Comparison of the Oral Direct Thrombin Inhibitor Ximelagatran With Enoxaparin as Prophylaxis Against Venous Thromboembolism After Total Knee Replacement

A Phase 2 Dose-Finding Study

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Background: Up to one third of patients who undergo total knee replacement develop deep vein thrombosis after surgery despite receiving low-molecular-weight heparin prophylaxis. Ximelagatran is a novel direct inhibitor of free and clot-bound thrombin.

Methods: We performed a randomized, parallel, dose-finding study of 600 adults undergoing elective total knee replacement at 68 North American hospitals to determine the optimum dose of ximelagatran to use as prophylaxis against venous thromboembolism after total knee replacement. Patients received either ximelagatran twice daily by mouth in blinded fixed doses of 8, 12, 18, or 24 mg or open-label enoxaparin sodium, 30 mg, subcutaneously twice daily, starting 12 to 24 hours after surgery and continuing for 6 to 12 days. We measured the 6- to 12-day cumulative incidence of symptomatic or venographic deep vein thrombosis, symptomatic pulmonary embolism, and bleeding.

Results: A total of 594 patients received at least 1 dose of the study drug; 443 patients were evaluable for efficacy. Rates of overall venous thromboembolism (and proximal deep vein thrombosis or pulmonary embolism) for the 8-, 12-, 18-, and 24-mg doses of ximelagatran were 27% (6.6%), 19.8% (2.0%), 28.7% (5.8%), and 15.8% (3.2%), respectively. Rates of overall venous thromboembolism (22.7%) and proximal deep vein thrombosis or pulmonary embolism (3.1%) for enoxaparin did not differ significantly compared with 24-mg ximelagatran (overall difference, −6.9%; 95% confidence interval, −18.0% to 4.2%; P = .3). There was no major bleeding with administration of 24 mg of ximelagatran twice daily.

Conclusion: Fixed-dose, unmonitored ximelagatran, 24 mg twice daily, given after surgery appears to be safe and effective oral prophylaxis against venous thromboembolism after total knee replacement.

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Venous thromboembolism is a common complication after total knee replacement surgery. In the absence of prophylaxis, approximately 60% of patients have venographic evidence of deep vein thrombosis at hospital discharge. Although prophylaxis with low-molecular-weight heparin is effective and safe, approximately 30% of patients still develop deep vein thrombosis. Most of these thrombi are small, asymptomatic, and confined to the deep veins of the calf. However, the prevalence of proximal (eg, popliteal or more proximal) deep vein thrombosis, which is most frequently associated with symptomatic venous thromboembolism and fatal pulmonary embolism, is still approximately 6%, possibly because heparins are poor inhibitors of clot-bound thrombin. Moreover, low-molecular-weight heparin currently must be given by subcutaneous injection, which is inconvenient for some patients. Although oral warfarin sodium prophylaxis is convenient, frequent laboratory monitoring and dose adjustment are required, and warfarin is not as effective as low-molecular-weight heparin. Clearly, more effective and convenient prophylaxis is needed. Recently, prophylaxis with a direct thrombin inhibitor (recombinant desulfatohirudin or desirudin), which potently inhibits clot-bound thrombin, was shown to be significantly more effective than and as safe as low-molecular-weight heparin after total hip replacement. However, the first dose was given immediately after spinal anesthesia and before surgery, which might increase the risk for operative bleeding and formation of spinal hematomas.
PATIENTS AND METHODS

