

# ORAL DIRECT THROMBIN INHIBITOR XIMELAGATRAN COMPARED WITH WARFARIN FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM AFTER TOTAL KNEE ARTHROPLASTY

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**Background:** Warfarin, which requires coagulation monitoring, is associated with relatively high rates of thromboembolism despite providing adequate prophylaxis. This study compared an oral direct thrombin inhibitor, ximelagatran, with warfarin in order to evaluate the safety and efficacy of the medication for the prevention of venous thromboembolism in patients undergoing total knee arthroplasty.

**Methods:** Following surgery, patients were randomly assigned to fixed-dose oral ximelagatran (36 mg twice daily) or warfarin (target international normalized ratio, 2.5), both administered for seven to twelve days in a double-blind, double-dummy design. Warfarin was initiated on the evening of the day of surgery, and ximelagatran, on the morning after surgery. The primary efficacy end point was the incidence of asymptomatic deep-vein thrombosis determined by bilateral venography, objectively confirmed symptomatic deep-vein thrombosis or pulmonary embolism, and death from all causes during treatment.

**Results:** Adequate venograms or confirmed symptomatic events (efficacy population) were obtained for 1949 patients. Venous thromboembolism and death from all causes occurred in 22.5% (221) of 982 ximelagatran-treated patients and in 31.9% (308) of 967 warfarin-treated patients ( $p < 0.001$ ). Proximal deep-vein thrombosis and pulmonary embolism were observed in 3.1% (thirty) and 0.2%, respectively, of the patients in the ximelagatran group and in 3.4% (thirty-three) and 0.4%, respectively, of the patients in the warfarin group. The six deaths from all causes included 0.3% (four) of the ximelagatran-treated patients and 0.2% (two) of the warfarin-treated patients. Major bleeding was noted in 1% (twelve) of the ximelagatran-treated patients and in 0.4% (five) of the warfarin-treated patients ( $p = 0.09$ ).

**Conclusions:** Oral ximelagatran (36 mg twice daily), administered without coagulation monitoring or dose adjustment and started the day after total knee arthroplasty, demonstrates superior efficacy compared with warfarin prophylaxis, with no wound complications and no significant difference with respect to bleeding events, although the rate of major bleeding events was greater with ximelagatran than with warfarin.

**Level of Evidence:** Therapeutic Level I. See Instructions to Authors for a complete description of levels of evidence.

In studies involving 199 patients who underwent total knee arthroplasty without thromboprophylaxis, deep-vein thrombosis developed in 67% and the thrombosis was proximal in 15%.<sup>1</sup> Serious sequelae of deep-vein throm-

bosis include pulmonary embolism, which was reported to occur in 7% of 517 patients<sup>2,3</sup>; recurrent venous thromboembolism, in 17% of 1719 patients<sup>4</sup>; and post-thrombotic syndrome, in 27% of 110 patients<sup>5,6</sup>. Prophylaxis with warfarin or low-molecular-weight heparin reduces the prevalence of venous thromboembolism, but warfarin is associated with relatively high rates of total deep-vein thrombosis and proximal deep-vein thrombosis, which have ranged from 38% to 55% and from 7% to 12%, respectively, in a combined cohort of 996 patients<sup>7-12</sup>. Furthermore, warfarin has a slow on-

\*The members of the EXULT B (Exanta Used to Lessen Thrombosis B) Study Group are listed in the electronic Appendix.



A commentary is available with the electronic versions of this article, on our web site ([www.jbjs.org](http://www.jbjs.org)) and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM).

set of action, has numerous food and drug interactions, and requires monitoring of coagulation and dose adjustment. Alternatively, low-molecular-weight heparin is associated with more bleeding events than is warfarin<sup>1</sup> and is administered parenterally, which can be difficult to manage after hospital discharge.

Ximelagatran, an orally administered direct thrombin inhibitor, is rapidly absorbed and converted into its active form, melagatran<sup>13</sup>, which inhibits both free and clot-bound thrombin<sup>14</sup>. Ximelagatran has predictable pharmacokinetics, no clinically known relevant interactions with food, and a low potential for drug interactions<sup>13,15</sup>, and it can be used without coagulation monitoring or dose adjustment. Ximelagatran has shown promise for the prevention of venous thromboembolism after total hip or total knee arthroplasty in clinical trials<sup>16,17</sup>. A dose-optimization study<sup>18</sup> was conducted to determine the superiority and safety of ximelagatran, at doses of 24 mg or 36 mg twice daily, compared with warfarin. That study showed a significant reduction in the prevalence of deep-vein thrombosis, pulmonary embolism, and/or death with no increase in major bleeding with a dose of 36 mg of ximelagatran twice daily compared with adjusted-dose warfarin ( $p = 0.003$ ). The present study was conducted to verify those results with use of 36 mg of ximelagatran.

