Clinical Review for NDA 21-686

NDA:	21-686
Sponsor:	AstraZeneca
Drug name:	Exanta (ximelagatran) Tablets
Indications:	

1) Prevention of venous thromboembolism (VTE; defined as deep vein thrombosis [DVT], pulmonary embolism [PE], or both), in patients undergoing knee replacement surgery;

2) Long-term secondary prevention of VTE after standard treatment for an episode of acute VTE;

3) Prevention of stroke and other thromboembolic complications associated with atrial fibrillation (AF). (see Medical Officer's review from the Division of Cardio-Renal Drug Products for details)

Date submitted:	December 23, 2003
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Reviewer:	Ruyi He, M.D.

NOTE: This is a preliminary/draft review that is not intended to provide any recommendations on the approvability of NDA 21,686. Any opinions expressed in the review do not necessarily reflect those of the Division/Office.

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Executive Summary

I. Summary of Clinical Findings

A. Brief Overview of Clinical Program

EXANTA ® (ximelagatran) is an oral anticoagulant and a prodrug of melagatran, a potent, reversible, competitive and direct inhibitor of thrombin. Ximelagatran prevents a key step in the coagulation cascade, the conversion of fibrinogen to fibrin.

Ximelagatran is in development for several indications, of which the following 3 are being submitted in this application: prevention of VTE (defined as deep vein thrombosis [DVT], pulmonary embolism [PE], or both), in patients undergoing knee replacement surgery; long-term secondary prevention of VTE after standard treatment for an episode of acute VTE; and prevention of stroke and other thromboembolic complications associated with atrial fibrillation (AF). All 3 indications are for the adult population only.

The studies were designed to demonstrate that fixed doses of ximelagatran, without coagulation monitoring or dosage adjustment, offers superiority to placebo (VTE Secondary Prevention), superiority to warfarin (Knee Replacement Surgery), and non-inferiority to warfarin (Atrial Fibrillation).

The development program includes 82 clinical studies with ximelagatran and/or melagatran (60 Phase I studies and 22 Phase II and III studies), in which 30,698 subjects were randomized. A total of 17,593 randomized subjects received the oral prodrug ximelagatran, or the active drug melagatran. In the long-term treatment populations, 6931 patients received ximelagatran, 5024 of whom received treatment for at least 6 months and 3509 for at least a year in patients with atrial fibrillation (up to 2.5 years in the pivotal SPORTIF studies and up to 4 years in the ongoing SPORTIF IV study).

Each Phase 3 study was conducted as a multi-center, randomized, parallel-group, comparator-controlled design. All studies were double-blind except for SH-TPA-0003 (SPORTIF III for the indication of prevention of stroke in patients with AF; which was an open-label in design). All studies used a central laboratory for all protocol-specified laboratory measurements.

For the indication of prevention of VTE in patients undergoing elective knee replacement surgery, the sponsor conducted three Phase 3 studies in comparison with warfarin in patients

undergoing primary, elective total knee replacement (TKR) surgery (SH-TPO-0006, EXULT A and EXULT B). A total of 5284 patients were randomized in these three studies (1927 to ximelagatran 36 mg bid, 2247 to warfarin, and 1110 to ximelagatran 24 mg bid).

To support the indication of prolonged prophylaxis of VTE after a six-month anticoagulation treatment for VTE, the sponsor provided only one 18-month study, SH-TPV-0003 (THRIVE III). A total of 1233 patients were randomized, with 914 completing the 15-month duration (475 on ximelagatran 24 mg bid and 439 on placebo) and only 193 completing the entire 18-month study (107 on ximelagatran 24 mg bid and 86 on placebo).

For the indication of prevention of stroke and systemic embolic events in patients with nonvalvular atrial fibrillation, Division of Cardio-Renal drug products (HFD-110) is conducting the review for both efficacy and safety.

B. Efficacy

Indication 1: prevention of VTE in patients undergoing elective total knee replacement (TKR) surgery

Oral ximelagatran 36 mg bid were superior to warfarin in reducing total VTE and/or all- cause mortality at end of 7-12 days therapy among patients undergoing TKR surgery in two Phase 3 studies.

In the pooled EXULT A and EXULT B analyses, the incidence of total VTE and/or all-cause mortality among patients undergoing TKR was 21.7% for patients in the ximelagatran 36 mg group and 30.2% for patients in the warfarin group ($p<0.001$). However, the benefit was mainly due to a reduction in asymptomatic distal DVT diagnosed by venography which is not clinically meaningful. There were no clinically or statistically significant differences between ximelagatran and warfarin groups in reducing the frequency of proximal DVT, PE, and/or all-cause mortality in this population.

There are several major problems with using warfarin as an active comparator in these two studies. Warfarin is not approved for this short term indication. The comparison is unfair, because warfarin will take about 3-5 days to reach therapeutic level, while Exanta reaches therapeutic levels within hours. Mean days of exposure were 8.1 days for ximelagatran and 6.7 days for warfarin in these two studies. The results show that 33.1% - 35.2% of patients receiving warfarin had an INR less than 1.8 at postoperative day 3, and 24.0 – 26.9% % of patients receiving warfarin had an INR less than 1.8 at end of treatment (day 7 – 12). Because this study is designed to show superiority of ximelagatran, efficacy results for ximelagatran in these studies may still be acceptable, since warfarin may be considered to be placebo.

In EXULT A ximelagatran 24 mg bid was not superior to warfarin in reducing total VTE and/or all-cause mortality (27.6% warfarin vs 24.9% ximelagatran 24 mg) at end of 7-12 days therapy.

Indication 2: long-term secondary prevention of VTE after standard treatment for an episode of acute VTE

Ximelagatran significantly reduced the recurrence rate of symptomatic, objectively confirmed VTE (the primary variable of the study) as compared to placebo over 18 months of treatment (cumulative risk of 2.8% versus 12.6%; hazard ratio 0.16; $p<0.0001$). The number of patients with a VTE event was 12 in the ximelagatran group and 71 in the placebo group. The number of patients with a PE event was lower in the ximelagatran group compared to the placebo group (2 and 23) respectively. The results for the secondary variable, all-cause mortality, showed no significant difference between the treatment groups (1.1% vs 1.4% for patients on ximelagatran and placebo, respectively) during the 18 months.

C. Safety

C.1. Safety of ximelagatran in patients undergoing a surgical procedure (use ≤ 35 days)

A total of 1913 patients were exposed to ximelagatran 36 mg bid, 1097 patients were exposed to ximelagatran 24 mg bid, and 2226 patients were exposed to warfarin with a mean duration of exposure of 8 days for the ximelagatran groups.

Overall, more than 55% of patients in each treatment group experienced at least 1 adverse event (AE). Post-operative complications were mostly related to bleeding and were reported at a higher frequency in the ximelagatran groups (17% at 36 mg, 23% at 24 mg) than in the warfarin groups (15% and 20%, respectively).

There were 18 deaths (12 patients exposed to ximelagatran and 6 patients exposed to warfarin). Of the 12 fatal SAEs reported among the 3010 patients who received ximelagatran (0.4%), 2 were fatal bleeding events (both on ximelagatran 36 mg). Six were fatal events in which 'PE could not be excluded'. The last 4 fatal SAEs in patients who received ximelagatran were adjudicated as 'death not associated with VTE or bleeding'. The investigators reported the causes of death in 1 patient on treatment as sudden death, and in the other 3 patients after treatment as intestinal perforation, acute MI, and pneumonia. Of the 6 deaths reported among the 2226 patients who received warfarin (0.3%), 2 were fatal events in which 'PE could not be excluded'. The causes of death in 2 patients on treatment were arrhythmia and MI and in the other 2 after treatment were colon carcinoma and AMI.

There were more adverse events leading to discontinuation of study drug (DAEs) in the ximelagatran 36-mg group (2.6%) than in the warfarin group (2.0%) and in the ximelagatran 24-mg group compared to warfarin group (3.1% versus 2.1%, respectively) with postoperative complication, the most common adverse event leading to study drug discontinuation.

With respect to on-treatment adjudicated events, major bleeding occurred in 0.9% of patients treated with ximelagatran 36 mg, compared to 0.5% of patients treated with warfarin. There were 2 fatal bleeding events (both on ximelagatran 36 mg). Major/minor bleeding occurred in 5.1% of patients treated with ximelagatran 36 mg and 4.1% of patients treated with warfarin.

Incidences of ALAT elevation reported as AEs were higher in the 36-mg ximelagatran group (2.1%) than other groups (1.3-1.5% warfarin; 1.4% ximelagatran 24-mg). There were no hepatobiliary fatal SAEs, non-fatal SAEs or DAEs in either ximelagatran group. During the follow-up period (4-6 weeks), 8 patients in the ximelagatran group, and 1 in the warfarin group had their first ALAT elevation >3x ULN. However, patients were only followed up for 4-6 weeks post operation. Drug effects on liver toxicity beyond 4-6 weeks are unknown. It should be noted that in studies with long-term exposure to ximelagatran elevation of hepatic enzymes was typically seen between 2nd and 6th month after starting ximelagatran.

In both studies Exult A and Exult B, the proportion of patients with coronary artery disease adverse events (MI or ischemia/angina) was significantly higher in the ximelagatran groups than in the warfarin groups. In patients undergoing TKR surgery (Exult A and Exult B), proportion of patients with coronary artery disease adverse events was statistically significantly higher in the ximelagatran group (20/2677, 0.75%) than in the warfarin group (5/1907, 0.26%) (p=0.02800). The proportion of patients with MI was also higher in the ximelagatran group (16/2677, 0.60%) than in the warfarin group (4/1907, 0.21%) in the TKR population (p=0.04951). There were no appreciable differences between the treatment groups for underlying diseases including hypertension, hypercholesterolemia, diabetes mellitus, coronary atherosclerosis, as well as age, gender and weight. Considering ximelagatran as an anticoagulant with potential to treat MI, these results are worrisome.