STUDY POPULATION

Patients were eligible for enrollment if they provided written informed consent, were 18 years or older and not of childbearing potential if female (eg, postmenopausal or surgically sterile), weighed 40 to 125 kg, and were scheduled for elective primary unilateral total knee replacement surgery. Patients were excluded for the following reasons: previous objectively confirmed deep vein thrombosis or pulmonary embolism; anticipated use of an epidural or spinal catheter for more than 12 hours after surgery or within 2 hours of administration of the first dose of study medication; traumatic epidural or spinal puncture; planned external pneumatic compression prophylaxis (except passive antiembolism stockings); immobilization because of trauma or other illness within 12 weeks of surgery; or long-term anticoagulant or antiplatelet therapy. Use of aspirin and nonsteroidal anti-inflammatory drugs was discontinued 24 hours before surgery; use of all other anticoagulants was stopped 7 days before surgery. Patients were also excluded if they had an allergy to contrast media or iodine, a clinical bleeding disorder, renal impairment (serum creatinine level >1.8 mg/dL [>160 µmol/L]) or a renal transplant, previous intracranial or retinal bleeding, previous or current drug or alcohol abuse, an ischemic stroke within the previous 3 months, gastrointestinal tract bleeding or ulcer verified by endoscopy within the previous year, major surgery within the previous 3 months, a malignant neoplasm being actively treated, uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg), liver disease or impairment (aspartate aminotransferase or alanine aminotransferase levels >2-fold higher than normal), anemia (hemoglobin level <10.0 g/dL), or thrombocytopenia (platelet count <100 × 10^3/µL). Patients who had previously participated in this study were excluded, as were patients who had received another investigational agent within the previous 30 days. Similarly, mentally or legally incapacitated patients and those with a condition that might interfere with study participation or for whom study participation might cause significant risk were excluded.

In addition, desirudin has not been studied as prophylaxis for total knee replacement; it also must be given as a subcutaneous injection, which potentially limits its convenience.

Melagatran is a small molecule that provides potent, competitive, and direct inhibition of free and clot-bound thrombin, but it must be administered parenterally. Ximelagatran (formerly known as H 376/95; Exanta) is an oral prodrug that is converted to melagatran, the active metabolite. In a recent international clinical trial of preoperative administration of subcutaneous melagatran followed by oral ximelagatran as prophylaxis against venous thromboembolism after total hip or knee replacement, the highest melagatran-ximelagatran dose was significantly more effective than and as safe as low-molecular-weight heparin (dalteparin sodium) prophylaxis started before surgery. In North America, however, prophylaxis usually is started after surgery because of concerns about operative bleeding. Consequently, we performed a phase 2 dose-finding study to assess the efficacy and safety of 4 different postoperative, fixed-dose, oral ximelagatran regimens compared with postoperative enoxaparin sodium as prophylaxis against venous thromboembolism after total knee replacement.

STUDY DESIGN

Using a multicenter, randomized, parallel study design, patients were randomly allocated to 1 of 5 treatment groups: ximelagatran at a fixed dose of 8, 12, 18, or 24 mg given twice daily by mouth or enoxaparin sodium (Lovenox, Rhone-Poulenc Rorer Pharmaceuticals Inc, Collegeville, Pa), 30 mg, given twice daily by subcutaneous injection. For all 5 treatment groups, the intensity of anticoagulation was not monitored and the drug dose was not adjusted. Randomization was performed using a computer-generated randomization list provided by AstraZeneca LP, Wayne, Pa; the randomization was stratified in blocks of 5 patients. Ximelagatran administration was blinded and enoxaparin administration was open label. Study drug was first administered after adequate hemostasis and within 12 to 24 hours after surgery and was continued for 6 to 12 days. Patients who were discharged from the hospital within 6 days after surgery received their remaining study drug as outpatients. Drug compliance was assessed by counting the number of tablets or syringes (1) used during the inpatient period, (2) dispensed at hospital discharge, and (3) returned unused by the patient at the end of the study. All patients were followed up clinically for at least 4 weeks after surgery. The study was conducted at 68 North American community, university, or university-affiliated hospitals. The protocol was approved by the institutional review board of each investigational center.