## Materials and Methods

### Study Design

This prospective, randomized, double-blind, double-dummy trial was conducted at 115 centers in the United States, Canada, Israel, Mexico, and Brazil. The institutional review board at each center approved the protocol, which was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki. Patients were screened preoperatively and were rescreened postoperatively before randomization to either ximelagatran or warfarin. Randomization was performed through a computer-generated list by means of an interactive voice-response system.

### Patients

Patients undergoing primary total knee arthroplasty, either women without childbearing potential or men, who were at least eighteen years old, weighed between 40 and 136 kg, and who had provided written informed consent were enrolled in the study. See the Appendix for other inclusion and exclusion criteria. If the use of an epidural or spinal catheter extended into the treatment period, the catheter was to be removed during trough levels at least six hours after the previous dose and at least one hour before the next dose of ximelagatran. Treatment with thrombolytic, anticoagulant, or antiplatelet agents was not allowed within seven days before surgery or during the period of administration of the study drug.

### Treatment Regimens

According to the double-dummy design, patients randomized to the ximelagatran group also received a warfarin placebo and those randomized to the warfarin group also received a

ximelagatran placebo. The first dose of warfarin (Coumadin; Bristol-Myers Squibb, Princeton, New Jersey) or warfarin placebo was administered on the evening of the day of surgery, and the warfarin was titrated to a target international normalized ratio of 2.5 (range, 1.8 to 3.0). Ximelagatran in 36-mg tablets (Exanta; AstraZeneca, Mölndal, Sweden) or ximelagatran placebo was administered twice daily commencing as early as possible on the morning after surgery (at least twelve hours after surgery) when adequate hemostasis had been achieved. Treatment was continued until venography was performed (between days 7 and 12).

