A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein–DVT Dose-Ranging Study

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We performed a randomized dose-ranging study, double-blind for rivaroxaban doses and open-label for the comparator (low-molecular-weight heparin followed by vitamin K antagonists) to assess the optimal dose of rivaroxaban for the treatment of deep vein thrombosis. A total of 543 patients with acute deep-venous thrombosis received rivaroxaban 20, 30, or 40 mg once daily or comparator. Treatment lasted for 84 days. The primary efficacy outcome was the 3-month incidence of the composite of symptomatic venous thromboembolic complications and asymptomatic deterioration in thrombotic burden as assessed by comparison of ultrasound and perfusion lung scanning at day 84 with baseline. The main safety outcome was the composite of major bleeding and clinically relevant nonmajor bleeding. A total of 449 (83%) of the 543 patients could be included in the per-protocol population. The primary efficacy outcome occurred in 6.1%, 5.4%, and 6.6% of the rivaroxaban 20-, 30-, and 40-mg treatment groups, respectively, and in 9.9% of those receiving standard therapy. The main safety outcome occurred in 5.9%, 6.0%, and 2.2% of the rivaroxaban 20-, 30-, and 40-mg treatment groups, respectively, and in 8.8% of those receiving standard therapy. These results with simple fixed-dose oral regimens justify phase 3 evaluations (www.ClinicalTrials.gov no. NCT00395772). (Blood. 2008;112:2242-2247)

Introduction

Current treatment of venous thromboembolism (VTE) is effective and relatively safe but has several limitations. Heparins require parenteral administration and the often unpredictable response of vitamin K antagonists (VKA) requires close monitoring for dose adjustment. Improved understanding of coagulation pathways has led to the development of several new parenterally or orally active agents which specifically target single steps in blood coagulation. These new compounds have the potential to maintain antithrombotic efficacy and possibly to improve safety when given in fixed doses without the need for monitoring across a wide spectrum of patients. Rivaroxaban is an orally active, specific, and direct inhibitor of activated factor X with predictable pharmacokinetics and pharmacodynamics. It has a half life of 5 to 9 hours in healthy young subjects and 11 to 12 hours in elderly subjects, and a dual mode of elimination: two-thirds is metabolized by the liver and one-third is excreted unchanged by the kidneys. Rivaroxaban, given once daily, was shown to be more effective than low-molecular-weight heparin (LMWH) and equally safe in the prevention of VTE after major orthopedic surgery.

We designed a phase 2 study investigating 3 once daily doses of rivaroxaban, given for the initial and subsequent treatment of symptomatic deep vein thrombosis (DVT), with a control group receiving standard therapy. The rationale for once-daily rivaroxaban was based, in addition to the known half-life of anti-Xa activity, on the observation that thrombin generation in humans is inhibited up to 24 hours. Study treatment duration was 12 weeks (84 days). To improve study sensitivity, both symptomatic and asymptomatic deterioration were used as efficacy outcome measures. The ultimate aim of this study was to guide dose selection for the phase 3 program in VTE treatment when considered together with the findings from other relevant investigations.

Methods

Study patients

Adult patients with acute symptomatic DVT (ie, proximal or isolated extensive calf vein thrombosis involving at least the upper one-third of the calf veins) confirmed by compression ultrasound (CUS) or venography were potentially eligible for the study. The sole criterion for the presence of DVT was noncompressibility on ultrasound or an intraluminal filling defect on venography. Patients were excluded if they had concomitant symptomatic pulmonary embolism (PE), were treated for more than 36 hours before randomization with therapeutic doses of unfractionated...
heparin or LMWH, or received more than a single dose of a VKA. Other exclusion criteria were active bleeding or high risk of bleeding, thrombocytopeny, insertion of a caval filter or use of a fibrinolytic agent to treat the current episode of DVT, other indication for VKA, life expectancy less than 3 months, uncontrolled hypertension (systolic blood pressure > 200 mm Hg or diastolic blood pressure > 110 mm Hg), creatinine clearance less than 30 mL/min, impaired liver function (ALT > 2 × the upper limit of normal [ULN]), participation in another pharmacotherapeutic study within the previous 30 days, pregnancy or childbearing potential without proper contraceptive measures, and any other contraindication listed in the labeling of permitted anticoagulants, systemic treatment withazole compounds or other strong CYP3A4 inhibitors such as HIV-protease inhibitors, within 4 days before randomization or during the study. The last basis for exclusion is based on the observation that coadministration of rivaroxaban with these inhibitors significantly increases its pharmacodynamic effects.