EVALUATION OF EFFICACY AND SAFETY

Patients were examined daily for symptoms and signs of venous thromboembolism and bleeding while in the hospital. After a minimum of 6 and a maximum of 12 days of treatment, and within 12 hours after the last treatment dose, patients underwent unilateral ascending venography of the operative leg. Each venogram was interpreted by an independent central adjudication committee consisting of experts who were blinded to treatment allocation and who categorized the venographic findings as diagnostic for deep vein thrombosis, normal, or inadequate. A venogram that lacked adequate views of the distal external iliac, common and superficial femoral, popliteal, and at least paired peroneal and posterior tibial veins was categorized as inadequate; visualization of the profunda femoris or anterior tibial veins was not a requirement. Deep vein thrombosis was diagnosed

RESULTS

PATIENT POPULATION

A total of 600 patients were randomized into the study; the first patient was randomized in October 1998, and the last patient completed the study in January 2000. Pa-
when a constant intraluminal filling defect was seen on at least 2 images; thrombi were further subcategorized as affecting the proximal leg veins (popliteal or more proximal deep vein) or isolated to the calf veins and as thrombi longer than 10 cm. Patients with clinically suspected acute pulmonary embolism underwent a ventilation/perfusion lung scan; a high-speed, high-resolution (eg, spiral or electron beam) computed tomographic scan of the chest with appropriate contrast injection; or a pulmonary angiogram. For patients undergoing a lung scan, pulmonary embolism was diagnosed when the scan was interpreted as high probability based on a segmental or larger perfusion defect(s) with normal ventilation.12 For patients undergoing computed tomography or pulmonary angiography, pulmonary embolism was diagnosed based on a constant intraluminal filling defect within 1 or more pulmonary arteries or abrupt cutoff of a vessel 2.3 mm or larger in diameter. Bleeding was categorized as major if it was clinically overt and involved a critical site (eg, intracranial, retroperitoneal, intraocular, spinal, or pericardial bleeding), caused a bleeding index of 2.0 or greater (defined as the change in prebleed and postbleed hemoglobin levels plus the number of red blood cell units transfused), or prompted medical or surgical intervention at the operative site. Overt bleeding that did not meet these criteria was categorized as minor. Bleeding episodes were also categorized as clinically significant based on the judgment of the local investigator. In addition to the venograms, all clinically suspected episodes of deep vein thrombosis, pulmonary embolism, and major bleeding were adjudicated by the central adjudication committee.

STATISTICAL METHODS

Baseline demographic and surgical characteristics were compared descriptively. The primary study objective was to assess the dose range of ximelagatran. The primary efficacy measure was the cumulative incidence of verified venous thromboembolism. The primary analysis was intention to treat and included all patients with an adequate venogram or symptomatic, objectively documented venous thromboembolism. We estimated that the incidence of venous thromboembolism would differ by 18% between the low- and high-dose ximelagatran groups. Assuming a linear dose response, we estimated differences in proportions (and corresponding 95% CIs) between treatments and tested for treatment difference using the Fisher exact test. A central data coordinating center (AstraZeneca) performed all statistical analyses. Data interpretation and manuscript preparation were performed by the writing committee. However, AstraZeneca retained the right to review and comment on the manuscript before publication.

INTERIM ANALYSIS

An independent safety committee monitored the conduct of the study. The safety committee received all fatal or life-threatening event reports within one business day and all other reports within 5 calendar days. In addition, the safety committee reviewed regular reports of bleeding and venous thromboembolism event rates by treatment group and made recommendations regarding continuing or stopping the study. At the recommendation of the safety and executive committees, the protocol was amended on September 28, 1999, to discontinue enrollment in the 8-mg ximelagatran arm. This recommendation was based on newly available data indicating that 1 mg of melagatran started before surgery and given twice daily by subcutaneous injection followed by 8 mg of oral ximelagatran twice daily was significantly inferior to low-molecular-weight heparin (dalteparin sodium) prophylaxis in a parallel study performed in Europe.9 To maintain blinding, investigators completed the existing blocks of drug supplies. Thereafter, new drug supplies for ximelagatran with only 3 dose levels (12, 18, and 24 mg) were provided. The original sample size was maintained across the remaining 4 treatment groups so that the numbers of patients in the remaining groups increased by approximately 10%.