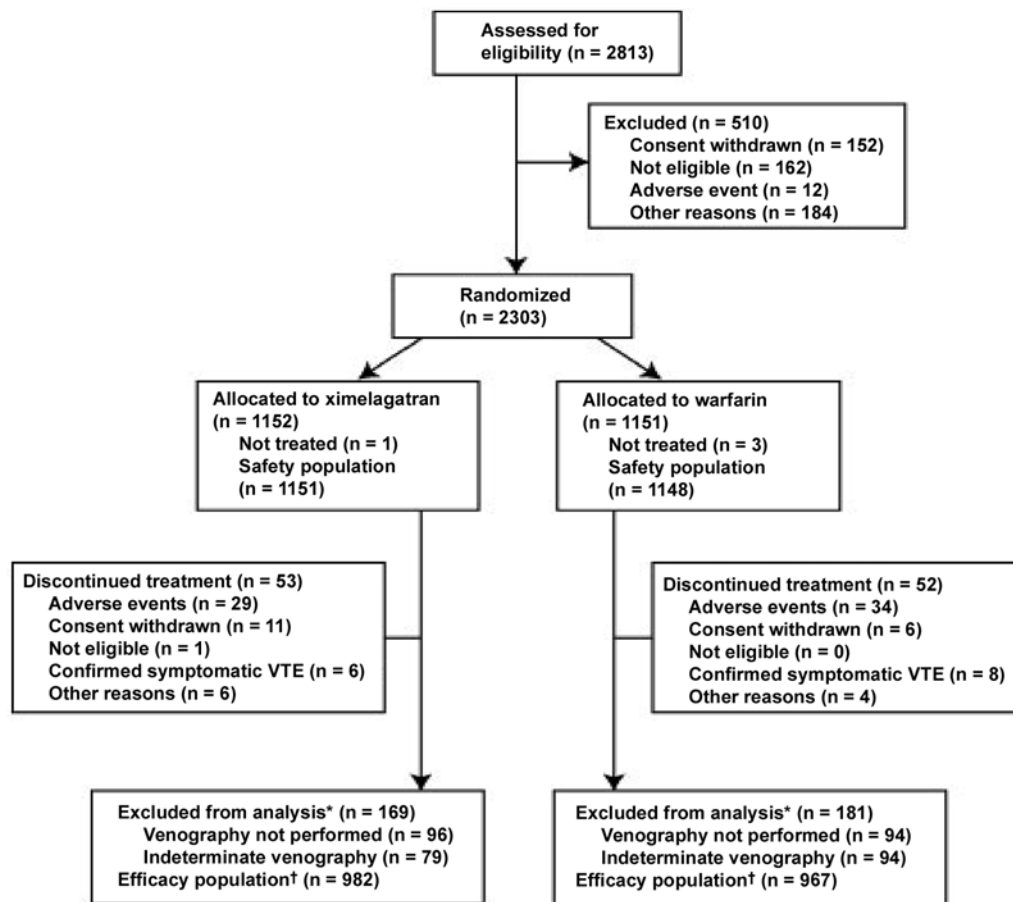
### Efficacy Assessments

The composite primary efficacy end point was the incidence of total venous thromboembolism (deep-vein thrombosis and pulmonary embolism) and mortality from all causes during treatment, as determined by an Independent Central Adjudication Committee. The composite secondary efficacy end point was the incidence of proximal deep-vein thrombosis, pulmonary embolism, and mortality from all causes during treatment. Deep-vein thrombosis was evaluated with bilateral ascending venography<sup>19,20</sup> performed seven to twelve days after the initiation of study treatment. In addition to central adjudication, venograms were assessed locally without knowledge of the assigned study treatment. See the Appendix for the criterion for deep-vein thrombosis and pulmonary embolism. Deaths were adjudicated as "cannot exclude pulmonary embolism," "fatal bleeding event," or "death not associated with pulmonary embolism or bleeding." All cases of symptomatic deep-vein thrombosis, pulmonary embolism, and death by any cause were objectively confirmed at the site and then were adjudicated centrally. For all efficacy assessments, the treatment period included up to two days after venography was performed or up to day 12 if venography was not performed. The follow-up period included the time from the end of treatment through the four to six weeks of follow-up after surgery.

### Safety Assessments

The principal variables used to assess safety were major bleeding events and major as well as minor bleeding events occurring up to forty-eight hours after the administration of the last dose of study medication and from the end of treatment through the four to six weeks after surgery. Any adverse event that was reported as a bleeding event was reviewed by the Independent Central Adjudication Committee and was categorized as "major," "minor," or "criteria for bleeding event not satisfied." See the Appendix for the specific bleeding criteria.

The investigators also subjectively assessed the wound appearance and the characteristics of the surgical wound (swelling, drainage, erythema, and bleeding) according to the categories "as expected," "better than expected," or "worse than expected." Follow-up clinical examinations for thromboembolic events and other adverse events were conducted four to six weeks postoperatively. Laboratory parameters were



\*No venogram adequate for analysis and no confirmed symptomatic venous thromboembolism (VTE) or death.

†Six patients in the ximelagatran group and seven in the warfarin group did not have a venogram that was adequate for evaluation but had confirmed symptomatic venous thromboembolism, died, or both.

Fig. 1

Disposition of the patients.

assessed at the time of screening on the last day of administration of the study drug and at the four to six-week visit.

### Statistical Methods

The primary analysis of this study was designed to confirm the superior efficacy of ximelagatran at a dose of 36 mg administered orally twice daily, compared with warfarin. The dose of ximelagatran that was selected and the sample size estimate were based on the results of a recent study of 1851 patients who underwent total knee arthroplasty<sup>18</sup>. In that study, the incidence of venous thromboembolism was 28% with warfarin and 20% with a 36-mg dose of ximelagatran. To detect a 25% relative risk reduction in venous thromboembolism in this study, it was estimated that approximately 860 patients with adequate venographic evaluation per treatment group would be necessary to provide 90% power to observe a difference between the two treatment groups at a 5% level of significance (two-sided p value of <0.05).

Differences between the treatment groups for categori-

cal variables including efficacy, bleeding, and wound parameters were analyzed with use of the Cochran-Mantel-Haenszel chi-square test, stratified by the type of surgery performed. Quantitative variables including blood loss and transfusion requirements were assessed with use of analysis of variance.

### Results

#### Patient Disposition, Study Populations, and Demographics

Of the 2813 patients assessed for eligibility between June 2002 and April 2003, 2303 were randomly assigned to the study treatment (Fig. 1). Of the 510 patients who were not randomized, 162 were not eligible, 152 withdrew consent, twelve had an adverse event, and 184 were excluded for other reasons. The safety population included 2299 patients who received at least one dose of study drug or placebo; the other four randomized patients did not receive study medication. The efficacy population included 1949 patients who underwent primary total knee arthroplasty, had taken at least