**Study design**

The Einstein–DVT study was a randomized, dose-ranging study that was double-blind for rivaroxaban doses and open-label for the LMWH/VKA comparator and had blinded outcome assessment for all groups.

Patients were randomized, via an interactive voice response system, to receive one of 3 dose regimens of rivaroxaban (20, 30, or 40 mg once daily) until day 84 or the combination of LMWH and VKA. Heparin permitted for initial treatment were unfractionated heparin (started with a 5000-U bolus and 1250-I.U./hour infusion), tinzaparin (175 IU/kg subcutaneously once daily), and enoxaparin (1.5 mg/kg subcutaneously once daily, or 1.0 mg/kg subcutaneously twice daily). The minimum duration of heparin treatment was 5 calendar days. The 5-day treatment period could include a period up to 36 hours before randomization if a permitted heparin was used. The permitted VKAs were warfarin, acenocoumarol, phenprocoumon, and fluindione. VKA treatment was started within 48 hours after randomization. VKA treatment was adjusted to maintain the international normalized ratio (INR) within the therapeutic range (target 2.5, range 2.0–3.0). Heparin treatment was continued until a stable INR greater than 2 was observed on 2 measurements at least 24 hours apart. Initially, the INR had to be measured every 2 to 3 days, and thereafter at least once monthly. VKA treatment was continued until day 84 (± 14). The choice of LMWH/VKA in each center was based on local healthcare agreements and/or routine hospital use.

Follow-up visits were scheduled at days 8, 15, 22, 43, and 84. Patients were asked to report any symptoms of recurrent DVT or PE and bleeding. Compression ultrasound and perfusion lung scan were obtained at baseline and at the end of study treatment (day 84).

An independent adjudication committee, unaware of treatment allocation, evaluated all suspected thromboembolic complications, deaths, baseline and repeat ultrasound and perfusion lung scans, as well as all episodes of suspected bleeding. A data safety monitoring board periodically reviewed the accumulated data.

Written informed consent was obtained from all patients in accordance with the Declaration of Helsinki. Good clinical practice guidelines, therapeutic products program regulations, and all applicable Food and Drug Administration (FDA) and Investigational New Drug regulations were followed. The study protocol was approved by all participating local institutional review boards (see Document S1, available on the Blood website; see the Supplemental Materials link at the top of the online article).

**Efficacy outcomes**

The primary efficacy outcome was the composite of symptomatic recurrent DVT, symptomatic fatal or nonfatal PE, and asymptomatic deterioration in thrombotic burden. Secondary efficacy outcomes were the individual components of the primary efficacy outcome. Symptomatic recurrent DVT and PE was considered present when confirmed by objective tests. All deaths were reviewed for the likelihood of PE as the cause of death. Deaths that could not be attributed to a known cause and for which PE could not be excluded were classified as due to PE.

Asymptomatic deterioration in thrombotic burden was assessed by comparison of the ultrasound and perfusion lung scan at day 84 with baseline. To allow a quantitative assessment, the residual diameters of the common femoral, superficial femoral, and popliteal veins were measured under full compression. Diameters at day 84 were compared with baseline and scored as deteriorated, if there was an increase of 4 mm or more. Perfusion lung scan was performed according to standard methods, and the results of the scan at day 84 were compared with baseline and the defects were scored by use of an anatomic reference chart. For each scan, an estimate was made of the remaining perfusion of each lobe at data points 0.0 (no perfusion), 0.25, 0.50, 0.75, and 1.0 (normal perfusion). The total perfusion score is the sum of the remaining perfusion of the 6 lobes corrected with a factor of 0.45 for the left lung and 0.55 for the right lung to reflect the difference in lung size. Day 84 findings were scored as “deteriorated” if the lobe score had decreased by more than 25% for any individual lobe. This method has been shown to have a high reproducibility.

**Safety outcomes**

The principal safety outcome was the composite of major and clinically relevant but nonmajor bleeding up to 48 hours after treatment cessation. Secondary safety outcomes were any bleeding, all-cause mortality, and the individual components of the principal safety outcome. Major bleeding was defined as clinically overt bleeding that was fatal, into a critical organ (intracranial, retroperitoneal, or pericardial), or led to a fall in hemoglobin of 2 g/dL or more, or transfusion of 2 or more units of packed red blood cells or whole blood.

