A randomized evaluation of betrixaban, an oral factor Xa inhibitor, for prevention of thromboembolic events after total knee replacement (EXPERT)

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Summary
Betrixaban is an oral direct inhibitor of factor Xa (FXa) being developed for the prevention of venous thromboembolism (VTE). Its antithrombotic effects had not been previously tested in patients. This exploratory clinical trial in the US and Canada randomized 215 patients undergoing elective total knee replacement (TKR) in a 2:2:1 ratio to receive post-operative betrixaban 15 mg or 40 mg p.o. bid or enoxaparin 30 mg s.c. q12h, respectively, for 10–14 days. The betrixaban dosage was blinded, but enoxaparin was not. Primary efficacy outcome was the incidence of VTE, consisting of deep-vein thrombosis (DVT) on mandatory unilateral (operated leg) venography, symptomatic proximal DVT, or pulmonary embolism (PE) through Day 10–14. Safety outcomes included major and clinically significant non-major bleeds through 48 h after treatment. All efficacy and bleeding outcomes were adjudicated by a blinded independent central adjudication committee. Of 214 treated patients, 175 (82%) were evaluable for primary efficacy. VTE incidence was 14/70 (20%; 95% CI: 11, 31) for betrixaban 15 mg, 10/65 (15%; 95% CI: 8, 27) for betrixaban 40 mg, and 4/40 (10%; 95% CI: 3, 24) for enoxaparin. No bleeds were reported for betrixaban 15 mg, 2 (2.4%) clinically significant non-major bleeds with betrixaban 40 mg, and one (2.3%) major and two (4.6%) clinically significant non-major bleeds with enoxaparin. A dose- and concentration-dependent effect of betrixaban on inhibition of thrombin generation and anti-Xa levels was observed. Betrixaban demonstrated antithrombotic activity and appeared well tolerated in knee replacement patients at the doses studied.

Keywords
Venous thrombosis, major bleed, betrixaban, direct factor Xa inhibitor, total knee replacement (TKR), clinical trials, oral anticoagulants

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Introduction
Knee replacement patients demonstrate a relatively high rate of venous thromboembolic events (VTE) despite adequate prophylaxis (1, 2). A novel oral agent that is easy to administer and manage without monitoring might improve the clinical utility of antithrombotic prophylaxis in this setting (3). One such agent is betrixaban, an oral inhibitor of factor Xa (FXa), both free and bound in the prothrombinase complex (4). Betrixaban is an active site-directed competitive inhibitor of FXa (Ki=117pM) which exhibits very high (>86,000-fold) specificity toward FXa versus other coagulation enzymes, including thrombin. It also has a number of favorable pharmacologic and pharmacokinetic characteristics that distinguish it from other oral FXa inhibitors in development. Clearance is primarily by biliary excretion with limited metabolism and minimal renal excretion with less than 5% of an administered dose excreted in the urine. Accordingly, dose adjustment may not be required in patients with impaired
renal function. Moreover, the lack of interaction with major cytochrome (CYP) P450 enzyme pathways gives betrixaban a low potential for important drug interactions. Lastly, its 20-hour (h) pharmacodynamic half-life is accompanied by little diurnal variation in drug concentrations and consequently, anti-FXa activity. This allows patients to be maintained within the optimal therapeutic range over each 24-h dosing period, with less risk of excursions into higher or lower levels, even with less than perfect adherence to the prescribed regimen.