**TABLE I Baseline Patient Characteristics (Safety Population)**

Characteristic	Ximelagatran (N = 1151)	Warfarin (N = 1148)
Age* (yr)	66.9 ± 9.4	67.1 ± 9.4
Female†	705 (61.3)	733 (63.9)
Weight (kg)*	84.3 ± 18.6	84.1 ± 17.6
Body mass index* (kg/m <sup>2</sup> )	30.8 ± 5.7	30.9 ± 5.5
Creatinine clearance (mL/min)*‡	99.2 ± 37.7	99.4 ± 38.9

\*The values are given as the mean and the standard deviation. †The values are given as the number of patients, with the percentage in parentheses. ‡Creatinine clearance estimated by Cockcroft-Gault formula<sup>18</sup>.

one dose of the study drug or placebo, and had a venogram adequate for evaluation or had objectively confirmed symptomatic venous thromboembolism or had died. During the follow-up period, an additional nine patients in the ximelagatran group and ten in the warfarin group withdrew from the study because of adverse events (two and one patients, respectively), consent was withdrawn (six patients each), or for other reasons (one and three patients, respectively). Baseline patient characteristics (Table I) were similar in the ximelagatran and warfarin groups. Further explanation of the characteristics is contained in the Appendix.

### Efficacy

The composite primary end point of total venous thromboembolism and death from all causes during treatment was observed in 221 (22.5%) of 982 patients receiving ximelagatran and in 308 (31.9%) of 967 patients receiving warfarin (absolute risk reduction, 9.3%; relative risk reduction, 29.3%;  $p < 0.001$ ; number needed to treat = 11; Table II) (see Appendix for an explanation of the number needed to treat and sensitivity analysis). The composite end point of total venous thromboembolism and death from all causes in the patients who underwent bilateral surgery performed under the same anesthesia session (4.5% of all of the patients underwent bilateral surgery; see electronic Appendix) was observed in thirteen (31.0%) of forty-two patients in the ximelagatran group and in twenty (43.5%) of forty-six patients in the warfarin group (absolute risk reduction, 12.5%), which was slightly higher than that in the overall efficacy population.

The composite secondary end point of proximal deep-vein thrombosis, pulmonary embolism, or death from any cause during treatment was observed in thirty-eight (3.9%) of 976 ximelagatran-treated patients and in forty (4.1%) of 964 warfarin-treated patients ( $p = 0.802$ , Table II). Confirmed symptomatic deep-vein thrombosis occurred in eight patients (0.7%) in the ximelagatran group and in fifteen patients (1.3%) in the warfarin group during the treatment period. Two (0.2%) of 1151 patients in the ximelagatran group and five (0.4%) of 1148 patients in the warfarin group had confirmed symptomatic pulmonary embolism during treatment.

During the follow-up period, symptomatic deep-vein thrombosis occurred in three patients in the ximelagatran group, one of whom also had pulmonary embolism. One pa-

tient had symptomatic deep-vein thrombosis and no patient had pulmonary embolism in the warfarin group. All four of these patients had deep-vein thrombosis detected at mandatory venography. An additional two patients had symptomatic venous thromboembolism develop during the follow-up period but did not have mandatory venography. Ten patients died during the study. Seven deaths occurred in the ximelagatran group; four patients died during the treatment period, including one who died because of gastrointestinal bleeding, and three died during the follow-up period. A pulmonary embolism could not be ruled out as a cause of one death during treatment and of two deaths that occurred during the follow-up period. In the warfarin group, three deaths occurred: two patients died during the treatment period, and one died during the follow-up period. The Independent Central Adjudication Committee judged that none of these deaths was associated with venous thromboembolism or bleeding.

In the patients assigned to warfarin treatment, the international normalized ratio was within or above the target range of 1.8 to 3.0 in 640 (67%) of 956 patients at postoperative day 3 and in 690 (73%) of 944 patients at the end of treatment. The mean international normalized ratio on the third day after surgery was 2.4. No appreciable differences were noted in the mean international normalized ratio values between patients with or without venous thromboembolism on either day.

### Safety

Major bleeding occurred in twelve patients in the ximelagatran group and in five in the warfarin group during treatment (Table III). One patient had a fatal bleeding event and one bled at a critical site during the trial; both patients were in the ximelagatran group. See the Appendix for a list of the bleeding events. A similar pattern was observed in both treatment groups for any bleeding event, i.e., the combination of major and minor bleeding events (see electronic Appendix). No significant differences were detected between the ximelagatran and warfarin groups with respect to mean operative blood loss, postoperative wound drainage, and transfusion volumes.