Clinically relevant nonmajor bleeding was defined as overt bleeding not meeting the criteria for major bleeding, but associated with medical intervention, unscheduled contact with a physician, (temporary) cessation of study treatment, or associated with any other discomfort for the patient, such as pain or impairment of activities of daily life. All other overt bleeding episodes were classified as minor bleeds.

**Laboratory assessments**

Blood samples for central assessment of hepatic function (total bilirubin and alanine aminotransferase [ALT]) were collected at baseline, on day 43, and on day 84. In patients receiving rivaroxaban, pharmacokinetics were evaluated before the next rivaroxaban administration on day 43 (trough level), and 2 to 6 hours after last intake of rivaroxaban on day 84 (peak level).

**Statistical analyses**

To detect an absolute difference of 20% in the incidences of recurrent VTE and deterioration in thrombotic burden between the lowest and the highest rivaroxaban dose groups, with a power of 80% and a 2-sided type I error of 5%, a sample size of 120 patients per group would be required. The sample size was set at 130 patients per group to allow for missing outcome data.

All efficacy analyses (primary and secondary) were performed in the per-protocol (PP) population (primary analysis) and in the modified intention-to-treat (ITT) population. The modified ITT population comprised all randomized patients who had received at least one dose of study treatment, had objectively confirmed DVT at baseline, and in whom the primary efficacy outcome was evaluable. The PP population consisted of all patients valid for ITT analysis without any major deviation from the protocol. Major deviations were prespecified and defined as performance of the ultrasound or perfusion lung scan more than 10 days after cessation of study medication, rivaroxaban intake less than 80% as assessed by tablet count, LMWH treatment less than 4 days, no INR measurement within the first week, or interval between INR determinations of more than 28 days. Trends among the rivaroxaban dose groups with respect to the primary efficacy outcome were assessed using logistic regression analyses.

All safety analyses were performed in the safety population, defined as all patients who were randomized and received at least one dose of study drug. The principal safety outcome was compared among the treatment groups using an approach similar to that used for the primary efficacy analysis. For the secondary safety analyses, major and clinically relevant nonmajor bleeding were analyzed separately using a similar approach.
Results

Study population

Between December 2004 and August 2005, 543 patients were randomized (Figure 1). The baseline characteristics of the 542 patients who received at least one dose of study treatment (i.e., safety population) were similar among the groups (Table 1). Of these, 487 (90%) met the criteria for the modified intention-to-treat population and 449 (83%) could be included in the per-protocol population.

Treatment and follow-up

Sixty-three patients interrupted study treatment with rivaroxaban (n = 48, 12%) or LMWH/VKA (n = 15, 11%) prematurely (Table 1). Among patients allocated to rivaroxaban, the median treatment duration was 85 days (interquartile range [IQR], 83-87). In 391 of 405 patients on rivaroxaban, tablet count revealed study medication intake above 80%. Rivaroxaban plasma concentrations increased dose proportionally (Table 1).

In the LMWH/VKA group, one patient was lost to follow-up (day 15). The average duration of LMWH treatment was 9.3 (± 7.8) days. The average number of INR measurements per patient was 11.6 (± 5.7), and 29.0%, 50.3%, and 20.7% were below, within, and above the therapeutic range, respectively.

Efficacy outcomes

The observed incidence of the primary efficacy outcome in the PP population was 5.4% to 6.6% in the rivaroxaban treatment groups, and 9.9% in the LMWH/VKA group (Table 2). The incidence of symptomatic recurrent VTE observed up to day 84 ranged between 1.7% and 3.6% for the rivaroxaban-treated patients and 6.9% for the LMWH/VKA-treated patients. Asymptomatic deterioration detected on ultrasound and/or perfusion lung scanning occurred in 1.8% to 5.0% in the rivaroxaban groups and in 3.0% of the LMWH/VKA group. Similar incidences of the efficacy outcomes were observed in the modified ITT population. The study did not demonstrate a dose trend for the primary efficacy outcome in rivaroxaban-treated patients. Rivaroxaban concentrations diminished with increasing body weight; however, this was not associated with an increased risk for the primary efficacy outcome (data not shown).