The doses used in this first phase 2 study of betrixaban were based on in-vitro and in-vivo experimental systems that established target plasma concentrations of betrixaban that would attain similar levels of anticoagulant activity as those attained by other FXa targeting agents at clinically effective doses. Betrixaban was inhibitory in a series of assays of tissue factor-initiated thrombin generation in human plasma and whole blood. The results indicated that inhibition by 5 to 25 ng/ml betrixaban was equivalent to that achieved by therapeutic levels of fondaparinux (target concentration 90–270 nM, corresponding to peak and trough levels of a 2.5 mg s.c. dose) (4). Other small-molecule FXa inhibitors have used animal models to establish proof of efficacy. Similarly, betrixaban also demonstrated concentration-dependent antithrombotic activity in animal models of thrombosis in rat carotid artery, rabbit vena cava and baboon arteriovenous shunts (5). Because the specificity of betrixaban for rat and rabbit FXa is considerably lower than that for human or baboon FXa, predictions of target plasma concentrations were based on antithrombotic activity determined in the baboon model. This model of thrombogenic device incorporation into an arteriovenous shunt has been validated by characterization of anticoagulants in clinical use and provides a suitable platform for comparison with pre-clinical agents (6). Under in-vivo conditions simulating venous blood flow, betrixaban produced a concentration-dependent antithrombotic effect (30–90% inhibition with average plasma concentrations ranging from 7 to 83 ng/ml) without significant changes in ex-vivo clotting parameters (prothrombin time [PT], activated clotting time [ACT]) or bleeding times. Values for activated partial thromboplastin time (aPTT) were minimally elevated at only the highest dose (average plasma concentration = 72 ng/ml). Results from the study showed that circulating plasma concentrations as low as 7 ng/ml produced a 30% reduction of deposition of radiolabeled platelets under thrombotic conditions which mimic venous blood flow. Thus, both in-vitro and in-vivo data for betrixaban suggested that target plasma concentrations of 5 to 25 ng/ml would produce antithrombotic activity in humans. Phase I data in healthy subjects (data on file, Portola Pharmaceuticals Inc) indicated that daily betrixaban doses of 30–80 mg would result in concentrations within this target range, given the slightly greater than dose-proportional increase in drug levels.

In this exploratory, “proof-of-concept” trial, we used the setting of total knee replacement (TKR) to confirm the antithrombotic potential and safety of betrixaban at dosages that were predicted to produce these plasma levels and to correlate anti-FXa activity and thrombin generation inhibition between treatment regimens. We included a small number of patients in a control enoxaparin group as an approximate benchmark as well as to be sensitive to gross short-term safety trends in the population under study, and to assist in the interpretation of PD data.

Methods

Study design

This trial was a multicenter, randomized, parallel-group investigation examining the efficacy and safety of two oral doses of betrixaban (15 mg and 40 mg) and enoxaparin administered subcutaneously for the prevention of VTE after TKR. Randomization was either to enoxaparin or one of two dose levels (15 or 40 mg bid) of betrixaban; patients and physicians were blinded to the betrixaban dose level, but unblinded to enoxaparin versus betrixaban. Recruitment of patients occurred at 19 sites in the US and Canada.

The study protocol and informed consent form were reviewed and approved by an Institutional Review Board or Ethics Committee for each participating center prior to study initiation. All patients provided written informed consent before undergoing any study-related procedures.

All primary efficacy data and suspected bleeding events were evaluated centrally by an Independent Central Adjudication Committee (ICAC) blinded to treatment allocation. The study was conducted under the supervision of a Steering Committee and Data Safety Monitoring Board (DSMB) comprised of experts in post-surgical VTE prophylaxis.

Patients

Men and women between 18 and 75 years of age and weighing between 50 and 120 kg scheduled to undergo elective primary unilateral TKR were screened for eligibility to the study 1–30 days before surgery. Female participants were required to be without reproductive potential, i.e. postmenopausal for ≥2 years or after hysterectomy. Patients with bleeding disorders, a recent episode of internal bleeding, or at high risk for bleeding and those with platelet count < 100,000/mm3, hemoglobin < 10 g/dl or haematocrit < 30% were excluded from the study. Use of thrombolytic agents and anticoagulants was prohibited within seven days prior to surgery and throughout the treatment period; use of aspirin up to 325 mg daily and non-steroidal anti-inflammatory drugs were allowed but discouraged.

Treatment regimens

Patients who remained eligible for the study after undergoing TKR were randomized within 6 h of surgery completion. The computer-generated randomization code provided assignments in a 2:2:1 ratio to either betrixaban 15 mg, betrixaban 40 mg, or enoxaparin 30 mg, respectively. The initial dose of betrixaban was taken 6–8 h after surgery and bid thereafter. Enoxaparin was administered subcutaneously 12–24 h after surgery and every 12 h (q12h) thereafter. While betrixaban has a half-life suitable for once daily administration, a bid dosing regimen was selected in order to mimic a possible future controlled-release formulation designed to further flatten the diurnal PK and PD profile. Treatment continued for 10 to 14 days unless a protocol-specified stopping criterion had been met. After discharge from the hospital, patients self-administered study medication. The last dose of study medication was administered the morning of the
scheduled mandatory venography of the operated leg (Day 10 to 14). Bexrixaban was supplied by the sponsor, Portola Pharmaceuticals Inc. (South San Francisco, CA, USA), in pre-packaged bottles as capsules containing either 15 mg or 40 mg of betrixaban maleate as base equivalent. The betrixaban capsules for both doses were identical in appearance. Enoxaparin (Lovenox®, Sanofi-aventis, Bridgewater, NJ, USA) was acquired through commercial channels and supplied to the sites by the sponsor.