Wound complications were assessed at three scheduled visits (postoperative day 3, end of treatment, and follow-up). The overall wound appearance was assessed as "as expected" or "better than expected" in the majority of patients in the

**TABLE II Incidence of Venous Thromboembolic Events During Treatment Period**

Event	Incidence*		Difference† Percentage (95% Confidence Interval)	P Value‡	Reduction in Risk§ Percentage (95% Confidence Interval)
	No. of Patients Who Had an Event/Total No.	Percentage (95% Confidence Interval)			
<b>Primary end point</b>					
Total venous thromboembolism or death					
Ximelagatran	221/982	22.5 (19.9 to 25.2)	-9.3 (-13.3 to -5.4)	<0.001	29.3 (18.1 to 39.1)
Warfarin	308/967	31.9 (28.9 to 34.9)			
<b>Secondary end point</b>					
Proximal venous thromboem- bolism or death					
Ximelagatran	38/976	3.9 (2.8 to 5.3)	-0.3 (-2.0 to 1.5)	0.802	6.2 (-45 to 39.3)
Warfarin	40/964	4.1 (3.0 to 5.6)			
<b>Findings on venography</b>					
Total deep-vein thrombosis					
Ximelagatran	214/976	21.9 (19.4 to 24.7)	-9.4 (-13.3 to -5.5)	<0.001	30.1 (18.7 to 39.9)
Warfarin	301/960	31.4 (28.4 to 34.4)			
Proximal deep-vein thrombosis					
Ximelagatran	30/969	3.1 (2.1 to 4.4)	-0.4 (-1.9 to 1.2)	0.686	10.2 (-46 to 44.8)
Warfarin	33/957	3.4 (2.4 to 4.8)			
Distal deep-vein thrombosis					
Ximelagatran	209/976	21.4 (18.9 to 24.1)	-9.7 (-13.6 to -5.8)	<0.001	31.1 (19.7 to 40.9)
Warfarin	298/959	31.1 (28.2 to 34.1)			
<b>Symptomatic events#</b>					
Venous thromboembolism or death					
Ximelagatran	14/1151	1.2 (0.7 to 2.0)	-0.7 (-1.7 to 0.3)	0.180	
Warfarin	22/1148	1.9 (1.2 to 2.9)			
Deep venous thrombosis					
Ximelagatran	8/1151	0.7			
Warfarin	15/1148	1.3			
Pulmonary embolism					
Ximelagatran	2/1151	0.2			
Warfarin	5/1148	0.4			
Death					
Ximelagatran	4/1151	0.3			
Warfarin	2/1148	0.2			

\*Exact confidence intervals are provided for within-group estimates. †Differences are the rate for the ximelagatran group minus the rate for the warfarin group. ‡Values were calculated with use of the Cochran-Mantel-Haenszel test, adjusted for the type of surgery performed (i.e., unilateral or bilateral). §The reduction in risk is in favor of ximelagatran. A minus sign indicates an increase in risk. #Symptomatic events or deaths occurring within two days after mandatory venography or up to day 12 if no venogram was available are included during the treatment period. Data are for patients who received at least one dose of study treatment and who underwent the appropriate surgery.

ximelagatran group (1035 [90.6%] of 1142 patients) and in the warfarin group (1042 [91.3%] of 1141 patients). Three wound hematomas in three patients in the warfarin group required a return to the operating room. In one of them, the surgical site was débrided because of an infection, the implant was removed, and a spacer was implanted; another had irrigation and débridement of the knee and closure of the wound and muscle; and one had irrigation and débridement

of the knee wound. Three wound hematomas in three patients in the ximelagatran group required bedside treatment. One of them was managed with elevation of the leg and application of a cold compress, another had surgical débridement, and the third had débridement of the knee wound and removal of an incisional hematoma. Treatment-emergent postoperative complications were similar in the two groups (see electronic Appendix).

**TABLE III Bleeding Events During Treatment (Safety Population)**

Bleeding Indicator	Ximelagatran (N = 1151)	Warfarin (N = 1148)	P Value*
Major bleeding†	12 (1.0)	5 (0.4)	0.087
Any bleeding†	58 (5.0)	44 (3.8)	0.158
Mean operative blood loss‡ (mL)	161 (151-170)	169 (159-178)	0.227
Mean postoperative wound drainage‡ (mL)	714 (685-743)	718 (690-747)	0.840
Mean transfusion volume‡ (mL)	213 (193-233)	208 (187-228)	0.728
Bleeding index‡§	3.4 (3.3- 3.5)	3.3 (3.3-3.4)	0.255

\*The values for major and any bleeding were calculated with use of the Cochran-Mantel-Haenszel chi-square test and adjusted for the type of surgery (unilateral or bilateral). Values for the remaining parameters were calculated with use of analysis of variance. †The values are given as the number of patients, with the percentage in parentheses. ‡The values are given as the mean, with 95% confidence intervals in parentheses. §The bleeding index was calculated as the baseline hemoglobin level (g/dL) minus the hemoglobin level at the end of treatment plus the number of units of red blood cells transfused.