CUMULATIVE INCIDENCE OF VENOUS THROMBOEMBOLISM

As shown in Figure 2, the distribution of total study medication doses was similar across the 5 treatment arms. Among the 4 ximelagatran groups, the 24-mg dose had the lowest overall incidence of venous thromboembolism (Table 3). Although the highest dose of ximelagatran (24 mg) provided a 42% relative risk reduction in the overall venous thromboembolism rate compared

tients in the 5 treatment arms were similar with regard to baseline patient and surgical characteristics (Table 1). Fifty-five patients prematurely discontinued study treatment; the 5 treatment arms did not differ significantly with regard to the reasons for premature discontinuation (Table 2). Combining patients who did not undergo venography with patients who had an adequate venogram, 157 patients had a nonevaluable study efficacy measure and were excluded. The intention-to-treat analysis included the remaining 440 patients plus 3 additional patients who had symptomatic, objectively documented pulmonary embolism (Figure 1). No emergency unblinding occurred during the study. Twenty-eight patients had 1 or more protocol violations (Table 2); the 5 treatment arms did not differ significantly with regard to the percentage of patients with protocol violations. After excluding these 28 patients, 415 patients remained and were included in the per-protocol analysis. Finally, 594 patients received at least 1 dose of study medication and were included in the safety analysis.
with the lowest dose of ximelagatran (8 mg), the absolute difference was not significantly different (absolute reduction, 11.2%; 95% CI, −2.0% to 24.4%; \( P = .11 \)), possibly owing to the small sample size. Similarly, the highest dose of ximelagatran provided a 52% relative risk reduction in the rate of proximal deep vein thrombosis or pulmonary embolism compared with the lowest dose of ximelagatran, but the absolute difference also was not significantly different (absolute difference, 3.4%; 95% CI, −3.7% to 10.5%; \( P = .4 \)). Thus, the tests for a linear dose response across the 4 ximelagatran groups for overall venous thromboembolism and proximal deep vein thrombosis or pulmonary embolism were not statistically significant (\( P = .3 \) and .7, respectively).

The rates of overall venous thromboembolism and of proximal deep vein thrombosis or pulmonary embolism among patients receiving enoxaparin were 22.7% and 3.1%, respectively (Table 3). Compared with enoxapa-

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### Table 1. Baseline Characteristics of 600 Patients Undergoing Total Knee Replacement by Treatment Assignment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ximelagatran Group</th>
<th>Enoxaparin Sodium Group, 30 mg (n = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8 mg (n = 65)</td>
<td>12 mg (n = 134)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>65 (10)</td>
<td>67 (11)</td>
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<tr>
<td>Health status, %</td>
<td>60</td>
<td>58</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>32.6 (5.7)</td>
<td>30.9 (6.0)</td>
</tr>
<tr>
<td>Duration of surgery, mean (SD), min</td>
<td>100 (37)</td>
<td>96 (39)</td>
</tr>
<tr>
<td>Surgical blood loss, mean (SD), mL</td>
<td>130 (132)</td>
<td>124 (177)</td>
</tr>
</tbody>
</table>

### Table 2. Disposition of 600 Randomized Patients Undergoing Total Knee Replacement by Treatment Assignment

<table>
<thead>
<tr>
<th>Characteristic, No. %</th>
<th>Ximelagatran Group</th>
<th>Enoxaparin Sodium Group, 30 mg (n = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued study</td>
<td>6 (7)</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>1 (1)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Stopped by sponsor or investigator</td>
<td>3 (4)</td>
<td>4 (3)</td>
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<tr>
<td>Withdrawal consent</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Ineligible</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Completed study</td>
<td>79 (93)</td>
<td>124 (93)</td>
</tr>
<tr>
<td>Venography not done or inadequate findings</td>
<td>22 (26)</td>
<td>33 (25)</td>
</tr>
<tr>
<td>Intention-to-treat analysis</td>
<td>63 (74)</td>
<td>101 (75)</td>
</tr>
<tr>
<td>Protocol violation*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Study medication noncompliance</td>
<td>3 (4)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Concurrent antiplatelet or anticoagulant therapy</td>
<td>1 (1)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Venography not performed within 6-12 d of surgery</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>First dose not given within 24.5 h of surgery</td>
<td>1 (1)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Per-protocol analysis</td>
<td>60 (71)</td>
<td>92 (69)</td>
</tr>
</tbody>
</table>

*Patients could have more than one protocol violation.