Overall, these studies raised some safe concerns for use of oral ximelagatran 36 mg bid for 7 to 12 days after surgery (beginning the morning after surgery) in the prevention of VTE in patients undergoing elective knee replacement surgery. There is a potential risk of higher coronary artery disease adverse events including acute myocardial infarction. Potential long-term use that will cause liver toxicity is high. Also, major bleeding events were higher in patients treated with ximelagatran than in patients treated with warfarin. The long-term follow up (6 months) data may also be considered to adequately assess liver toxicity for short-term use of ximelagatran.

C.2. Safety of ximelagatran in patients with long-term exposure (> 35 days)

A total of 6931 patients received doses from 20 to 60 mg of ximelagatran, for a median of 370 days. A total of 5024 patients were exposed to ximelagatran for at least 6 months and 3509 for at least 12 months. A total of 6216 patients were exposed for a median of 455 days to warfarin (n=4967) and placebo (n=1249).

C.2.1. Death

There were 224 deaths during active treatment, 112 in the ximelagatran treatment groups and 112 in the comparator groups. A further 331 patients died after stopping study drug (166 in the ximelagatran group and 165 in the comparator group). There was no differences between the treatment groups. The most common fatal SAE was myocardial infarction.

C.2.2. Non-fatal SAE

A total of 26.3% of patients in the ximelagatran group and 27.1% of patients in the comparator group experienced a non-fatal SAE during treatment. A further 5.5% of patients in the ximelagatran group and 4.3% of patients in the comparator group experienced a non-fatal SAE after stopping study drug. The most common non-fatal SAEs were cardiovascular events. The most common non-fatal SAEs considered to be causally related to ximelagatran were increases in hepatic transaminases.

C.2.3. Discontinuation

The proportion of patients who discontinued study drug was higher in the ximelagatran group (1189/6931, 17.2%) than in the comparator group (801/6216, 12.9%). This was mostly due to the discontinuation of study drug due to elevated hepatic transaminases. Data from discontinuation of ximelagatran secondary to AEs indicate that "coronary artery disorders (CAD)" were more common in the ximelagatran group than in the comparator group (0.6% vs. 0.3%, respectively) whereas thromboembolic events were less common DAEs in the ximelagatran group (0.4% vs.1.3%, respectively), because of a placebo control. Other common causes of discontinuations included bleeding events, with no difference between ximelagatran and the comparators, except for haematuria and rectal haemorrhage/ melaena, which caused slightly more discontinuations in the ximelagatran group than in the comparator groups.

C.2.4. Bleeding Events

In patients with atrial fibrillation (AF), ximelagatran 36 mg was associated with fewer major bleeding events than warfarin (AF pool; 2.4% and 3.4% for the ximelagatran and warfarin group, respectively, p=0.0288). However, there were no significant differences for major bleeding events between the groups in each of the 2 pivotal studies (SH-TPA-0003 and STP-0005). In patients with acute VTE, ximelagatran 36 mg was associated with numerically fewer major bleeding events than enoxaparin/warfarin. In patients undergoing extended secondary prophylaxis for VTE, ximelagatran 24 mg was associated with a similar incidence of major bleeding events to placebo. A total of 38 patients experienced bleeding-related SAEs with a fatal outcome, 19 cases in each treatment group (ximelagatran or comparator).

C.2.5. Hepatobiliary Toxicity

In patients receiving long-term administration of ximelagatran (>35 days) an increase in ALAT >3xULN occurred in 6-13% (average 7.6%, 531/6948) compared to 0-2% (average 1.1%, 68/6230) of patients receiving comparator treatments. Including local laboratory data, 620 patients showed an ALAT elevation >3xULN during the studies, 546 patients in the ximelagatran group (cumulative incidence 7.8%) and 74 patients in the comparator group (cumulative incidence 1.1%). Among the 531 patients in the ximelagatran group who presented with an ALAT >3xULN, 206 (39%) completed the study on study drug. The remaining 325 patients (61%) discontinued study drug prematurely.

The time pattern of ALAT elevations was consistent across patients. The increase typically occurred between 1 and 6 months after the initiation of ximelagatran. Before and after this time frame the incidence of ALAT increase was similar to that in the comparator groups. Of the 531 ximelagatran-treated patients who had an ALAT elevation >3xULN recorded by the central laboratory, 502 (95%) had their ALAT return to <2xULN (235 with study drug continued). Most

cases show a peak of ALAT within the first 2 to 3 months post-randomization and a decline back towards baseline within about 6 months post-randomization in patients who discontinued or in patients continued on ximelagatran.

Eighteen patients who discontinued study drug with elevations of ALAT subsequently resumed treatment after ALAT had returned to the normal range. Of these 18 patients, 2 again experienced elevations of ALAT after drug was resumed.

An evaluation of potential risk factors for increase in ALAT indicated an increased risk in the post acute coronary syndrome (ACS) (p=0.0009), VTE-treatment (VTE-T) populations (p=0.0003), in female patients (p=0.0002), in patients with low BMI (<27 kg/m^2) (p<0.0001), and in patients receiving concomitant treatment with statins (p=0.019). Asian patients were found to have a decreased risk (p=0.0038). Although a single factor identified above may not be strong enough to eliminate the subgroup population, consideration may be given to contraindicating ximelagatran in patients who have 2 or more risk factors, such as, female patients with low body weight or who are taking a statin.

ALAT >3xULN was associated with bilirubin >2xULN (within one month following the rise in ALAT) in 0.53% (37/6948) of all patients who were exposed to ximelagatran >35 days as compared to 0.08% (5/6230) of patients exposed to comparators. Concomitant elevations of ALAT >3xULN and bilirubin >2xULN were observed during the first month of ximelagatran therapy in 6 of 37 patients. Nine ximelagatran-treated patients (24.3%, 9/37) died with concomitant ALAT >3xULN and bilirubin >2xULN. Among these, 3 died from heart failure; 3 died from carcinomas with hepatic metastases; 2 (ID# 7259, and 7859) died from GI bleeding with coagulopathy (1 with biopsy documented hepatic necrosis) and 1 (ID# 5442) died from hepatitis B. Liver failure/toxicity by ximelagatran might have caused or at least contributed to these deaths. Only one autopsy was done in these 9 deaths and it showed a small, friable and diffusely mottled liver suggestive of severe diffuse hepatic necrosis.

C.2.6. Adverse Events of Coronary Artery Disease

In all study populations except the post acute coronary syndrome, the proportion of patients with coronary artery disease adverse events was higher in the ximelagatran groups than in the comparator groups (7.0% and 6.7% for the AF pool, 1.3% and 0.1% for the VTE-treatment (VTE-T) pool and 2.6% and 2.0% for the VTE-prevention (VTE-P) pool, for the ximelagatran and comparator groups, respectively). This trend was consistent across the pools for myocardial infarction.

The proportion of patients with coronary artery disease adverse events was statistically significantly higher in the ximelagatran group (32/1848, 1.7%) than in the warfarin/placebo group (12/1859, 0.7%) in the VTE (VTE-T + VTE-P) population (p=0.00411). The proportion of patients with MI was also significantly higher in the ximelagatran group (13/1848, 0.7%) than in the warfarin/placebo group (3/1859, 0.16%) in the VTE population (p=0.01183). There were no appreciable differences between the treatment groups for underline diseases including hypertension, diabetes mellitus, hypercholesterolemia, coronary atherosclerosis, as well as age,

gender and weight. Considering ximelagatran as an anticoagulant with potential to treat MI, these results are worrisome.

D. Dosing

For the indication of prevention of VTE in patients undergoing elective knee replacement surgery, the proposed dose is oral ximelagatran 36 mg bid for up to 12 days. For the indication of prolonged prophylaxis VTE after a six-month anticoagulation treatment for VTE, the proposed dose is oral ximelagatran 24 mg bid.

In term of hepatobiliary toxicity, there was not a marked dose response over the dose range 24 mg to 60 mg ximelagatran, but there was a noticeably lower incidence of elevation of liver transaminases at the 24 mg dose compared to the higher doses.

E. Special Populations

For short-term use (≤ 35 days)
For the indication of prevention of VTE in patients undergoing elective knee replacement surgery, the majority of the patients were female (61.5%); most were Caucasian (95.1%); and most were greater than 64 years of age (65.6%). The mean age was approximately 67 years, but ranged from 26 years to 91 years. Almost half the patients had a body mass index >30 kg/m^2, which is typical for TKR surgery patients but higher than the general population.

The incidence of VTE and/or all-cause mortality was significantly higher in female and older patients. Results for these subgroups are summarized in the following Table:

Table 1: Incidence of total VTE and/or all-cause mortality for selected subgroups (efficacy ITT population) – Pooled 36 mg bid

Subgroup factor		Ximelagatran 36 mg (n=1611)	Warfarin (n=1575)
Category	p-value[1]	% (n/N)	% (n/N)
Sex	<0.001		
Male		18.9 (119/628)	24.9 (149/599)
Female		23.4 (230/983)	33.5 (327/976)
Age	0.001		
<65 years		19.7 (110/559)	25.6 (137/536)
65 to 74 years		22.1 (148/671)	33.3 (230/691)
≥75 years		23.9 (91/381)	31.3 (109/348)

The subgroup factors that had no significant impact on the incidence of total VTE and/or all-cause mortality were: race, body mass index, estimated CrCL, general anaesthesia (yes/no), time to first dose, and time to ambulation.

For long-term use (> 35 days)

For the indication of prolonged prophylaxis of VTE after a six-month anticoagulation treatment for an episode of acute VTE, the majority of the patients were male (54%), Caucasian (93%), and less than 60 years of age (52%). The mean age was approximately 57 years, but ranged from 18 years to 90 years. Subgroup factors that had no significant impact on the VTE events were: sex, age, race, body mass index, estimated CrCL, initial proximal/or distal DVT (yes/no), previous VTE events (yes/no).