**Efficacy assessments**

Patients were assessed daily for signs and symptoms of DVT and PE while hospitalized. The primary efficacy outcome was the occurrence of VTE up to Day 10 to 14, where VTE represented the composite of proximal and/or distal DVT identified by unilateral mandatory venography of the operated leg, symptomatic proximal DVT, or PE. In addition, any diagnosis of VTE between mandatory venography and 6 (± 2) weeks post-TKR was also reported. A follow-up contact either in person or by telephone occurred every 2 to 4 days while the patient was on study medication and 6 (± 2) weeks after TKR surgery.

Evaluable mandatory venograms required visualization of all of the deep veins except the muscular, anterior tibial and deep femoral veins. A diagnosis of DVT was made if an intraluminal filling defect was observed on at least two images. Diagnosis by ultrasound or venography was required for suspected symptomatic DVT occurring prior to the scheduled venogram. Patients were withdrawn and treated appropriately if proximal DVT was diagnosed by ultrasound; mandatory venography was not required in this case. Suspected PE was evaluated by radionuclide lung (V/Q) scan, computed tomography (CT) pulmonary angiography or conventional angiography. Results from all VTE investigations were reviewed and adjudicated independently by at least two members of the ICAC (blinded central adjudication committee) according to procedures described in an adjudication manual. The results of the central adjudication were used in the primary analysis.

**Safety assessments**

Overt bleeding events, the primary safety outcome of the study, were categorized as major (i.e. fatal; involving vital organs; requiring additional surgery or a new therapeutic procedure; or a Bleeding Index ≥ 2.0) and clinically significant non-major bleeding. Bleeding Index was defined as the number of units of packed red blood cells or whole blood transfused plus the haemoglobin values before the bleeding episode minus the haemoglobin values after the bleed had stabilized (in g/dl). As with the efficacy data, all suspected bleeding events were adjudicated centrally in a blinded manner. Safety was also evaluated by monitoring adverse events, vital signs, 12-lead electrocardiograms (ECGs) and clinical laboratory parameters.

**Pharmacokinetic/pharmacodynamic assessments**

Blood samples for assessment of plasma drug concentrations and pharmacodynamic measurements were obtained at screening, 1–4 hours after administration of the morning dose of study medication on Day 2, on the day of discharge and prior to the mandatory venogram on Day 10 to 14. Plasma samples were analyzed for betrixaban using high-performance-liquid-chromatography with tandem mass spectrometry. The method was validated for a range from 0.100–50.0 ng/ml, based on the analysis of 0.2 ml plasma. Quantitation was performed using a calibration standard curve generated from weighted least square regression analysis.

Anticoagulation was measured by a thrombin generation inhibition assay (7) and anti-Xa activity in addition to aPTT, PT and international normalized ratio (INR). The anti-Xa unit assay was adapted from the Coatest LMW heparin kit (Diapharma) and modified to a 96-well plate format. In this assay, standards and patient samples were assayed in duplicate and the limit of quantification was 0.05 anti-Xa U/ml. Thrombin generation was initiated by the addition of tissue factor (109 pM Innovin, Dade Behring) and calcium (15 mM) to citrate anticoagulated patient plasma (0.1 ml). Formation of thrombin was measured by cleavage of a specific thrombin substrate (100 µM Z-GGR-AMC, Bachem) over a 10-min period. Relative fluorescence units (RFU) were measured in a FlexStation fluorescence reader (Molecular Devices) and used for quantitation of thrombin generation. All patient plasma samples were assayed in triplicate and thrombin generation reported as RFU for each individual.