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**Table 1. Baseline Characteristics of 600 Patients Undergoing Total Knee Replacement by Treatment Assignment**

**Table 2. Disposition of 600 Randomized Patients Undergoing Total Knee Replacement by Treatment Assignment**
Three cases of nonfatal pulmonary embolism occurred during treatment—2 in the 18-mg ximelagatran group and 1 in the 24-mg ximelagatran group. Two additional patients developed pulmonary embolism during follow-up—both were in the 24-mg ximelagatran group. One case occurred 2½ months after treatment ended, and the other occurred 7 days after treatment ended; the latter patient subsequently died. The rate of pulmonary embolism among the treatment groups was too low for meaningful comparison.

**CUMULATIVE INCIDENCE OF BLEEDING**

The total number of major bleeding events was low in the 4 ximelagatran groups. There was no significant trend in major bleeding (P = .4), major or minor bleeding (P = .9), or clinically significant bleeding events (P = .3) by ximelagatran group (Table 4). The number of wound hematomas also was low, and the incidence of wound hematomas, the volume of postoperative blood loss or wound drainage, and the time to onset of major or minor bleeding did not differ significantly among the 4 groups. Although the mean number of transfused red blood cell units was low (<1) for all ximelagatran groups, there was a possible trend toward a higher mean number of transfused units with increasing ximelagatran dose (P = .09).

Compared with the 8-mg ximelagatran group, the mean number of transfused units was marginally but significantly greater in the 24-mg group (P = .048). However, the bleeding index did not differ significantly among the 4 groups.

The rates of major bleeding, major plus minor bleeding, and clinically significant bleeding events in the enoxaparin group were 0.8%, 9.6%, and 1.6%, respectively; these rates did not differ significantly compared with the 24-mg ximelagatran group (Table 4). Moreover, the rate of wound hematomas, mean volume of postoperative blood loss and wound drainage, mean number of transfused red blood cell units, and bleeding index also were similar for the 2 groups. The bleeding indices, however, were lower in the 18-mg (3.0) and 24-mg (3.0) ximelagatran groups compared with the enoxaparin group (3.4), and these differences approached statistical significance (P = .07 and .051, respectively). Compared with the 8-mg ximelagatran group, the mean number of transfused units also was marginally but significantly greater in the enoxaparin group (P = .047).
cally important. The 24-mg dose of ximelagatran also appeared to be safe. There were no major bleeding events in the 24-mg dose group. The major or minor bleeding, significant bleeding event, and wound hematoma rates; the total volume of postoperative blood loss and wound drainage; and the bleeding indices did not differ significantly between the 8- and 24-mg dose groups. However, the 24-mg group had a slightly but significantly higher transfusion requirement than the 8-mg group.

Administering 24 mg of ximelagatran twice daily also appears to be as effective, or possibly even more effective, than the current standard of prophylaxis in North America—low-molecular-weight heparin started after surgery. Compared with enoxaparin, the 24-mg dose of ximelagatran provided a 30% relative risk reduction in overall venous thromboembolism incidence in our study. Our findings are consistent with the results of the METHRO II study,9 in which 3 mg of melagatran given by subcutaneous injection before surgery followed by 24 mg of oral ximelagatran twice daily after surgery provided a 35% relative risk reduction in overall venous thromboembolism compared with administration of dalteparin sodium. In addition, our findings are also consistent with those of other trials7,14-16 investigating direct thrombin inhibitors as venous thromboembolism prophylaxis after total joint replacement. For example, compared with enoxaparin, recombinant desulfato-hirudin (desirudin) provided a 28% relative risk reduction in overall venous thromboembolism in patients undergoing total hip replacement (absolute difference, 7.1%; P = .001) and a 40% reduction in the relative risk of proximal deep vein thrombosis (absolute difference, 3.0%; P = .01).16 Finally, our data indicate that the safety of the 24-mg dose of ximelagatran and enoxaparin (both started after surgery) appears to be comparable, with similar rates of bleeding complications and blood loss, and similar transfusion requirements.

