, showed postnecrotic fibrosis with compensatory hyperplasia without acute inflammatory changes. The most likely cause of liver failure was fatal hepatitis B infection; however, a contribution from rivaroxaban or 1 of the concomitant medications the patient had received cannot be excluded. One patient stopped rivaroxaban because of an increased creatinine level on the day of study drug initiation, seen before the first intake of study drug (167 μmol/L; ULN 106 μmol/L).

Like the previous dose-ranging studies of injectable indirect FXa inhibitors (fondaparinux19 and idraparinux20), the present trial showed only minimal and statistically nonsignificant trends for a dose-efficacy relationship with rivaroxaban. The most likely explanation is that effectiveness had reached a plateau across the relatively narrow (3-fold) dosing range of 20 to 60 mg of rivaroxaban per day. These doses were selected for the present study after considering the pharmacokinetics and pharmacodynamics of rivaroxaban and the results of VTE prevention trials in major orthopedic surgery, in which rivaroxaban 10 mg/d appeared to be the optimal regimen.12–14 It was thought that twice the prophylactic dose should be the minimum when treating for established thrombosis. Similar considerations may have contributed to the previously observed relatively flat dose-response curves for efficacy in DVT treatment of other FXa inhibitors. Whether the present study included the lowest effective daily dose of rivaroxaban therefore remains unknown.

Fewer patients given once-daily rivaroxaban (40 mg) had improved thrombus burden after 21 days of treatment, compared with patients given the same or higher total daily doses twice daily. In addition, the rate of recurrent thromboembolic events at 84±14 days was similar in the 4 rivaroxaban groups. Therefore, the present study does not indicate whether once- or twice-daily dosing of rivaroxaban is optimal. Nevertheless, when the present results are considered together with those from another recently concluded dose-ranging study that explored daily rivaroxaban doses of 20 to 40 mg, it appears the lowest (20 mg/d) dose shows the most promise for further clinical development.21

The present study, like other recent phase II dose-ranging treatment trials in DVT,19,20 used change in thrombus burden combined with perfusion lung scanning as a surrogate measure of efficacy. Change in thrombus burden as a surrogate outcome measurement has been validated by consistent findings demonstrating that changes in thrombus burden, as assessed by venography, are related to recurrent VTE events during therapy.22–24 However, venography is uncomfortable for patients and exposes them to radiation and the risk of contrast media–related adverse events. Furthermore, a significant proportion of patients are likely to refuse the second
examination, thereby increasing the likelihood of incomplete evaluations. CCUS is accurate in patients with symptomatic DVT. For thus, for the purposes of the present study, we converted the validated venographic surrogate measure to ultrasound using a standardized examination protocol (CCUS) that was validated internally and externally in previous studies. We also designed a scoring system that closely resembled the venographic Marder score. The blinded central adjudication process, with 2 independent adjudicators and consensus reading in cases of discrepancy, provided a high standard of procedural quality. The reliability of the 3 week-outcome measurement is supported by a previous study, in which pairs of venograms were obtained 3 weeks apart to assess treatment efficacy. In that study, the proportion of patients with treatment response after 3 weeks in the standard treatment arm was consistent with the results of the present study.

Concern about the possible hepatotoxicity of orally absorbed, direct-acting, clotting factor–specific anticoagulants was raised by the recent experience with ximelagatran, an orally absorbed prodrug for the direct thrombin inhibitor melagatran. Rivaroxaban, unlike melagatran, is an FXa inhibitor, but it is essential to seek evidence of possible effects on liver function. Enoxaparin is known to raise ALT levels, and the incidence of treatment-emergent ALT elevations >3×ULN during the first 3 weeks of drug exposure was substantially lower in the rivaroxaban groups. Beyond 21 days, the pooled point estimates of 1.9% for ALT >3×ULN with rivaroxaban and 0.9% in the VKA group had similar 95% CIs. Liver failure in the patient who died was attributed to acute hepatitis B infection; however, a contribution from rivaroxaban or 1 of the other concomitant medications the patient received cannot be excluded. The case emphasizes the need for continuing surveillance for liver toxicity in large-scale phase III studies. Although more deaths occurred in the rivaroxaban group, most were attributed to malignancies, including metastatic cancer and lung cancer, and none were considered drug related.

The strengths of the present study include its double-blind, parallel-group comparison among rivaroxaban dosing regimens, central randomization, and central adjudication of all outcomes by expert committees blinded to treatment allocation. Furthermore, a large proportion of patients met the criteria for the primary efficacy analysis. In this phase II study, patient safety was reinforced by reevaluation of the thrombosis burden after 3 weeks, to minimize the chance of exposing patients to an ineffective dose and to allow investigators to react if patients showed a significant but asymptomatic increase in thrombus burden, as interpreted locally at the time of repeat testing.

One limitation of the present trial is that compared with phase III evaluations, study patients were younger, and fewer had active cancer (<3%), which may have reduced the likelihood of thrombus extension or bleeding events. Another limitation is that as in most phase II VTE treatment studies, efficacy was evaluated with a surrogate end point (the change in thrombus burden, derived by scoring the extent of thrombosis observed on repeated extended CCUS examinations). In conclusion, this proof-of-concept and dose-finding study suggests that rivaroxaban, an orally active, direct FXa inhibitor, may have efficacy and safety in the treatment of proximal DVT across a 3-fold daily dosing range. Large phase III trials comparing clinical outcomes with rivaroxaban or low–molecular-weight heparin/VKA across a wide spectrum of patients are needed to confirm these observations.

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References

CLINICAL PERSPECTIVE

Currently available anticoagulants are effective but are administered parenterally (eg, low–molecular-weight heparins) or are difficult to manage because they require laboratory monitoring to adjust the dose (eg, vitamin K antagonists). Rivaroxaban is an oral direct factor Xa inhibitor in advanced clinical development. Rivaroxaban has been shown to be safe and effective as enoxaparin for prophylaxis of venous thromboembolism after major orthopedic surgery. This randomized, parallel-group phase II trial in patients with proximal deep-vein thrombosis explored the efficacy and safety of rivaroxaban 10, 20, or 30 mg twice daily or 40 mg once daily compared with enoxaparin 1 mg/kg BID followed by a vitamin K antagonist. Thrombus burden after 3 and 12 weeks of treatment was consistently reduced with each rivaroxaban dose, to a similar extent as with enoxaparin/vitamin K antagonist therapy. Recurrent venous thromboembolism events and major bleeding events were uncommon in all treatment groups. The predictable pharmacological profile of rivaroxaban, which does not include the need for coagulation monitoring, makes it an attractive proposition for both short- and long-term anticoagulation. Confirmation of this potential therapeutic benefit for any clinical thromboembolic indication would require completion of multiple investigations to verify the observed benefit and risk. In addition, the long-term safety of this potential new therapeutic molecule will require careful evaluation in a larger population of individuals who would be anticipated to receive such treatment.
Treatment of Proximal Deep-Vein Thrombosis With the Oral Direct Factor Xa Inhibitor Rivaroxaban (BAY 59-7939): The ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis) Study

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