An evaluation of potential risk factors for increase in ALAT indicated an increased risk in the Post ACS ($p=0.0009$), and VTE-T ($p=0.0003$) populations and also in female patients ($p=0.0002$), patients with low BMI (<27 kg/m^2) ($p<0.0001$) and patients receiving concomitant treatment with statins ($p=0.019$); Asian patients were found to have a decreased risk ($p=0.0038$). Although single factor identified above may not be strong enough to eliminate the subgroup population, consideration may be given to contraindicating ximelagatran in patients who have 2 or more factors, such as, female patients with low body weight or who are taking a statin.

All three indications are for the adult population only. AstraZeneca requests a waiver for pediatric studies for the indications claimed in this application. It is unlikely that a substantial number of pediatric patients will be treated with EXANTA for the claimed indications. The estimated number of pediatric patients diagnosed with atrial fibrillation in the US in 2002 is less than 1,500 children. The estimated total number of pediatric patients treated for VTE (of which prevention of recurrent events, the indication claimed in this application, is a subset of patients) in the US in 2002 is less than 3,000 children. The estimated cumulative number of pediatric patients diagnosed with conditions for which EXANTA will be indicated is less than 5,000 children. Thus, the number of pediatric patients likely to be treated with EXANTA for the claimed indications is well below the number defined as a substantial number in the Pediatric Final Rule. Therefore, I recommend that the sponsor's requests for waiver of the requirements to conduct pediatric studies be granted for the indications claimed in this application.

Subjects with renal impairment

Melagatran, the active metabolite of ximelagatran, is eliminated primarily via renal excretion. Renal function decreases with age and the target patient population for ximelagatran is of older age (median age about 65 years). As expected, subjects with severe renal impairment had higher plasma concentrations of melagatran. The mean (SD) half-lives of melagatran were 6.8 (2.0) h and 9.3 (3.5) h after subcutaneous injection melagatran and oral ximelagatran dosing, respectively, in the subjects with renal impairment. These half-lives were about 3-fold higher than for control subjects with normal renal function. Therefore, usage of ximelagatran in patients with severe (CrCL < 30mL/min) renal impairment is not recommended. A dosing reduction should be considered for the patients who have moderate renal impairment (CrCL < 80mL/min).

Subjects with hepatic impairment

The absorption of ximelagatran and the metabolic biotransformation to its active form, melagatran, are not influenced for subjects with mild and moderate hepatic impairment. However, patients who have abnormal liver function or history of liver diseases have been excluded from the studies. Due to high risk of liver toxicity, the use of ximelagatran in patients

with hepatic disease and/or ALT > 2 times the upper limit of normal at the start of therapy is contraindicated.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

EXANTA ® (ximelagatran) is an oral anticoagulant and a prodrug of melagatran, a potent, reversible, competitive and direct inhibitor of thrombin.

Ximelagatran is in development for several indications, of which the following 3 are being submitted in this application: prevention of VTE (defined as deep vein thrombosis [DVT], pulmonary embolism [PE], or both) in patients undergoing knee replacement surgery; long-term secondary prevention of VTE after standard treatment for an episode of acute VTE; and prevention of stroke and other thromboembolic complications associated with atrial fibrillation (AF). All 3 indications are for the adult population only.

For the indication of prevention of VTE in patients undergoing knee replacement surgery, the proposed dosing is EXANTA 36 mg twice-daily for a treatment period of 7 to 12 days. Provided hemostasis has been established, the first dose should be given the morning after surgery, but no sooner than 12 hours from the time of surgery. For the indication of long-term secondary prevention of VTE, it is proposed that patients who have received standard anticoagulant treatment for DVT or PE be treated with EXANTA 24 mg twice-daily. For the indication in patients with atrial fibrillation, please see Medical Officer's review from the Division of Cardio-Renal Drug Products for details. No dosage adjustment is necessary with EXANTA in patients with a creatinine clearance (CrCL) $\geq$30 mL/min. Usage of EXANTA in patients with severe renal impairment (CrCL <30 mL/min) is not recommended. The use of EXANTA in patients with hepatic disease and/or ALT >2 times the upper limit of normal at the start of therapy is contraindicated.

B. State of Armamentarium for Indication(s)

Warfarin is approved for:

- the prophylaxis and/or treatment of venous thrombosis and its extension, and PE;
- the prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement;
- reducing the risk of death, recurrent MI, and thromboembolic events such as stroke or systemic embolization after MI.

The "Dosage and Administration" section of warfarin labeling refers to "longer term therapy" for indications such as VTE, in patients with A-Fib or mechanical and bioprosthetic heart valves. It also states that the duration of therapy in each patient should be individualized and anticoagulant

therapy should be continued until the danger of thrombosis and embolism has passed. Thus, the indications and dosing recommendations for warfarin are sufficiently broad to encompass extended prophylaxis of DVT.

Lovenox (enoxaparin sodium), a low molecular weight heparin, is approved for the indication of the prophylaxis of DVT in patients undergoing knee replacement surgery. Arixtra (fondaparinux sodium) injection, a synthetic inhibitor of activated Factor X (Xa), is approved for the indication of the prophylaxis of DVT in patients undergoing hip or knee replacement surgery.

C. Important Milestones in Product Development

The clinical studies conducted in the United States to support the proposed indications were conducted under INDs 56,611 and 59,151. End of Phase II meetings were held on March 10, 2000, June 16, 2000 and April 6, 2001. The CMC End of Phase II meeting was held on March 27, 2000 and Pre-NDA meeting was held on July 14, 2003. Because significant liver toxicity with use of Exanta was identified during the clinical trials, a special meeting held on October 9, 2003 to discuss the Risk Management Program for Exanta. CDER Office of Drug Safety (ODS) participated in the discussion.

D. Other Relevant Information

A Marketing Authorization Application (MAA) was submitted to the European Union (EU) in June 2002 and approved by France in December 2003 for the prevention of VTE in patients undergoing hip or knee replacement surgery. National Marketing Authorizations for additional 14 countries in EU are issued in June 2004. UK and Ireland have been withdrawn from the Mutual Recognition Procedure. However, approved dose in EU is 24 mg twice a day, instead of 36 mg twice a day proposed in this submission.

E. Important Issues with Pharmacologically Related Agents

EXANTA ® (ximelagatran) is the first oral direct inhibitor of thrombin. Iprivask (desirudin for injection) is an iv inhibitor of thrombin that was approved for the indication of the prevention of VTE in patients undergoing hip (not knee) replacement surgery.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

The prodrug ximelagatran is a poor inhibitor of thrombin, while the active metabolite, melagatran, is a potent, rapid and reversible direct thrombin inhibitor. Melagatran prolongs coagulation times in all species studied and inhibits the thrombin-induced aggregation of human, dog and rat platelets. In plasma coagulation assays such as Activated Partial Thromboplastin Time (APTT) and Prothrombin Time (PT) there is a variation in the response to fixed melagatran

plasma concentrations between available various test kits for each assay. Thrombin Time (TT) and Ecarin Clotting Time (ECT) are assays that have been used in order to characterize synthetic or recombinant direct thrombin inhibitors, such as melagatran and hirudin.

In the Safety Pharmacology study investigating intestinal motility in rats, the highest dose, 200 mmol/kg (95 mg/kg), of ximelagatran, inhibited intestinal motility. Oral, but not subcutaneous, administration of melagatran inhibited gastrointestinal motility at doses above 10 mmol/kg (4.3 mg/kg). Based on the equal exposure to melagatran after sc and oral administration it was concluded that the effect is elicited from the mucosal side of the gastrointestinal tract. High doses of melagatran given iv to dogs induced vasodilatation and increased vascular permeability, which was explained by histamine release. No liver toxicity or cardiac toxicity were reported from pre-clinical toxicology studies.

III. Human Pharmacokinetics and Pharmacodynamics

According to the sponsor's report, ximelagatran has following PK/PD profiles.

A. Pharmacokinetics

After oral administration to healthy subjects, the absorption of ximelagatran and the bioconversion to melagatran is rapid. The bioavailability of melagatran after oral dosing with ximelagatran to healthy subjects is about 20%, with low inter- and intra-individual variability. Melagatran is mainly excreted unchanged in urine with a renal clearance that corresponds to the glomerular filtration rate. The half-life of melagatran is about 3 hours after oral dosing with ximelagatran to young healthy subjects.

The pharmacokinetics of melagatran, following oral administration of ximelagatran and parenteral administration of melagatran to healthy subjects, are dose proportional, i.e., the exposure of melagatran increases linearly in proportion to the given dose (15 to 60 mg). No time-dependent changes in the pharmacokinetics of melagatran are observed during repeated oral dosing with ximelagatran to healthy subjects. The interindividual variability in melagatran exposure is low (coefficient of variation (CV) ~20%) and the intraindividual variability is even lower (CV ~10%).

The pharmacokinetics of melagatran, following oral administration of ximelagatran and parenteral administration of melagatran, are consistent across the different patient populations studied, and in agreement with pharmacokinetic properties observed in healthy subjects. After oral administration of ximelagatran, the half-life of melagatran is about 4 to 5 hours in the patient populations studied, which is longer than in young healthy subjects. This appears to a large extent to be due to the age-related lower renal function in patients.

The interindividual variability of melagatran exposure is higher for patients (CV ~50%) than for healthy volunteers, which to a large extent appears to be due to the interindividual variability in renal function. No time-dependent changes in the pharmacokinetics of melagatran are observed

for patients receiving long-term oral treatment with ximelagatran. The intraindividual variability of melagatran exposure is low (CV ~25%), suggesting that the pharmacokinetics of melagatran are predictable and reproducible.

Race has no influence on the absorption and metabolism of ximelagatran. Compared to patients with normal renal function (CrCL >80 mL/min), the melagatran exposure was about 1.5 and 2.5 times higher for patients with mild renal impairment (CrCL 50 to 80 mL/min) and moderate renal impairment (CrCL 30 to <50 mL/min), respectively.