### Liver Enzymes

Transient elevations of alanine aminotransferase have been observed in patients in long-term studies of ximelagatran<sup>21</sup>, but such elevations were rare in the ximelagatran-treated patients in the present study. Further explanation appears in the Appendix. No clinical signs or symptoms were attributed to the alanine aminotransferase elevations.

### Discussion

This study showed that postoperative administration of 36 mg of oral ximelagatran twice daily was safe and superior to postoperative warfarin in reducing the composite end point of venous thromboembolism and death from all causes, according to both independent central adjudication and local site assessment. The incidence of proximal deep-vein thrombosis, symptomatic deep-vein thrombosis, and pulmonary embolism in this trial was low, as in previous total knee arthroplasty trials of venous thromboprophylaxis with ximelagatran<sup>22,23</sup>.

In randomized trials and cohort studies, both warfarin and low-molecular-weight heparin have been shown to provide effective and safe prophylaxis after total knee arthroplasty. In studies directly comparing low-molecular-weight heparin with warfarin, the prevalence of venographically determined total deep-vein thrombosis ranged from 16% to 45% (mean, 28%) of a combined total of 1263 patients in the low-molecular-weight heparin groups compared with 27% to 55% (mean, 43%) of a combined total of 1207 patients in the warfarin groups<sup>1,7-11,24</sup>. Bleeding complications and transfusion requirements have generally been higher with low-molecular-weight heparin than with warfarin<sup>1,7,9,24</sup>. Fondaparinux lowered the risk of venous thromboembolism in comparison with enoxaparin in one trial involving total knee arthroplasty, but it was also associated with a significantly ( $p = 0.006$ ) higher rate of major bleeding than was the low-molecular-weight heparin<sup>25</sup>. The advantage of warfarin over low-molecular-weight heparins and fondaparinux is its oral administration, which can facilitate prophylaxis in the hospital and after discharge. Nevertheless, warfarin has major

limitations, such as a delayed onset of action, numerous drug and food interactions, and the need for coagulation monitoring and dose adjustment. Warfarin was chosen as the comparator because it is the most commonly used pharmacologic prophylaxis in patients undergoing total knee arthroplasty in North America<sup>26,27</sup> and because it received the highest rating in the American College of Chest Physicians guidelines<sup>1</sup>.

The incidence of major bleeding was low (1.0% in ximelagatran-treated patients and 0.4% in warfarin-treated patients), and, although twice as many events occurred in the ximelagatran-treated patients, the difference was not significant. Major bleeding rates were lower than those reported in previous studies comparing low-molecular-weight heparins and warfarin in patients managed with total knee arthroplasty, which have ranged from 2.1% to 7.9%<sup>7,9,10,24</sup>.

This study was a multicenter, randomized, double-blind trial performed with a double-dummy technique. A high percentage (84.8%) of the randomized patients completed the protocol treatments and assessments for independent objective evaluation, assuring an accurate and unbiased comparison for both efficacy and safety outcomes. To our knowledge, the present study is the largest trial of warfarin and a comparator in patients managed with total knee arthroplasty only that has been performed to date, with the lowest reported rates of total and proximal venous thromboembolism and very low rates of bleeding events. A 36-mg dose of oral ximelagatran taken twice daily for seven to twelve days without coagulation monitoring or dose adjustment was significantly superior to well-controlled warfarin in reducing the prespecified composite primary end point of total venous thromboembolism (deep-vein thrombosis and pulmonary embolism) and death from all causes after primary total knee arthroplasty. The result was driven by a reduction in calf-vein thrombosis. The rates of major and minor bleeding events with both treatments were low and were not significantly different, although they were numerically greater with ximelagatran. ■