**Statistical analyses**

This study was exploratory and descriptive in nature with relatively small sample sizes; therefore, formal statistical comparisons between treatments (betrixaban vs. enoxaparin) or between doses (betrixaban 15 mg vs. betrixaban 40 mg) were not planned. The 2:2:1 randomization ratio weighted enrollment toward treatment with betrixaban to provide a better estimate of the relative efficacy and safety of the two doses of betrixaban versus appropriate published enoxaparin data from recent comparable studies. A small enoxaparin control group was included chiefly to aid in the interpretation of safety and pharmacodynamic data.

Efficacy analyses included all patients with adjudicated evaluable venograms and, for patients without such venograms, adjudicated confirmatory investigations for symptomatic DVT and/or PE. The safety population included all randomized patients who received at least one dose of study medication. Plasma concentrations and pharmacodynamic parameters (thrombin generation inhibition and anti-Xa activity) were summarized by descriptive statistics and graphical displays.

**Results**

**Patients**

Between May and November 2006, 215 patients were randomized to treatment after undergoing unilateral TKR. Of these, 214 received at least one dose of betrixaban or enoxaparin. Withdrawn consent (5 [2.3%] patients) and adverse events (3 [1.4%] patients) accounted for the majority of study withdrawals (Fig. 1). Of the 214 treated patients, 181 (84.6%) underwent mandatory venography, of which 10 (5.5%) were judged by the ICAC to be indeterminate. Overall, 82% of patients qualified for the evaluation of primary efficacy (evaluable mandatory venogram or confirmed proximal DVT or PE prior to Day 10 to 14).

The study population was predominantly women (60%), with a higher proportion of women randomized to betrixaban com-
Demographic characteristics were otherwise similar between groups (Table 1). The mean age was 64 years (range 43–75 years). There were no clinically meaningful differences between treatment groups with respect to baseline values for vital signs, ECG or laboratory parameters. Average baseline values for liver and renal function parameters were within normal limits. Prophylactic treatment with betrixaban or enoxaparin continued for an average of 10.8 days. The length of hospitalization ranged from 2–15 days (median stay of 4 days). These numbers were similar across the three groups. The high degree of treatment compliance assessed by comparing actual versus expected doses for individual treatment durations (≥98% in each group) indicated excellent adherence to the self-administration of study medication after discharge from the hospital.

### Efficacy outcomes

The incidence of centrally adjudicated VTE up to the mandatory venogram on Day 10 to 14 is summarized in Table 2 and Figure 2. The occurrence of VTE was 20%, 15.4%, and 10% for betrixaban 15 mg, betrixaban 40 mg, and enoxaparin, respectively, with

### Table 1: Baseline characteristics of all treated patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Betrixaban</th>
<th>Enoxaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>87</td>
<td>84</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>55 (63.2)</td>
<td>52 (61.9)</td>
</tr>
<tr>
<td>Mean age (range), years</td>
<td>63 (47 – 75)</td>
<td>65 (47 – 75)</td>
</tr>
<tr>
<td>Mean weight, kg</td>
<td>90 (53 – 120)</td>
<td>90 (52 – 120)</td>
</tr>
<tr>
<td>Mean duration of treatment (range), days</td>
<td>11.4 (1 – 16)</td>
<td>10.6 (2 – 16)</td>
</tr>
<tr>
<td>Median length of hospitalization (range), days</td>
<td>4 (3 – 9)</td>
<td>4 (2 – 15)</td>
</tr>
</tbody>
</table>
mostly overlapping confidence intervals (CI). Most events were asymptomatic distal DVTs. Symptomatic DVT was confirmed prior to mandatory venography in two patients (one each in the betrixaban 15 mg and enoxaparin groups). PE was diagnosed by V/Q lung scan or CT scan prior to mandatory venography in one patient in each betrixaban group. One additional VTE (PE, postoperative Day 22) was identified a few days after the mandatory venogram in the enoxaparin group (not included in the primary endpoint).

Safety outcomes
Bleeding events were monitored and adjudicated as a study outcome according to the definitions described previously. One major bleed at the surgical site (Bleeding Index ≥ 2.0) occurred during the study (enoxaparin group). Two clinically significant non-major bleeds were identified in both the betrixaban 40 mg and enoxaparin group (Table 2).