After oral administration of ximelagatran to patients with severe renal impairment (CrCL 10 to 30 mL/min), the melagatran exposure was 5 times higher than for control subjects with normal renal function. Compared with the average for the studied patient populations, melagatran exposure is increased about 3-fold and the half-life is increased about 2-fold in patients with severe renal impairment. For patients with end-stage renal disease requiring dialysis, the clearance of melagatran is low and comparable to the non-renal clearance in healthy subjects. Melagatran clearance is increased during dialysis, suggesting that dialysis is effective in accelerating the elimination of melagatran. Mild to moderate liver impairment has no influence on the absorption or metabolism of ximelagatran. Gender, age, body weight and obesity have no influence on the absorption and metabolism of ximelagatran. The influence of these intrinsic factors on the elimination of melagatran appears to a large extent to be related to differences in renal function.

The extent of absorption and conversion of ximelagatran is not affected by food. Oral administration of ximelagatran with food causes a 1-hour delay of the tmax of melagatran but the AUC and Cmax of melagatran are unaffected. The pharmacokinetics of ximelagatran is not influenced by concomitant intake of alcohol. *In vivo* drug interaction studies with drugs that are substrates of CYP3A4 (nifedipine, atorvastatin, amiodarone, diazepam), CYP2C9 (diclofenac) and CYP2C19 (diazepam) showed no interaction and confirmed that ximelagatran has a low potential for drug interactions mediated by cytochrome P450 metabolism. Upon co-administration of ximelagatran and erythromycin to healthy subjects, the bioavailability of melagatran increased by approximately 80%. Erythromycin is known to interact with many drugs, as it is metabolized by and inhibits CYP3A4. However, this isoenzyme is not judged to be the site of the interaction as *in vitro* studies with ximelagatran and melagatran have shown that they are not substrates of CYP3A4. Concomitant chronic treatments had no significant influence on the pharmacokinetics of melagatran for any of drugs or drug classes evaluated in the studied patient populations.

B. Pharmacodynamics

Statistically significant concentration-response relationships were detected between melagatran plasma concentrations and inhibition of thrombin generation, platelet activation and thrombus formation. Oral administration of ximelagatran results in a predictable and rapid onset of action as indicated by statistically significant inhibition of thrombin generation, platelet activation and thrombus formation measured at 2 hours post-dosing.

Melagatran induces a relatively small prolongation of the Capillary bleeding time (CBT) (up to 35%) following doses of 24 to 72 mg oral ximelagatran. These prolongations were additive with therapeutic doses of ASA and diclofenac (up to 43% prolongation in combination) but synergistic with a therapeutic dose of clopidogrel (98% prolongation in combination).

Oral ximelagatran prolongs to varying degrees and with varying sensitivity conventional coagulation-time assays such as the activated partial thromboplastin time (APTT), activated clotting time (ACT), thrombin time (TT) and prothrombin time/international normalized ratio (PT/INR). The coagulation time assay prolongations occur in a concentration-dependent and non-linear (APTT, ACT, PT/INR) or linear (TT) manner. The APTT, ACT, and PT/INR assays are rather insensitive and show variable responses to melagatran concentrations whereas the TT is very sensitive to melagatran plasma concentrations. The ecarin clotting time (ECT), an experimental assay that is not widely available, was prolonged by melagatran in a concentration-dependent and linear manner. Oral dosing with ximelagatran results in a predictable and rapid onset of anticoagulation. The APTT is prolonged within 20 minutes of dosing with oral ximelagatran and peak prolongations are observed 2 hours postdosing. Melagatran-induced prolongation of the APTT is largely independent of the intrinsic (age, renal impairment, mild to moderate hepatic impairment, obesity, ethnicity, and disease) and extrinsic (food, alcohol, ASA, diclofenac, clopidogrel, amiodarone, atorvastatin, erythromycin, digoxin) factors studied.

The offset of action of 24 or 36 mg ximelagatran is rapid, with low but pharmacologically active concentrations of melagatran remaining for approximately 12 to 24 hours following the last dose. There are no currently available haemostatic agents that have been demonstrated to have clinical value in reversing the anticoagulant effects of ximelagatran.

IV. Description of Clinical Data and Sources

A. Overall Data

The development program for ximelagatran has been designed to offer an oral alternative anticoagulant to warfarin for major indications. Ximelagatran has been evaluated in various patient populations in large controlled, worldwide, clinical studies.

The development program includes 82 clinical studies with ximelagatran and/or melagatran (60 Phase 1 studies and 22 Phase 2 and 3 studies), in which 30698 subjects were randomized. A total of 17593 randomized subjects received the oral prodrug ximelagatran, or the active drug melagatran. In the long-term treatment populations, 6931 patients received ximelagatran, 5024 of whom received treatment for at least 6 months and 3509 for at least a year (up to 2.5 years in the pivotal SPORTIF studies and up to 4 years in the ongoing SPORTIF IV study).

The design of the clinical studies has varied between indications but some important features are common to most of them, as described below:

Overall design: Each Phase 3 study was conducted as a multi-center, randomized, parallel-group, comparator-controlled design. All studies were double-blind except for SH-TPA-0003 (SPORTIF III; which was open-label in design). All studies used a central laboratory for all protocol-specified laboratory measurements.

Control groups and randomization: Each Phase 3 study included a control group and treatment allocation randomized by a central randomization service (interactive voice response system [IVRS]) to reduce bias.

Independent adjudication of clinical endpoint events: In each pivotal study, the endpoint events (efficacy, all-cause mortality, and bleeding events) were identified and assessed by the investigator but the primary efficacy evaluation was based on endpoint events confirmed by an independent expert adjudication committee who were blinded to the treatment taken by the patient.

Independent committees: In addition to the independent committee adjudicating the endpoint events, each study incorporated an Independent Drug Safety Monitoring Board (DSMB; responsible for reviewing safety during the conduct of the study), and an Independent Executive Committee (EC; responsible for oversight of the conduct and reporting of the study).

B. Tables Listing the Clinical Trials

Table 2 Scope of the clinical development program for ximelagatran

Phase I studies	**61 studies[a]**
Phase II and III studies other than the pivotal studies for the proposed indications	**17 studies**
Pivotal Phase III studies in the proposed indications (detailed below)	**5 studies**

Pivotal Phase III studies for indications sought in this application

Indication	Treatment goal	Target patient population	Study number (name)	No. of patients randomized
OS: Prevention of VTE in patients undergoing knee replacement surgery.	Reduce the incidence of developing VTE (DVT or PE) following orthopedic surgery.	Patients undergoing primary TKR.	SH-TPO-0010 (EXULT A) SH-TPO-0012 (EXULT B)	4604
VTE-P: Long term secondary prevention of VTE after standard treatment for an episode of acute VTE.	Reduce the incidence of recurrent symptomatic VTE (DVT or PE) events.	Patients considered at risk of recurrence after completing standard treatment for primary VTE event.	SH-TPV-0003 (THRIVE III)	1233
AF: Prevention of stroke and other thromboembolic complications associated with atrial fibrillation.	Reduce the incidence of stroke and systemic embolic events.	Patients with nonvalvular atrial fibrillation at increased risk for stroke.	SH-TPA-0003 (SPORTIF III) SH-TPA-0005 (SPORTIF V)	7329[b]

[a] Includes 1 bioequivalence study of over-encapsulated warfarin tablets (Study SH-TP1-0024).
[b] Excludes 3 patients randomized to SPORTIF III in violation of the entrance criteria who were immediately discontinued and were excluded from all analyses (Section 2.7.3AF.3.1.1).
OS orthopedic surgery; VTE venous thromboembolism; DVT deep vein thrombosis; PE pulmonary embolism; TKR total knee replacement; VTE-P secondary prevention of VTE; AF nonvalvular atrial fibrillation.

C. Postmarketing Experience

There are no postmarketing data available as of July 2004.

D. Literature Review

The reviewer has searched the literatures related to ximelagatran up to July 2004 and incorporated them into the review.

V. Clinical Review Methods

A. How the Review was Conducted

The efficacy evaluation of the indication for prevention of VTE in patients undergoing knee replacement surgery is based on 2 clinical trials conducted by the sponsor (EXULT A and EXULT B). The sponsor conducted 3 multi-center, double-blind, parallel-group, Phase 3 studies in patients undergoing primary, elective TKR surgery (SH-TPO-0006, EXULT A and EXULT B). A total of 5284 patients were randomized in these 3 studies (1927 to ximelagatran 36 mg bid, 2247 to warfarin, and 1110 to ximelagatran 24 mg bid). All 3 studies evaluated ximelagatran administered postoperatively (beginning the morning after surgery) for 7 to 12 days compared to warfarin titrated to an INR of 2.5 (INR range 1.8 to 3.0) that was initiated the evening of the day of surgery.

Ximelagatran 36 mg bid was used in both studies EXULT A and EXULT B and ximelagatran 24 mg bid only was used in study SH-TPO-0006. The sponsor proposed 36 mg bid for this indication. Therefore, in this review, I mainly examine studies EXULT A and EXULT B for the efficacy evaluation of indication for prevention of VTE in patients undergoing knee replacement surgery.

For the indication of prolonged prophylaxis of VTE after a six-month anticoagulation treatment, the sponsor provided only one study, SH-TPV-0003 (THRIVE III). This was a multi-center, double-blind, parallel-group, placebo control study. Ximelagatran 24 mg bid or placebo were given as prolonged prophylaxis after a 6-month anticoagulation treatment for VTE. A total of 1233 patients were randomized, with 903 completing the study on the study drug (468 on ximelagatran 24 mg bid and 435 on placebo).

The medical officers from the Division of Cardio-Renal Drug Products will conduct the review for the indication of prophylaxis of stroke in patients with atrial fibrillation.

The safety evaluation included assessment of the data from all clinical studies which were divided into short term use ($\leq$35 days) and long-term use (> 35 days). There is no post-marketing safety data available.