Safety outcomes

The observed incidence of the principal safety outcome (i.e., any clinically relevant bleeding) ranged between 2.2% and 6.0% for the
rivaroxaban groups and was 8.8% for the LMWH/VKA group (Table 3). Major bleeding occurred in 3 patients (0.7%) receiving rivaroxaban and in 2 patients (1.5%) receiving LMWH/VKA.

Rivaroxaban concentrations were higher with increasing age, decreasing renal function and lower body weight, however, this was not associated with an increased risk for bleeding (data not shown). Overall, 14 (3.5%) of the 405 patients in the rivaroxaban groups and 5 (3.6%) of the 137 patients in the LMWH/VKA group died (Table 3). Study medication was prematurely stopped due to adverse events in 4% to 7% of the rivaroxaban-treated patients and in 4% of the LMWH/VKA-treated patients (Table 1).

No combined increases in ALT levels more than 3× ULN and bilirubin levels more than 2× ULN, were observed. Isolated transient increases in ALT more than 3× ULN occurred with an incidence of 0.7% in rivaroxaban recipients, and 0.7% in the LMWH/VKA group.

### Discussion

In this phase 2 dose-ranging study, patients who presented with an acute symptomatic DVT were given 20 mg, 30 mg, or 40 mg rivaroxaban once daily or standard therapy for 12 weeks. Efficacy and safety appeared to be similar among all groups.

Peak and trough levels of rivaroxaban showed the expected increase with dose. This suggests that efficacy in these DVT patients has reached its plateau with the lowest evaluated dose of 20 mg daily, whereas a doubling of the daily dose to 40 mg may not increase the bleeding risk. The apparently flat dose response between 20 mg and 40 mg daily is consistent with results from a recently published and comparable trial where the daily rivaroxaban dose range was 20 mg to 60 mg, given as 2 divided doses.10 Liver function tests showed no evidence of toxicity.

Some methodologic aspects of this study require comment. The number of efficacy outcomes was approximately doubled, increasing study power, by adding the results of assessment for asymptomatic deterioration of thromboembolism to the clinical outcomes. The study design was like that of previous dose-ranging trials, using similar outcomes and allocating patients to either an open comparator or one of the blinded parallel rivaroxaban dosing groups.9,10,15 An independent central adjudication committee, unaware of treatment allocation, was used to minimize bias when comparing open and blinded treatment arms and comparisons between rivaroxaban doses were further strengthened by blinding.

### Table 1. Baseline characteristics and treatment details of the safety population

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Rivaroxaban</th>
<th>LMWH/VKA n = 137</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>64 (47)</td>
<td>73 (53)</td>
</tr>
<tr>
<td>Age, y (range)*</td>
<td>58 (22-87)</td>
<td>57 (21-92)</td>
</tr>
<tr>
<td>Weight, kg (range)</td>
<td>80 (45-140)</td>
<td>81 (57-154)</td>
</tr>
<tr>
<td>BMI, kg/m² (range)</td>
<td>28 (16-47)</td>
<td>27 (15-45)</td>
</tr>
<tr>
<td>Active cancer, n (%)</td>
<td>11 (8)</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Previous DVT or PE, n (%)</td>
<td>28 (21)</td>
<td>21 (15)</td>
</tr>
<tr>
<td>Recent surgery or trauma, n (%)</td>
<td>26 (19)</td>
<td>24 (17)</td>
</tr>
<tr>
<td>Recent immobilization for &gt;3 days, n (%)</td>
<td>18 (13)</td>
<td>18 (15)</td>
</tr>
</tbody>
</table>

### Most proximal DVT location, n (%)

<table>
<thead>
<tr>
<th>Location</th>
<th>Rivaroxaban</th>
<th>LMWH/VKA n = 137</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trifurcation</td>
<td>8 (6)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Popliteal vein</td>
<td>48 (37)</td>
<td>44 (33)</td>
</tr>
<tr>
<td>Superficial femoral vein</td>
<td>31 (24)</td>
<td>32 (24)</td>
</tr>
<tr>
<td>Common femoral vein</td>
<td>44 (34)</td>
<td>45 (34)</td>
</tr>
<tr>
<td>Perfusion defect at baseline, n (%)</td>
<td>90 (67)</td>
<td>91 (67)</td>
</tr>
</tbody>
</table>