Adverse events
No patients died during the study and relatively few (4.7% overall) experienced serious adverse events (SAEs). In general, there were no notable differences in the overall AE profile between betrixaban and enoxaparin. Similarly, no consistent dose-response was observed with regard to adverse events for the 15 mg and 40 mg doses of betrixaban.

Other safety assessments
Laboratory safety data did not suggest any consistent adverse effect of treatment with betrixaban on the haematopoietic system, renal function, hepatic function or electrolyte balance. ALT values > 3 times the upper limit of normal at completion of therapy were more prevalent with enoxaparin compared with betrixaban.

Table 2: Incidence of composite and individual efficacy and safety outcomes during the treatment period.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Betrixaban</th>
<th>Enoxaparin</th>
</tr>
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<tbody>
<tr>
<td>Overall VTE – n/Ne (%)</td>
<td>14/70 (20.0)</td>
<td>10/65 (15.4)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(11.4, 31.3)</td>
<td>(7.6, 26.5)</td>
</tr>
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Asymptomatic events

| DVT – n | 12 | 9 | 3*a |
| Proximal – n | 2 | 1 | 0 |
| Distal only – n | 10 | 8 | 2 |

Symptomatic events

| VTE – n | 2 | 1 | 1 |
| DVT – n | 1 | 0 | 1 |
| Proximal – n | 0 | 0 | 1 |
| Distal only – n | 1 | 0 | 0 |
| PE - n | 1 | 1 | 0 |
| Bleeding event – n/N (%) | 0 | 2/84 (2.4) | 3/43 (7.0) |
| (95% CI) | (0.4, 2.2) | (0.3, 8.3) | (1.5, 19.1) |
| Major bleed – n | 0 | 0 | 1 (2.3) |
| Clinically significant non-major bleed – n | 0 | 2 (2.4) | 2 (4.6) |

CI, confidence interval; DVT, deep vein thrombosis; n, number of patients with event; N, number of treated patients; Ne, number of patients with evaluable venogram as determined by the central adjudication committee or adjudicated confirmed DVT and/or PE prior to scheduled venography; VTE, venous thromboembolic event. *Includes one patient for whom the type of DVT was not specified.

Figure 2: VTE rates and 95% confidence intervals for betrixaban and enoxaparin as determined in the EXPERT study with unilateral venography between Days 10 and 14 and for enoxaparin historical controls from studies using bilateral venography performed between Days 10 and 14 post-TKR. *Blood 2003; 102 (11): Abstract 41. **J Thromb Haemost 2007; 5: 2363-2375.
Elevated values generally returned to normal during follow-up and no patient had both an increase in ALT ≥3x ULN and an increase in total bilirubin ≥2x ULN. Heart rate increased in the post-surgical period in all treatment groups and remained 10 to 12 bpm above baseline at the time of mandatory venography. Other vital sign parameters did not show any clinically relevant changes. Assessment of on-therapy ECGs versus baseline showed no consistent effects on PR interval, QRS complex or QT interval corrected for changes in heart rate using either the Bazett or Fridericia formulae.

Pharmacokinetic/pharmacodynamic outcomes

Figure 3 depicts plasma betrixaban concentrations after the second dose (Day 2), on discharge and at the time of venography. As expected given the long half-life of betrixaban, mean drug concentrations increased after the first few doses and appeared to reach steady-state by discharge (median Day 4) for both betrixaban dose groups. Betrixaban exhibited a dose-dependent and concentration-dependent effect on inhibition of thrombin generation and anti-Xa levels (Fig. 4). The effect of betrixaban 15 mg on the inhibition of thrombin generation was similar to that observed with enoxaparin whereas the effect seen with betrixaban 40 mg was more pronounced. Conversely, the effect seen on anti-Xa activity was similar for betrixaban 40 mg and enoxaparin and less with betrixaban 15 mg. Treatment with betrixaban did not appreciably affect other coagulation parameters (i.e. aPTT, PT and INR).