Data from 10 Phase 2 and Phase 3 studies are presented in 4 pools based on the indication that was investigated. These indications were AF, VTE treatment (VTE-T), VTE secondary prevention (VTE-P) and post ACS. A fifth pool, the long-term exposure (LTE) pool, combines data from all of these indications.

The long-term (>35 days) safety of ximelagatran has been studied in a large population of 6931 patients comprising 3838 patients with atrial fibrillation (AF), 1236 patients for treatment (VTE-T), 612 patients for secondary prevention (VTE-P) of VTE and 1245 patients with recent acute coronary syndrome (post ACS). These 6931 patients received doses from 20 to 60 mg, for a median of 370 days, representing an overall exposure of 6768 patient-years. A total of 5024 patients were exposed to ximelagatran for at least 6 months (>180 days) and 3509 for at least 12 months (>360 days). All the studies were controlled, thus enabling comparison with a cohort of 6216 patients exposed for a median of 455 days mainly to the reference anticoagulant warfarin (n=4967), but also to placebo in a smaller number of patients (n=1249).

B. Overview of Materials Consulted in Review

In this review, I have examined material in following sections: Cover letter, Labeling, Summaries, and clinical study reports, including data listings and case report forms (CRF).

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The Division of Scientific Investigations has been consulted to conduct inspection for the following sites:

Indication	Protocol #	Site (Name and Address)	Number of Subjects
Prevention of stroke and other thromboembolic complications associated with atrial fibrillation	SH-TPA-005 (SPORTIF V)	(Center 50) Dr. Jalal K. Ghall Cardiac Centers of Louisiana, LLC 2551 Greenwood Road Suite 350 Shreveport, LA 71103	87
Prevention of venous thromboembolism (VTE) in patients undergoing knee replacement surgery	EXULT 290A and B	(Center 227) Dr. Anthony Chris 751B Victoria Strret South Kitchener, ON, Canada, N2M 5N4	116

Long term secondary prevention of VTE after standard treatment for an episode of acute VTE	SH-TPV-003 (THRIVE III)	(Center 502) Prof Dr. J. Harenberg Universitatsklinikum Mannheim Fakultat fur Klinische Medizin Ruprecht Karls Universitat Heidelberg I. Medizinische Klinik Theodor-Kutzer-Ufer 68167 Mannheim Germany	33
Prevention of stroke and other thromboembolic complications associated with atrial fibrillation	SH-TPA-003 (SPORTIF III)	(Center 172) Dr. Med T Horacek Evangel Krankenhaus Innere Abteilung Pferdebachstr 27 58455 Witten Germany	99

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor has submitted informed consent with each clinical trial protocol. According to the sponsor, the protocol and all amendments for this study were reviewed by an Independent Ethics Committee (IEC), and monitoring and audit procedures performed prior to, during, and upon completion of this study have verified that this study was conducted in accordance with the ethical principles.

E. Evaluation of Financial Disclosure

The sponsor submitted a FDA Form 3454 certifying that no investigator of any of the covered clinical studies had any financial interests to disclose.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Indication 1: prevention of VTE in patients undergoing elective knee replacement surgery

Oral ximelagatran 36 mg bid was superior to warfarin in reducing total VTE and/or all- cause mortality among patients undergoing TKR surgery in 2 large Phase III studies.

In the pooled EXULT A and EXULT B analyses, the incidence of total VTE and/or all-cause mortality among patients undergoing TKR was 21.7% for patients in the ximelagatran 36 mg

group and 30.2% for patients in the warfarin group, for an absolute risk reduction (ARR) of 8.6% ($p<0.001$). The ARR of 8.6% provided an number needed to treat (NNT, 1/ARR) of 12 (95% CI: 9 to 18).

The benefit was mainly due to a reduction in asymptomatic distal DVT diagnosed by venography which is not clinically meaningful. There were no clinically or statistically significant differences between ximelagatran and warfarin in reducing the frequency of proximal DVT, PE, and/or all-cause mortality in this population.

There are several major problems for comparison with warfarin as an active comparator in these two studies. Warfarin is not approved for the indication of prevention of DVT in patients undergoing elective knee replacement surgery. The comparison is unfair, because warfarin will take about 3-5 days to reach therapeutic level, while Exanta reaches therapeutic levels within hours. The results show that 33.1% - 35.2% of patients receiving warfarin had an INR less than 1.8 at postoperative day 3, and 24 – 26.9% % of patients receiving warfarin had an INR less than 1.8 at end of treatment (day 7 – 12). Because the study is designed to show superiority of ximelagatran, efficacy results for ximelagatran in these studies are still acceptable, considering warfarin group as placebo.

Indication 2: Prolonged prophylaxis VTE after a six-month anticoagulation treatment for a acute episode of VTE

Ximelagatran significantly reduced the recurrence rate of symptomatic, objectively confirmed VTE (the primary variable of the study) as compared to placebo over 18 months of treatment (cumulative risk of 2.8% versus 12.6%; hazard ratio 0.16; $p<0.0001$). The number of patients with a VTE event was 12 in the ximelagatran group and 71 in the placebo group. The number of patients with a PE event was lower in the ximelagatran group compared to the placebo group (2 and 23 in ximelagatran and placebo group respectively).

The results for the secondary variable, all-cause mortality, showed no significant difference between the treatment groups (1.1% vs 1.4% for patients on ximelagatran and placebo, respectively) during the 18 months.

B. General Approach to Review of the Efficacy of the Drug

The efficacy evaluation of indication for prevention of VTE in patients undergoing knee replacement surgery is based on 2 clinical trials conducted by the sponsor (EXULT A and EXULT B).

For the indication of prolonged prophylaxis VTE after a six-month anticoagulation treatment, the sponsor provided only one study, SH-TPV-0003 (THRIVE III). This was a multi-center, double-blind, parallel-group, placebo control study and this study was reviewed in detail.

The medical officers from the Division of Cardio-renal Drug Products will conduct the review for the indication of prophylaxis of stroke in patients with atrial fibrillation. Therefore, for the

efficacy evaluation regarding the indication of prophylaxis of stroke in patients with atrial fibrillation, please see Dr. Desai's Meidcal Officer Review on this submission.

C. Detailed Review of Trials by Indication

Indication 1: prevention of VTE in patients undergoing elective knee replacement surgery

The sponsor conducted 3 multi-center, double-blind, parallel-group, Phase 3 studies in patients undergoing primary, elective TKR surgery (EXULT A, EXULT B and SH-TPO-0006). A total of 5284 patients were randomized in these 3 studies (1927 to ximelagatran 36 mg bid, 2247 to well-controlled warfarin, and 1110 to ximelagatran 24 mg bid). All 3 studies evaluated ximelagatran administered postoperatively (beginning the morning after surgery) for 7 to 12 days compared to warfarin titrated to an INR of 2.5 (INR range 1.8 to 3.0) that was initiated the evening of the day of surgery.

Ximelagatran 36 mg bid was used in both studies EXULT A and EXULT B and ximelagatran 24 mg bid was used in study SH-TPO-0006. The sponsor proposed 36 mg bid for this indication. Therefore, in this review, I mainly examine studies EXULT A and EXULT B. Please see Appendix B for detailed review of the trials.

Indication 2: Prolonged prophylaxis VTE after a six-month anticoagulation treatment for an acute episode of VTE

The sponsor provided only one study, SH-TPV-0003 (THRIVE III) to support this indication. This was a multicentre, double-blind, parallel-group, placebo control study. Ximelagatran 24 mg bid or placebo were given as prolonged prophylaxis after a 6-month anticoagulation treatment for VTE. A total of 1233 patients were randomized, with 903 completing the study on the study drug (468 on ximelagatran 24 mg bid and 435 on placebo). Please see Appendix B for detailed review of the trial.

Indication 3: prevention of strokes and systemic embolic event in patients with nonvalvular atrial fibrillation

Division of Cardio-Renal Drug Products (HFD-110) was consulted to review this indication. Please see medical officer's review from HFD-110 for details.

D. Efficacy Conclusions

Indication 1: prevention of VTE in patients undergoing elective knee replacement surgery

Oral ximelagatran 36 mg bid was superior to warfarin in reducing total VTE and/or all- cause mortality among patients undergoing TKR surgery in 2 large Phase 3 studies. Table 3 summarizes

primary endpoints- incidence of total VTE and/or all-cause mortality (efficacy ITT population) from both studies EXULT A and EXULT B, and Pooled 36 mg bid.

Table 3: Incidence of total VTE and/or all-cause mortality (efficacy ITT population) – EXULT A, EXULT B, and Pooled 36 mg bid

				Ximelagatran vs Warfarin		
Study Treatment group	%	(n/N)	Exact 95% CI	%	95% CI	CMH p-value[a]
EXULT A						
Ximelagatran 36 mg	20.3	(128/629)	(17.3, 23.7)	-7.3	(-12.0, -2.5)	0.003
Warfarin	27.6	(168/608)	(24.1, 31.4)			
EXULT B						
Ximelagatran 36 mg	22.5	(221/982)	(19.9, 25.2)	-9.3	(-13.3, -5.4)	<0.001
Warfarin	31.9	(308/967)	(28.9, 34.9)			
Pooled						
Ximelagatran 36 mg	21.7	(349/1611)	(19.7, 23.8)	-8.6	(-11.6, -5.5)	<0.001
Warfarin	30.2	(476/1575)	(28.0, 32.6)			

Data derived from Table 5.3.5OS.3(36) – 2.1.1.
[a] Treatment differences were tested using the Cochran-Mantel-Haenszel (CMH) test, adjusted for the type of surgery performed (unilateral/bilateral).
Note: Total venous thromboembolism includes distal DVT, proximal DVT, and pulmonary embolism.
CI confidence interval; DVT deep vein thrombosis; ICAC Independent Central Adjudication Committee; ITT intention-to-treat.