It is unlikely that the results of this study are due to bias. The treatment groups had similar demographic and surgical characteristics. The efficacy outcomes were determined by objective testing and were interpreted centrally by experts who were blinded to treatment assignment. Unlike in total hip replacement, deep vein thrombosis seldom occurs in the nonoperative leg after total knee replacement.1 Therefore, we performed unilateral venography of only the operative leg to avoid the additional contrast dye volume from bilateral venography. The safety outcomes (eg, major and minor bleeding) were also based on objective measures of hemoglobin change and transfusion requirement. Moreover, the 4 ximelagatran groups were blinded, and all major bleeding events were adjudicated centrally. The distribution of total study medication doses was similar among treatment groups, and the results of the per-protocol analysis were entirely consistent with those of the intention-to-treat analysis.

In summary, oral administration of ximelagatran after surgery and continued for at least 6 to 12 days

| Table 3. Cumulative Incidence of Venous Thromboembolism by Treatment Group |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Characteristic   | Ximelagatran Group | Enoxaparin Sodium Group, 30 mg |
| Intention-to-treat analysis | n = 63 (n = 84) | n = 125 (n = 134) | n = 87 (n = 124) | n = 95 (n = 127) |
| Overall venous thromboembolism, % | 27 | 20 | 29 | 16 |
| Proximal deep vein thrombosis or pulmonary embolism, % | 7 | 2 | 6 | 3 |
| Pulmonary embolism, No. | 0 | 0 | 2 | 1 |
| Deep vein thrombosis >10 cm long, % | 14 | 8 | 9 | 5 |
| Per-protocol analysis | n = 60 (n = 80) | n = 92 (n = 129) | n = 82 (n = 114) | n = 91 (n = 120) |
| Overall venous thromboembolism, % | 28 | 20 | 29 | 15 |

| Table 4. Cumulative Incidence of Bleeding by Treatment Group |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Characteristic   | Ximelagatran Group | Enoxaparin Sodium Group, 30 mg |
| Major bleeding, % | 0 | 0 | 2 | 0 |
| Total bleeding, % | 10 | 16 | 2 | 10 |
| Significant bleeding events, % | 0 | 0 | 2 | 2 |
| Postoperative blood loss, mean (SD), mL | 165 (256) | 189 (310) | 164 (260) | 146 (274) |
| Wound hematoma, % | 4 | 2 | 4 | 2 |
| Wound drainage, mean (SD), mL | 258 (341) | 253 (331) | 250 (362) | 255 (359) |
| Transfused red blood cells, Mean, units | 0.4 | 0.6 | 0.6 | 0.7 |
| Any transfusion, % | 22 | 25 | 35 | 35 |
| Bleeding index score, mean (SD) | 3.2 (1.3) | 3.2 (1.8) | 3.0 (1.3) | 3.0 (1.5) |

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appears to be safe and effective as prophylaxis against ve-
rous thromboembolism after total knee replacement sur-
ry. This was accomplished without laboratory moni-
toring of the intensity of ximelagatran anticoagulation or 
adjustment of the ximelagatran dose. Of the 4 post-
operative oral ximelagatran dose regimens tested, we be-
lieve that the most effective is 24 mg twice daily; this regi-
men appears to provide at least comparable efficacy and 
safety to postoperative low-molecular-weight heparin pro-
phylaxis. This hypothesis requires further testing in a 
phase 3 clinical trial.

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