Discussion

This study demonstrated that betrixaban has antithrombotic activity at the doses tested and that it was well tolerated in patients who have undergone unilateral TKR. In particular, there was no indication of any increase in bleeding events. The VTE rates obtained in the betrixaban groups were within the same range as those recently published in comparable trials (8, 9) using the same adjudication committee. While the point estimates appear to indicate a dose response, the confidence intervals for the VTE rates overlap considerably among the three groups and thus do not justify a firm conclusion in this regard. Nevertheless, the efficacy results seen in this study support a therapeutic plasma concentration range for betrixaban of 5–25 ng/ml, as predicted from preclinical and phase I studies (5). Steady-state plasma concentrations were at the lower limit of the estimated therapeutic range with the 15 mg dose of betrixaban, yet this dose appeared to show benefit. On the other hand, it is possible that greater efficacy may be achievable safely using higher doses and/or a loading dose. With regard to the latter, a doubling of the first dose is expected to result in near (80%) steady-state levels on Day 1 rather than Day 3 to 4.

The enoxaparin comparator group was included as a contemporaneous standard for safety and to facilitate the interpretation of pharmacodynamic markers rather than to provide a benchmark for determination of efficacy. The 2:2:1 randomization scheme limited enrollment in the enoxaparin group compared

| Table 3: Percentage of patients with liver enzymes >3x upper limit of normal. |
|--------------------------------|--------------|----------------|
|                                | Betrixaban   | Enoxaparin    |
| ALT (SGPT) (IU/l)              |              |                |
| Baseline                       | 0%           | 0%             |
| Discharge                      | 1.3%         | 2.7%           |
| Venogram                       | 1.3%         | 0%             |
| AST (SGOT) (IU/l)              |              |                |
| Baseline                       | 1.2%         | 0%             |
| Discharge                      | 0%           | 2.7%           |
| Venogram                       | 0%           | 0%             |

Figure 3: Mean (± SEM) plasma concentration over time for betrixaban. Patients discharged on Day 2 are also represented in the average value for that study day.
with betrixaban contributing to the lack of precision in the estimate for enoxaparin in the present study. We observed four events (10%) in the enoxaparin group with the 90% CI ranging from 2.8% to 23.7%. While the low point estimate is most likely a function of the small sample size for the enoxaparin group, another factor contributing to this low VTE rate may be the timing of the mandatory venogram. In this trial, patients received 10 to 14 days of prophylaxis prior to undergoing mandatory venography for identification of VTE. In earlier studies with enoxaparin yielding 25% VTE rates, venography typically occurred after 5–10 days of treatment (10–13). In more recent investigations of other FXa inhibitors using the same adjudication committee which used enoxaparin as a comparator and performed venography between Day 10 and 14 post-TKR, the observed VTE rates (approximately 16%) were similar to those seen in the present study (Fig. 4) (8, 9), while the rates obtained in studies using different adjudication committees were considerably higher (14). Another factor which may have contributed to the lower event rate was the choice of unilateral venography on the operated leg rather than bilateral venography. On the other hand, the large majority of DVTs occur in the operated extremity (15), hence the choice of unilateral venography in the current study in an attempt to minimize patient discomfort and procedural risks.

As expected, the majority of VTEs were distal DVTs identified from mandatory venography on Day 10 to 14 of the study. The 1.9% incidence of symptomatic events confirmed to be either DVT (2 patients) or PE (2 patients) prior to the planned mandatory venography is consistent with other reports of symptomatic VTE rates during prophylaxis (2, 16).

Bleeding events were few overall. One major bleed in the operated knee occurred in the enoxaparin group and none was noted for betrixaban. There was no evidence of an impact on mean values for aPTT, PT or INR. Other evaluations of safety supported the tolerability of betrixaban. No deaths occurred dur-

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**Figure 4: Pharmacodynamic assessments.**

A) Relative fluorescence units (± SEM) of thrombin generation, by visit and treatment.

B) Mean (± SEM) anti-FXa activity (U/ml), by visit and treatment. The detectable limit for anti-FXa activity was 0.05 U/ml; values below the detectable limit were set to 0.025. Patients discharged on Day 2 are also represented in the average value for that study day.
or after treatment with either betrixaban or enoxaparin. SAEs were reported as isolated occurrences in each treatment group. There was parity in the overall AE profiles between betrixaban and enoxaparin despite the open-label nature of the study which typically favors the more familiar control treatment. Betrixaban did not demonstrate any adverse effects on haematology parameters. Laboratory profiles were consistent with a peri-operative or post-operative study population. Based on the constancy of mean values for serum creatinine and blood urea nitrogen (BUN) throughout the study, there was no evidence for deterioration in renal function.