In EXULT A, the incidence of total VTE and/or all-cause mortality among patients undergoing TKR was 20.3% for patients in the ximelagatran 36 mg group and 27.6% for patients in the warfarin group, for an absolute risk reduction (ARR) of 7.3% (p=0.003). The ARR of 7.3% provided a relative risk reduction (RRR) of 26.5% and a number needed to treat (NNT=1/ARR) of 14 (95% CI: 8 to 40).

EXULT B replicated the superior efficacy of ximelagatran 36 mg bid versus warfarin group demonstrated in EXULT A. In EXULT B, the incidence of total VTE and/or all-cause mortality among patients undergoing TKR was 22.5% for patients in the ximelagatran 36-mg group and 31.9% for patients in the warfarin group, for an ARR of 9.3%. (p<0.001). The ARR of 9.3% provided an RRR of 29.5% and an NNT (1/ARR) of 11 (95% CI: 8 to 19).

In the pooled EXULT A and EXULT B analyses, the incidence of total VTE and/or all-cause mortality among patients undergoing TKR was 21.7% for patients in the ximelagatran 36 mg group and 30.2% for patients in the warfarin group, for an ARR of 8.6% (p<0.001). The ARR of 8.6% provided an RRR of 28.1% and an NNT (1/ARR) of 12 (95% CI: 9 to 18).

However, the benefit was mainly due to a reduction in asymptomatic distal DVT diagnosed by venography which is not clinically meaningful (Table 4). There were no clinically or statistically significant differences between ximelagatran and warfarin in reducing the frequency of proximal DVT, PE, and/or all-cause mortality in this population.

Table 4: Objectively confirmed symptomatic and asymptomatic VTE over the entire study (efficacy ITT population) – EXULT A and B 36 mg bid

	EXULT A		EXULT B	
Component of the primary endpoint[a]	**Ximelagatran 36 mg % (n/N)**	**Warfarin % (n/N)**	**Ximelagatran 36 mg % (n/N)**	**Warfarin % (n/N)**
Asymptomatic total DVT[b]	19.8 (124/625)	27.4 (166/606)	21.9 (214/976)	31.4 (301/960)
Proximal DVT	2.1 (13/625)	3.8 (23/601)	3.1 (30/969)	3.4 (33/957)
Distal DVT[c]	19.2 (120/625)	26.7 (161/604)	21.4 (209/976)	31.1 (298/959)
Symptomatic total DVT				
Proximal DVT	0.5 (3/629)	0.7 (4/608)	0.4 (4/982)	0.2 (2/967)
Distal DVT	0.8 (5/629)	0.8 (5/608)	0.7 (7/982)	1.4 (14/967)
Pulmonary embolism	0.3 (2/629)	0.2 (1/608)	0.3 (3/982)	0.5 (5/967)
Death	0.5 (3/629)	0.2 (1/608)	0.7 (7/982)	0.3 (3/967)

Data derived from Tables 5.3.5OS.3(36) – 2.3 and 2.14.2.

[a] Each patient is counted only once within the categories of Asymptomatic DVT and Symptomatic DVT using the worst case principle.

[b] Asymptomatic DVT recorded at mandatory venography. N excludes patients included in efficacy ITT solely because of a symptomatic event or death (these patients are counted in the N for the symptomatic events).

[c] Distal DVT = Total DVT minus proximal DVT.

DVT deep vein thrombosis; ITT intention-to-treat.

In EXULT A, the incidence of proximal DVT, PE, and/or all-cause mortality among patients undergoing TKR was 2.7% for patients randomized to ximelagatran 36 mg and 4.1% for patients randomized to warfarin (1.4% reduction; p=0.171). In EXULT B, the incidence of proximal DVT, PE, and/or all-cause mortality among patients undergoing TKR was 3.9% for patients randomized to ximelagatran 36 mg and 4.1% for patients randomized to warfarin (0.3% reduction; p=0.802).

Approximately 95% of patients in each treatment group had unilateral surgery performed and, therefore, the reductions in total VTE and/or all-cause mortality for the combined surgeries approximated the reduction for patients with unilateral surgery.

In both studies, a higher frequency of total VTE and/or all-cause mortality was observed across both treatment groups for female patients (relative to males), older patients (relative to younger patients), patients enrolled at sites in Canada (relative to those in the United States and the rest of the world).

In EXULT A ximelagatran 24 mg bid was not superior to warfarin in reducing the rate of total VTE and/or all-cause mortality (27.6% warfarin vs 24.9% ximelagatran 24 mg).

There are several major problems for comparison of ximelagatran with warfarin in these two studies. Warfarin is not approved for this short-term indication. The comparison is unfair, because warfarin will take about 3-5 days to reach therapeutic level, while Exanta reaches therapeutic levels within hours. The results show that 33.1% - 35.2% of patients receiving

warfarin had an INR less than 1.8 by postoperative day 3, and 24 – 26.9% % of patients receiving warfarin had an INR less than 1.8 by end of treatment (day 7 – 12).

Indication 2: Prolonged VTE prophylaxis after a six-month anticoagulation treatment for an acute episode of VTE

Ximelagatran significantly reduced the recurrence rate of symptomatic, objectively confirmed VTE as compared to placebo over 18 months of treatment (cumulative risk of 2.8% versus 12.6%; hazard ratio 0.16; p<0.0001). The number of patients with a VTE event was 12 in the ximelagatran group and 71 in the placebo group. The number of patients with a PE event was lower in the ximelagatran group compared to the placebo group (2 and 23 in ximelagatran and placebo group respectively (Table 5).

Table 5: The number of patients with VTE events in ximelagatran and placebo groups

Event	Ximelagatran	Placebo
Total VTE	12	71
DVT only	10	48
PE only	2	15
DVT and PE	0	8

The results for the secondary variable, all-cause mortality, showed no significant difference between the treatment groups (1.1% vs 1.4% for patients on ximelagatran and placebo, respectively) during the 18 months.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

A1. Safety of Ximelagatran in Patients Undergoing a Surgical Procedure (use ≤35 days)

A total of 1913 patients undergoing keen surgery were exposed to ximelagatran 36 mg bid, 1097 patients were exposed to ximelagatran 24 mg bid, and 2226 patients were exposed to warfarin with a mean duration of exposure of 8 days for the ximelagatran groups.

Overall, more than 55% of patients in each treatment group experienced at least 1 adverse event (AE). The frequency of AEs was similar between the treatment groups. Post-operative complications were mostly related to bleeding and were reported at a higher frequency in the ximelagatran groups (17% at 36 mg, 23% at 24 mg) than in the warfarin groups (15% and 20%, respectively).

There were 18 deaths (12 patients exposed to ximelagatran and 6 patients exposed to warfarin). Of the 12 fatal SAEs reported among the 3010 patients who received ximelagatran (0.4%), 2 were fatal bleeding events (both on ximelagatran 36 mg). Six were fatal events in which 'PE could not be excluded'. The last 4 fatal SAEs in patients who received ximelagatran were adjudicated as 'death not associated with VTE or bleeding'. The investigators reported the causes of death in 1 patient on treatment as sudden death, and in the other 3 patients after treatment as intestinal perforation, acute MI, and pneumonia. Of the 6 deaths reported among the 2226 patients who received warfarin (0.3%), 2 were fatal events in which 'PE could not be excluded'. The causes of death in 2 patients on treatment were arrhythmia and MI and in the other 2 after treatment were colon carcinoma and AMI. None of the on-treatment major bleeding events in the ximelagatran 24 mg group or warfarin group was fatal.

Adverse events leading to discontinuation of study drug (DAEs) were higher in the ximelagatran 36 mg group (2.6%) than in the warfarin group (2.0%) as well as in the ximelagatran 24 mg group compared to warfarin (3.1% versus 2.1%, respectively) with postoperative complication the most common reason for a DAE.

With respect to on-treatment adjudicated events, major bleeding occurred in 0.9% of patients treated with ximelagatran 36 mg, compared with 0.5% of patients treated with warfarin. Major/minor bleeding occurred in 5.1% of patients treated with ximelagatran 36 mg and 4.1% of patients treated with warfarin. Similar results were observed for ximelagatran 24 mg bid compared with warfarin.

Incidences of ALAT elevation reported as AEs were higher in the 36 mg ximelagatran group (2.1%) than other groups (1.3-1.5% warfarin; 1.4% ximelagatran 24 mg). There were no hepatobiliary fatal SAEs, non-fatal SAEs or DAEs in either ximelagatran group. During the follow-up period (4-6 weeks), 8 patients in the ximelagatran group, and 1 in the warfarin group had their first ALAT elevation >3x ULN. However, patients were followed up only for 4-6 weeks post operation. Drug effects on liver toxicity beyond 4-6 weeks are unknown. It should be noted that elevation of hepatic enzymes was typically seen between 2nd and 6th month after starting ximelagatran.

In both Exult A and Exult B, the proportion of patients with coronary artery disease adverse events (MI or ischemia/angina) was higher in the ximelagatran groups than in the warfarin groups. The proportion of patients with coronary artery disease adverse events was statistically significantly higher in the ximelagatran group (20/2677, 0.75%) than in the warfarin group (5/1907, 0.26%) in the TKR population (Exult A and Exult B) (p=0.02800). The proportion of patients with MI was also higher in the ximelagatran group (16/2677, 0.60%) than in the warfarin group (4/1907, 0.21%) in the TKR population (p=0.04951). There were no appreciable differences between the treatment groups for underlying diseases which include hypertension, hypercholesterolemia, diabetes mellitus, coronary atherosclerosis, as well as age, gender and weight. Considering ximelagatran as an anticoagulant with potential to treat MI, these results are worrisome.

A2. Clinical Safety of Ximelagatran in Patients with long-term exposure (> 35 days)

A total of 6931 patients received doses from 20 to 60 mg of ximelagatran for > 35 days, with a median of 370 days. A total of 5024 patients were exposed to ximelagatran for at least 6 months and 3509 for at least 12 months. A total of 6216 patients were exposed for a median of 455 days to warfarin (n=4967) and placebo (n=1249).