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## Appendix

### Surgical Details of the Efficacy Population

#### Materials and Methods

##### Patients

Eligible patients were women without childbearing potential or men who were at least eighteen years old, who weighed between 40 and 136 kg, and who provided written informed consent. Only patients undergoing primary total knee arthroplasty were included. The criteria for exclusion were major surgery, stroke, myocardial infarction, or administration of any investigational drug within thirty days before surgery; immobilization for three or more days before surgery; traumatic epidural and/or spinal puncture at surgery; planned pneumatic leg compression; a history of intracranial, retroperitoneal, or intraocular bleeding; a history of gastrointestinal bleeding or other disorder associated with an increased risk of bleeding within ninety days before surgery; an endoscopically verified peptic ulcer disease within thirty days of surgery; uncontrolled hypertension; a malignant tumor receiving cytostatic treatment or being the reason for the knee arthroplasty; an alanine or aspartate aminotransferase level greater than two times the upper limit of normal; renal impairment (defined as estimated creatinine clearance of  $<30$  mL/min)<sup>18</sup>; thrombocytopenia; a history of drug or alcohol abuse in the past six months; an allergy to venographic contrast media or iodine; and a contraindication to warfarin.

##### Treatment Regimens

###### Warfarin Management

To guide warfarin dosing, international normalized ratios were measured at the study site (with treatment blinding maintained) on postoperative days 1, 2, and 3; the day of venography; and as required. International normalized ratios were measured either at the point of care with use of encrypted devices provided or at local laboratories with a system that prevented access to the international normalized ratios by the local study team. All international normalized ratios were reported by means of an interactive voice-response system, which then relayed back to the local sites either the actual international normalized ratios for the warfarin patients or, for those patients receiving ximelagatran, the sham international normalized ratios generated to mimic values typically observed in warfarin-treated patients. A warfarin-dosing nomogram was provided, but the choice of either the warfarin or the placebo dose was made at the individual investigator's discretion. Treatment compliance was assessed for ximelagatran by the number of doses taken (and missed) during the study as reported in the medication logs and for warfarin by the percentage of patients within the therapeutic range.

##### Efficacy Assessments

###### Assessment for Deep-Vein Thrombosis and Pulmonary Embolism

The criterion for a diagnosis of deep-vein thrombosis was a consistent intraluminal filling defect visible on at least two im-

ages. To be considered adequate for evaluation, venograms needed to show all deep veins except the deep femoral vein, the muscular veins of the calf, and the anterior tibial veins, although these veins were included in the evaluation if visible or if a clot was detected. Venograms were classified as indeterminate if there was a lack of filling of a region of the deep-vein system without a filling defect in the same region. Symptomatic proximal deep-vein thrombosis could be diagnosed by compression ultrasound, but diagnosis of symptomatic distal deep-vein thrombosis required venography. A diagnosis of pulmonary embolism was made if (1) a ventilation-perfusion lung scan revealed one or more segmental pulmonary perfusion defects in at least two views with corresponding normal ventilation, (2) pulmonary angiography showed a persistent intraluminal defect or an abrupt cutoff of a vessel that was  $>2.5$  mm in diameter, (3) a spiral computed tomographic scan demonstrated a distinct filling defect in a large vessel, (4) embolectomy was performed, or (5) it was determined by autopsy.

##### Safety Assessment

###### Bleeding Criteria

Bleeding events were classified as "major" if they were clinically overt (defined as clinically apparent bleeding or signs and/or symptoms suggestive of bleeding with confirmatory imaging studies [e.g., ultrasound or computed tomography]) and met one or more of the following criteria: (1) involvement of a critical site (intracranial, retroperitoneal, intraocular, intraspinal, or pericardial); (2) a bleeding index of 2.0 or more (calculated as the baseline hemoglobin level [in grams per liter] minus the hemoglobin level at the end of treatment plus the number of units of packed red-blood cells or whole blood transfused); (3) a need for medical or surgical intervention; or (4) fatal bleeding. Clinically overt bleeding episodes that did not meet any of these criteria were classified as "minor," and, if bleeding episodes were not clinically overt, they were classified as "criteria for bleeding event not satisfied."

##### Statistical Analysis

To ensure that adequate objective efficacy assessments could be made on at least 1720 patients at the end of the study, we planned to randomize approximately 2300 patients, anticipating that, at most, 25% of the venograms would be inadequate for evaluation. The efficacy analyses included all patients who had received at least one dose of study medication and had a venogram adequate for evaluation; had symptomatic, objectively confirmed deep-vein thrombosis or pulmonary embolism; or had died during treatment. Bilateral venography was required, but patients undergoing unilateral surgery were included in the efficacy analysis even if a venogram adequate for evaluation could be obtained only in the leg on which surgery was performed or if a clot was visualized in the contralateral side. For patients who underwent bilateral knee surgery, venograms adequate for evaluation in both legs were required unless deep-vein thrombosis was detected in one leg. Symptomatic venous thromboembolism or deaths occurring within two days after venography or up to day 12 if no venography was performed

were deemed to have occurred during the treatment period.