Rivaroxaban trough levels at day 43, median (IQR) ng/mL

<table>
<thead>
<tr>
<th>Rivaroxaban</th>
<th>LMWH/VKA n = 137</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg, n = 135</td>
<td>32 (19-60)</td>
</tr>
<tr>
<td>30 mg, n = 134</td>
<td>47 (24-83)</td>
</tr>
<tr>
<td>40 mg, n = 136</td>
<td>50 (31-96)</td>
</tr>
</tbody>
</table>

Rivaroxaban peak levels at day 84, median (IQR) ng/mL

<table>
<thead>
<tr>
<th>Rivaroxaban</th>
<th>LMWH/VKA n = 137</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg, n = 135</td>
<td>244 (175-360)</td>
</tr>
<tr>
<td>30 mg, n = 134</td>
<td>293 (184-399)</td>
</tr>
<tr>
<td>40 mg, n = 136</td>
<td>365 (205-564)</td>
</tr>
</tbody>
</table>

### Premature discontinuation, n (%)

<table>
<thead>
<tr>
<th>Rivaroxaban</th>
<th>LMWH/VKA n = 137</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg, n = 135</td>
<td>17 (13)</td>
</tr>
<tr>
<td>30 mg, n = 134</td>
<td>19 (14)</td>
</tr>
<tr>
<td>40 mg, n = 136</td>
<td>12 (9)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; and VTE, venous thromboembolism.

*Two-sided 95% confidence intervals are presented.

†One patient presented with both DVT and PE.
These results raise a possibility that doses lower than 20 mg might be effective. However, our findings suggest the 3 dose levels evaluated have good efficacy and safety. Finally, like most phase 2 studies, the sample size was limited and hence the confidence intervals were wide.

What would be the appropriate dose regimen of rivaroxaban to take forward in a phase 3 program for patients with DVT and/or PE? In our study, which followed DVT patients for 3 months, 20 mg of rivaroxaban given once daily appeared to offer satisfactory protection from extension and recurrence after DVT. The other dose-ranging study with this compound in patients with DVT, which focused on changes in thrombotic burden after 3 weeks of treatment (measured by repeat venous ultrasonography) and mainly studied twice-daily regimens, raised the possibility that an initial twice-daily regimen might be associated with better clot resolution. Furthermore, pharmacokinetic modeling supports the concept that when starting treatment and before reaching steady state, twice-daily rivaroxaban may better avoid the lower trough concentrations seen with once-daily dosing. In addition, there is some evidence to suggest that patients with PE, or with important comorbidity, may need once-daily dosing. In addition, there is some evidence to suggest that patients with PE, or with important comorbidity, may need once-daily dosing. Regarding safety, the 2 dose-ranging studies with this compound concur that doses up to 40 mg/day may not increase the risk of bleeding. In view of the above mentioned clinical and pharmacokinetic data, it may be prudent to precede a 20-mg once-daily maintenance dose of rivaroxaban with an initial regimen consisting of a 3-week course of twice-daily rivaroxaban at a somewhat higher total daily dose.

Effective clinical management requires simple regimens that apply equally across a wide spectrum of patients and their therapeutic indications. In our study, oral rivaroxaban shows promise of meeting this requirement because it appeared to be effective and safe over the range of doses tested. A simple fixed-dose regimen with a single drug is likely to increase adherence, minimize errors, and improve effectiveness and safety.

### Acknowledgment
This work was sponsored by Bayer HealthCare. The Executive Committee and Study Management and Coordination Committee (including 2 nonvoting representatives of the sponsor) had final responsibility for the study design, protocol, statistical analysis plan, study oversight, verification of data, and data analyses. The data were gathered and maintained by the sponsor.

### Authorship
Contribution: H.R.B., A.W.A.L., and A.S. designed and supervised the study and wrote the paper; M.H.P. and G.R. analyzed data and wrote the paper; and G.A., A.C., A.S.G., F.M., and S.S. reviewed the data and wrote the paper.

Conflict-of-interest disclosure: A.W.A.L. and F.M. are employees of Bayer HealthCare, and F.M. owns stocks in the company. The remaining authors (except A.S.) were members of the Einstein Executive Committee and received an honorarium from Bayer HealthCare for their involvement in this committee. A.S. is an employee of International Clinical Trial Organization and Management (ICTOM), which received consultancy fees from Bayer HealthCare for the coordination and management of the study.

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### References
9. A novel long-acting synthetic factor Xa inhibitor


A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein–DVT Dose-Ranging Study

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