A2.1 Death

There were 224 fatal cases during active treatment, 112 in the ximelagatran treatment groups and 112 in the comparator groups. A further 331 patients died after stopping study drug (166 in the ximelagatran group and 165 in the comparator group). There was no difference between the treatment groups. The most common fatal SAE was myocardial infarction.

A2.2 Non-fatal SAE

A total of 26.3% of patients in the ximelagatran group and 27.1% of patients in the comparator group experienced a non-fatal SAE during treatment. A further 5.5% of patients in the ximelagatran group and 4.3% of patients in the comparator group experienced a non-fatal SAE after stopping study drug. The most common non-fatal SAEs were cardiovascular events. The most common non-fatal SAEs considered to be causally related to ximelagatran were increases in hepatic enzymes.

A2.3 Discontinuation

The proportion of patients who discontinued study drug was higher in the ximelagatran group (1189/6931, 17.2%) than in the comparator group (801/6216, 12.9%). This was mostly due to the discontinuation of study drug due to elevated liver function tests. Data from discontinuation of ximelagatran secondary to AEs indicates that coronary artery disorders were more common in the ximelagatran group (0.6% vs. 0.3%) whereas thromboembolic events were more common DAEs in the comparators group (1.3% vs. 0.4%), because of placebo control. Other common causes of discontinuations included bleeding events, with no difference between ximelagatran and the comparators, except for haematuria and rectal haemorrhage/ melaena, which caused slightly more discontinuations in the ximelagatran group than in the comparators group.

A2.4 Bleeding Events

In patients with AF, ximelagatran 36 mg was associated with fewer major bleeding events than warfarin (AF pool; 2.4% and 3.4% for the ximelagatran and warfarin group, respectively, p=0.0288). However, there were no significant differences for major bleeding events between the groups in each of 2 pivotal studies (SH-TPA-0003 and STP-0005). In patients with acute VTE, ximelagatran 36 mg was associated with numerically fewer major bleeding events than enoxaparin/warfarin. In patients undergoing extended secondary prophylaxis for VTE, ximelagatran 24 mg was associated with a similar incidence of major bleeding events to placebo. A total of 38 patients experienced bleeding-related SAEs with a fatal outcome, 19 cases in each treatment group (ximelagatran or comparator).

A2.5 Hepatobiliary toxicity

In patients receiving long-term administration of ximelagatran (>35 days) an increase in ALAT >3xULN occurred in 6-13% (average 7.6%, 531/6948) compared to 0-2% (average 1.1%, 68/6230) of patients receiving comparator treatments. Including local laboratory data, 620 patients showed an ALAT elevation >3xULN during the studies, 546 patients in the ximelagatran group (cumulative incidence 7.8%) and 74 patients in the comparator group (cumulative incidence 1.1%). Among the 531 patients in the ximelagatran group who presented with an ALAT >3xULN, 206 (39%) completed the study on study drug. The remaining 325 patients (61%) discontinued study drug prematurely.

The time pattern of ALAT elevations was consistent across patients. The increase typically occurred between 1 and 6 months after the initiation of ximelagatran. Before and after this time frame the incidence of ALAT increase was similar to comparators. Of the 531 ximelagatran-treated patients who had an ALAT elevation >3xULN recorded by the central laboratory, 502 (95%) had their ALAT return to <2xULN with treatment continued in 235 patients (46.8%). Most cases show a peak of ALAT within the first 2 to 3 months post-randomization and a decline back towards baseline within about 6 months post-randomization.

Eighteen patients who discontinued study drug with elevations of ALAT subsequently resumed treatment after ALAT had returned to the normal range. Of these 18 patients, 2 again experienced elevations of ALAT after drug was resumed.

An evaluation of potential risk factors for increase in ALAT indicated an increased risk in the Post ACS ($p=0.0009$), and VTE-T ($p=0.0003$) populations and also in female patients ($p=0.0002$) patients with low BMI (<27 kg/m2) ($p<0.0001$) and patients receiving concomitant treatment with statins ($p=0.019$); Asian patients were found to have a decreased risk ($p=0.0038$). Although single factor identified above may not be strong enough to eliminate the subgroup population, presence of 2 or more risk factors, such as, female patients with low body weight or who are taking a statin, should be considered a contraindication for ximelagatran.

ALAT >3xULN was associated with bilirubin >2xULN (within one month following the rise in ALAT) in 0.53% (37/6948) of all patients who were exposed to ximelagatran >35 days as compared to 0.08% (5/6230) of patients exposed to comparators. Nine ximelagatran-treated patients (24.3%, 9/37) died with concomitant ALAT >3xULN and bilirubin >2xULN. Among these, 3 died from heart failure; 3 died from carcinomas with hepatic metastases; 2 (ID# 7259, and 7859) died from GI bleeding with coagulopathy (1 with biopsy documented hepatic necrosis) and 1 (ID# 5442) died from hepatitis B. Liver failure/toxicity by ximelagatran might have caused or at least contributed to these deaths. Only one autopsy was done in these 9 deaths and it showed a small, friable and diffusely mottled liver suggestive of severe diffuse hepatic necrosis.

A2.6 Adverse Events of Coronary Artery Disease

In all study populations except the post acute coronary syndromes, the proportion of patients with coronary artery disease adverse events was higher in the ximelagatran groups than in the comparator groups (7.0% and 6.7% for the AF pool, 1.3% and 0.1% for the VTE-T pool and

2.6% and 2.0% for the VTE-P pool, for the ximelagatran and comparator groups, respectively). This trend was consistent across the pools for myocardial infarction.

The proportion of patients with coronary artery disease adverse events was statistically significantly higher in the ximelagatran group (32/1848, 1.7%) than in the warfarin/placebo group (12/1859, 0.7%) in VTE (VTE-T + VTE-P) population (p=0.00411). Proportion of patients with MI was also significantly higher in the ximelagatran group (13/1848, 0.7%) than in the warfarin/placebo group (3/1859, 0.16%) in VTE population (p=0.01183). There were no appreciable differences between the treatment groups for underlying diseases. Considering ximelagatran as an anticoagulant with potential to treat MI, these results are worrisome.

B. Description of Patient Exposure

An overview of days of exposure to treatment for the surgical population who received study drug for ≤ 35 days is provided in Table 6.

Table 6: Overview of exposure: Warfarin-comparison Pool

	Warfarin-comparison Pool			
	36-mg (EXULT) Pool		24-mg Pool	
Exposure	Ximelagatran 36 mg bid (n=1913)	Warfarin[a] (n=1897)	Ximelagatran 24 mg bid (n=1097)	Warfarin[a] (n=1081)
Days of exposure				
1 to 6, n (%)	113 (5.9)	859 (45.3)	60 (5.5)	505 (46.7)
7 to 9, n (%)	1391 (72.7)	825 (43.5)	804 (73.3)	459 (42.5)
10 to 12, n (%)	397 (20.8)	207 (10.9)	225 (20.5)	115 (10.6)
>12, n (%)	12 (0.6)	6 (0.3)	8 (0.7)	2 (0.2)
Mean (SD)	8.1 (1.8)	6.7 (2.3)	8.1 (1.9)	6.7 (2.2)
Range	1 to 14	1 to 14	1 to 14	1 to 13
Total (days/years)	15400/42.2	12750/34.9	8831/24.2	7271/19.9

Data derived from the AstraZeneca safety database.
[a] Per the definition of exposure, the first dose of warfarin given on the evening of surgery is not included in the reported warfarin exposure.
SD standard deviation.

In the 36-mg (EXULT) Pool, 1913 and 1897 patients were exposed to active ximelagatran 36 mg and warfarin, respectively. In the 24 mg Pool, 1097 patients received active ximelagatran 24 mg and 1081 patients received warfarin. In total, the Warfarin-comparison Pool comprised 1913 patients exposed to ximelagatran 36 mg, 1097 patients exposed to ximelagatran 24 mg, and 2226 patients exposed to warfarin. Mean days of exposure were 8.1 days for ximelagatran 24 mg or 36 mg, 6.7 days for warfarin, which does not include the first dose of warfarin given the evening of surgery. More patients (73%) in each of the ximelagatran 24-mg or 36-mg groups remained on treatment from 7 to 9 days, compared to the warfarin group (43%). This finding probably reflects warfarin treatment being withheld due to INRs within normal range.

For non-Surgical Populations who received study drug for > 35 days, data from 10 Phase II and Phase III studies, in which patients received ximelagatran for up to 4 years, are presented in 4 pools based on the indication that was investigated. These indications were AF, VTE treatment

(VTE-T), VTE secondary prevention (VTE-P) and post ACS. A fifth pool, the long-term exposure (LTE) pool, combines data from all of these indications.

The long-term (>35 days) safety of ximelagatran has been studied in a large population of 6931 patients comprising 3838 patients with atrial fibrillation (AF),1236 patients for treatment (VTE-T) and 612 patients for secondary prevention (VTE-P) of venous thromboembolism (VTE) and 1245 patients with recent acute coronary syndrome (post ACS). These 6931 patients received doses from 20 to 60 mg, for a median of 370 days, representing an overall exposure of 6768 patient-years. A total of 5024 patients were exposed to ximelagatran for at least 6 months (>180 days) and 3509 for at least 12 months (>360 days). All the studies were controlled, thus enabling comparison of a cohort of 6216 patients exposed to ximelagatran for a median of 455 days mainly to the reference anticoagulant warfarin (n=4967), but also to placebo in a smaller number of patients (n=1249).

Demographic and other characteristics: the long-term exposure (LTE) pool

The treatment groups were well-balanced regarding demographic characteristics. Nearly all (>93%) of the patients were Caucasian and the majority (64%) were males. The majority of the females (89%) were over 45 years of age (an arbitrary cut-off to distinguish females of childbearing potential). Most patients (64.1%) were 65 years or over although there was a wide range of ages in the program (18 to 97 years). Demographic characteristics of all treated patients in the LTE pool are shown in Table 7.