Thrombin generation assays have been used as key markers of anticoagulation (17, 18). Anticoagulant activity of betrixaban was demonstrated by inhibition of thrombin generation and anti-FXa activity, both of which increased in a dose- and concentration-dependent manner. In-vitro studies show that the predicted range of anti-FXa activity for betrixaban concentrations between 5–25 ng/mL ranges from 0.09 to 0.44 U/ml. Thus, the results from this study demonstrate the expected levels of anti-FXa activity for the betrixaban concentrations obtained. Similarly, inhibition of thrombin generation during the course of study was in the range predicted by in-vitro studies. On the other hand, inhibition of thrombin generation in enoxaparin-treated patients on the venogram day was somewhat lower than expected from results in vitro. Indeed, the addition of enoxaparin at 0.27 anti-Xa U/ml (corresponding to the mean level observed at steady-state in this study) to pooled human plasma produces ~50% inhibition of thrombin generation (7). We and others have shown reduced levels of thrombin generation inhibition by short chain heparins (7, 19). Based on available data, it is possible that low-molecular-weight heparins and FXa inhibitors may differ in their thrombin generation inhibition profile. Thus, the apparent discrepancy between measured anti-FXa units and inhibition of thrombin generation in enoxaparin-treated patients may be due to disparity in assay sensitivity between the anticoagulants in the current study.

In summary, betrixaban demonstrated antithrombotic activity and appeared well tolerated at the doses studied. The dose with the most favorable balance between risk and benefit should be determined in a larger trial. Betrixaban has the potential to be a well tolerated oral anticoagulant that does not require dose titration and whose pharmacological properties are ideally suited for both acute and chronic indications.

Acknowledgements
We thank the investigators and study coordinators who participated in this study (see Appendix) and the members of the Independent Central Adjudication Committee at McMaster University, Hamilton, Ontario, Canada. In addition, we wish to acknowledge the many important contributions made by Kevin Romanko (Portola Pharmaceuticals Inc.), Cathy Michalsky (Prosoft Software, Inc.), Kenneth Borow and Virginia Frame (Encorum Group, Inc.) to the trial’s clinical operations, data analysis, and oversight of patient safety.

Conflict of interest
The trial was sponsored by Portola Pharmaceuticals Inc. K. Bauer, Portola consultant; B.L. Davidson, Portola consultant; W.D. Fisher, Portola consultant; M. Gent, Portola consultant; D.D. Greter, Portola employee; M. Hsu, Portola consultant; U. Sinha, Portola employee; A. G. G. Turpie, Portola consultant.

Appendix
The members of the EXPERT Study Group were as follows: Steering Committee – A. G. G. Turpie (Chair), K. Bauer, W.D. Fisher, B.L. Davidson, M. Gent, D.D. Greter, M. Hsu, K. Borow (non-voting member), V.B. Frame (non-voting member); Drug Safety Monitoring Board – M. Gent (Chair), K. Bauer, A. G. G. Turpie, B.L. Davidson, D.D. Greter, C. Michalsky (unblinded statistician); Independent Central Adjudication Committee (McMaster University, Hamilton, ON, Canada) – M. Levine (Chair), J. Hirsh, C. Kearon, J. Weitz; Investigators – J. Jove (Decatur, GA, USA), D.L. Fox (San Antonio, TX, USA), A. Profitt (Charlestown, PE, Canada), W. Bowen (Little Rock, AR, USA), V. Vasicek (Lexington, KY, USA), S. Gill (Lubbock, TX, USA), Sherwin Siff (Houston, TX, USA), E. Desouki (Ajax, ON, Canada), M. Hsu (Dallas, TX, USA), F. Abuzgaya (Ajax, ON, Canada), D. Puskas (Thunder Bay, ON, Canada), R.L. Kruse (Denver, CO, USA), J.E. Muntz (Houston, TX, USA), M. Swank (Cincinnati, OH, USA), W.D. Fisher (Montreal, QC, Canada), J. Turnbull (Chatham, ON, Canada), M. Mant (Edmonton, AB, USA), H. Blum (Houston, TX, USA).

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