## Results

### Baseline Characteristics of the Patients

Within the efficacy population, forty-four (4.5%) of 982 patients assigned to ximelagatran and thirty-one (3.2%) of 967 patients assigned to warfarin had a history of venous thromboembolism. The details of the operation and the course of hospitalization were also similar between the treatment groups. The surgical position was supine for all patients. The surgical approach was medial parapatellar in 888 (90.4%) of 982 ximelagatran-treated patients and 868 (89.8%) of 967 warfarin-treated patients, and a tibial tuberosity osteotomy was performed in only eight (0.8%) of 982 patients in the ximelagatran group and in twelve (1.2%) of 967 patients in the warfarin group. Approximately 130 (13.2%) of 982 patients in the ximelagatran group and 145 (15%) of 967 patients in the warfarin group underwent epidural catheter placement, with a mean duration of use between nine and eleven hours. The mean time to the first dose of medication on the day after surgery was 20.2 hours. The mean time to walking was 1.9 days, and the mean hospital stay was 5.6 days. Most patients (1082 [94%] of 1151 patients in the ximelagatran group and 919 [80%] of 1148 patients in the warfarin group) received study medication for seven to twelve days, with the lower percentage of patients in the warfarin group being primarily due to the need to withhold doses when a therapeutic or elevated international normalized ratio was obtained. Efficacy data adequate for evaluation were available for 1949 (84.8%) of 2299 treated patients. After the treatment period, 30% of the patients in each group received follow-up anticoagulant therapy.

### Efficacy Assessment

The number of patients needed to treat to prevent one composite primary end-point event with ximelagatran compared with warfarin was eleven patients (95% confidence interval, eight to nineteen patients). Stated another way, the relative risk reduction indicates nine fewer venous thrombosis events per 100 patients undergoing total knee arthroplasty with ximelagatran than with warfarin. In a sensitivity analysis of patients who had total knee arthroplasty that excluded sixty-two patients (thirty-four in the ximelagatran group and twenty-eight in the warfarin group) in whom unilateral but not bilateral venography was performed, similar reductions were achieved (absolute risk reduction, 9.5%; relative risk reduction, 28.9%;  $p < 0.001$ ).

### Local Interpretation of Venograms

The incidence of total venous thromboembolism and death from all causes with use of the local interpretation of venograms was 300 (30.1%) of 996 ximelagatran-treated patients compared with 363 (35.8%) of 1014 warfarin-treated patients ( $p = 0.007$ ). The superior efficacy of ximelagatran was consistent across all subgroups analyzed, on the basis of gender, age, country, history of venous thromboembolism, body weight, estimated creatinine clearance, type of anesthesia, and time to venography. No significant interactions were found between

treatment and any of the subgroup factors ( $p \geq 0.304$ ), indicating that the efficacy of ximelagatran (relative to warfarin) was consistent in all of the examined subgroup categories.


### Safety

The types of major bleeding events included wound hematoma (four patients in the ximelagatran group and three in the warfarin group), gastrointestinal bleeding (four and one, respectively), wound bleeding (three and one, respectively), and a subdural hematoma (an exacerbation of a chronic subdural hematoma due to a recent fall) in one patient in the ximelagatran group. The gastrointestinal bleeding event in one patient in the ximelagatran group was due to a bleeding duodenal ulcer and was judged to be the cause of death in that patient. One additional major bleeding event occurred in each treatment group during the follow-up period. Approximately half (seven) of all thirteen major bleeding events in the ximelagatran-treated patients occurred in the first three postoperative days, while five of the six bleeding events in the warfarin group occurred after day 4.

### Liver Enzymes

The first onset of an elevation of alanine aminotransferase levels greater than three times the upper limit of normal was detected in five (0.5%) of 1078 patients in the ximelagatran group and in six (0.6%) of 1071 patients in the warfarin group at the end of treatment and in five (0.5%) of 1091 patients and one (0.1%) of 1083 patients, respectively, at the follow-up visit (more than two days after the last dose of study medication). The alanine aminotransferase values normalized in all of the ximelagatran-treated patients within four weeks of onset. No clinical signs or symptoms were attributed to the alanine aminotransferase elevations.

### Electronic Appendix

 The membership of the EXULT B Study Group, a figure presenting the cumulative proportion of bleeding events, and tables presenting the surgical details of the efficacy population and evaluation of the surgical wounds are available with the electronic versions of this article, on our web site at [jbjs.org](http://jbjs.org) (go to the article citation and click on "Supplementary Material") and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM). ■

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