Table 7: Demographic description: LTE pool

Drug:	ximelagatran		comparators	
	n	%	n	%
Total	**6931**	**100.0**	**6216**	**100.0**
Gender				
Male	4462	64.4	3998	64.3
Female	2469	35.6	2218	35.7
Females aged ≤45	*261*	*10.6*	*247*	*11.1*
Females aged >45	*2208*	*89.4*	*1971*	*88.9*
Race				
Caucasian	6467	93.3	5778	93.0
Black	113	1.6	94	1.5
Asian	264	3.8	254	4.1
Other	87	1.3	90	1.4
Age (years)				
<65	2487	35.9	2188	35.2
65-74	2417	34.9	2171	34.9
≥75	2027	29.2	1857	29.9
Mean	66.3		66.5	
Range	18 - 97		18 - 97	
Weight (kg)				
<50	82	1.2	78	1.3
50-100	5759	83.1	5178	83.3
>100	1082	15.6	953	15.3
Missing	8	0.1	7	0.1
BMI (kg/m^2)				
<25	1768	25.5	1604	25.8
25-30	2870	41.4	2544	40.9
>30	2255	32.5	2035	32.7
Missing	38	0.5	33	0.5
Calc. CrCL (mL/min)				
<30	40	0.6	31	0.5
≥30<50	697	10.1	664	10.7
≥50<80	2417	34.9	2088	33.6
≥80	3665	52.9	3351	53.9
Missing	112	1.6	82	1.3
History of diabetes mellitus				
Yes	1369	19.8	1202	19.3
No	5562	80.2	5014	80.7

Note that the % of females for the sub-sets ≤45 and >45 are % of the total number of females

C. Methods and Specific Findings of Safety Review

1: The surgical population who received study drug for ≤ 35 days

The treatment groups were well-balanced regarding demographic characteristics. Nearly all (>94%) of the patients were Caucasian and there were more females (62%) than males (38%). Approximately two-thirds of patients were 65 years or older (66%) although there was a wide range of ages in the program (24 to 91 years of age). There were 18% to 20% of patients above 100 kgs and about 50% with a BMI >30 kg/m^2 . A total of 16 patients had severe renal impairment (CrCL <30 mL/min) (in violation of entry criteria). Approximately 35% of the patients had some renal impairment (CrCL <80 mL/min).

1.1 Most common AEs –Warfarin-comparison Pool

Overall, more than 55% of patients in each treatment group experienced at least 1 AE. The frequency of AEs was similar in the ximelagatran 24-mg and the warfarin groups (66% and 61%, respectively). The frequency of AEs was similar in the ximelagatran 36-mg and the warfarin groups (58% and 56%, respectively).

The incidence of SAEs was higher in the ximelagatran treatment groups than in the concurrent warfarin group (3.8 vs. 3.2% for 36 mg of ximelagatran vs. warfarin and 3.2% vs. 2.7% for 24 mg of ximelagatran vs. warfarin).

The incidence of discontinuations was higher in the ximelagatran treatment groups than in the concurrent warfarin group (2.6% vs. 2.0% for 36 mg of ximelagatran vs. warfarin and 3.1% vs. 2.1% for 24 mg of ximelagatran vs. warfarin respectively).

1.2 Deaths

There were 18 fatal cases in the Warfarin-comparison Pool (12 patients exposed to ximelagatran and 6 patients exposed to warfarin) with 4 and 3 fatalities occurring during the treatment period, respectively.

Of the 12 fatal SAEs reported among the 3010 patients who received ximelagatran (0.4%), 2 were fatal bleeding events (both on ximelagatran 36 mg). Six were fatal events in which 'PE could not be excluded'. The last 4 fatal SAEs in patients who received ximelagatran were adjudicated as 'death not associated with VTE or bleeding'. The investigators reported the causes of death in 1 patient on treatment as sudden death, and in the other 3 patients after treatment as intestinal perforation, acute myocardial infarction, and pneumonia.

Of the 6 fatal SAEs reported among the 2226 patients who received warfarin (0.3%), 2 were fatal events in which 'PE could not be excluded'. The last 4 fatal SAEs in warfarin-treated patients were adjudicated as 'death not associated with VTE or bleeding'. The investigators reported the causes of death in 2 patients on treatment as arrhythmia and MI and in the other 2 after treatment as colon carcinoma and acute myocardial infarction.

Two fatal cases of GI hemorrhage occurred during treatment in the ximelagatran 36-mg group. The number and percentage of patients who died during or after treatment in the Warfarin-comparison Pool is presented in Table 8.

Table 8: Number (%) of patients with fatal SAEs during or after treatment, presented by preferred term: The Warfarin- comparison Pool (exposed safety population)

	Warfarin-comparison Pool															
	36-mg (EXULT) Pool								24-mg Pool							
	Ximelagatran 36 mg				Warfarin[a]				Ximelagatran 24mg				Warfarin[a]			
	During		After		During		After		During		After		During		After	
	(n=1913)		(n=1883)		(n=1897)		(n=1885)		(n=1097)		(n=1083)		(n=1081)		(n=1070)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total no. of patients with fatal SAE	*4*	*(0.2)*	*6*	*(0.3)*	*2*	*(0.1)*	*2*	*(0.1)*	*0*		*2*	*(0.2)*	*1*	*(0.1)*	*2*	*(0.2)*
GI haemorrhage	2	(0.1)	0		0		0		0		0		0		0	
Hypotension	1	(0.1)	0		0		0		0		0		0		0	
Multiorgan failure	1	(0.1)	0		0		0		0		0		0		0	
Myocardial infarction	1	(0.1)	2	(0.1)	1	(0.1)	2	(0.1)	0		0		0		1	(0.1)
Sudden death	1	(0.1)	0		0		0		0		0		0		0	
AV block	0		0		1	(0.1)	0		0		0		0		0	
Cardiac arrest	0		0		1	(0.1)	0		0		0		1	(0.1)	0	
Colon carcinoma	0		0		0		0		0		0		0		1	(0.1)
Death	0		1	(0.1)	0		0		0		1	(0.1)	0		0	
Embolism pulmonary	0		2	(0.1)	0		1	(0.1)	0		0		1	(0.1)	1	(0.1)
Intestinal perforation	0		0		0		0		0		1	(0.1)	0		0	
Pneumonia	0		1	(0.1)	0		0		0		0		0		0	

Data derived from Appendix Table 2.7.4SP.7.3-6 and individual CSRs.
The events are sorted by the ximelagatran 36 mg during treatment column.
[a] One patient (SH-TPO-0010-504-9089) was part of the 752 patients common to both warfarin groups and is therefore, counted twice: once in the 36 mg warfarin comparison and once in the 24 mg warfarin comparison. This patient had 2 fatal SAEs: pulmonary embolism and myocardial infarction.
SAE serious adverse event; GI gastrointestinal.

1.3 Serious Adverse Events other than deaths – Warfarin-comparison Pool

Within both 36-mg (EXULT) and 24-mg pools, the frequency of non-fatal SAEs was higher in either ximelagatran treatment group (3.7% and 3.5%) than in their respective warfarin groups (3.1 and 2.6%) during treatment.

Including both during study treatment and after study treatment periods, the most frequently occurring non-fatal SAEs were postoperative complications and myocardial infarction, which occurred more frequently in the ximelagatran groups, and atrial fibrillation, which occurred more frequently in the warfarin group.

The number of patients with the most commonly reported non-fatal SAEs during and after treatment is presented in Table 9.

Table 9 Number (%) of patients with the most commonly reported non- fatal SAEs during and after treatment: The Warfarin- comparison Pool (exposed safety population)

	Warfarin-comparison Pool															
	36-mg (EXULT) Pool								24-mg Pool							
	Ximelagatran 36 mg				Warfarin				Ximelagatran 24mg				Warfarin			
	During		After		During		After		During		After		During		After	
	(n=1913)		(n=1883)		(n=1897)		(n=1885)		(n=1097)		(n=1083)		(n=1081)		(n=1070)	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total no. of patients with non-fatal SAE	*70*	*(3.7)*	*48*	*(2.5)*	*59*	*(3.1)*	*51*	*(2.7)*	*38*	*(3.5)*	*36*	*(3.3)*	*28*	*(2.6)*	*37*	*(3.5)*
Postoperative complications	15	(0.8)	15	(0.8)	8	(0.4)	13	(0.7)	4	(0.4)	10	(0.9)	2	(0.2)	9	(0.8)
Fibrillation atrial	5	(0.3)	0		5	(0.3)	4	(0.2)	1	(0.1)	0		4	(0.4)	2	(0.2)
Ileus	5	(0.3)	0		3	(0.2)	1	(0.1)	1	(0.1)	0		1	(0.1)	1	(0.1)
Myocardial infarction	5	(0.3)	2	(0.1)	1	(0.1)	0		6	(0.5)	1	(0.1)	1	(0.1)	0	
GI haemorrhage	3	(0.2)	0		2	(0.1)	1	(0.1)	1	(0.1)	2	(0.2)	2	(0.2)	2	(0.2)
Pneumonia	3	(0.2)	2	(0.1)	1	(0.1)	1	(0.1)	1	(0.1)	0		1	(0.1)	1	(0.1)
Chest pain	2	(0.1)	1	(0.1)	1	(0.1)	1	(0.1)	1	(0.1)	0		1	(0.1)	3	(0.3)
INR increased	1	(0.1)	0		5	(0.3)	2	(0.1)	0		1	(0.1)	0		2	(0.2)
Dyspnoea	0		0		1	(0.1)	0		1	(0.1)	4	(0.4)	1	(0.1)	0	
Urinary tract infection	0		4	(0.2)	1	(0.1)	0		1	(0.1)	0		0		0	

Data derived from Appendix Table 2.7.4SP.7.3-18.
Note: AEs reported by at least 3 patients in any column are presented. The events are sorted by the ximelagatran 36 mg during treatment column.
SAE serious adverse event; GI gastrointestinal, INR International Normalised Ratio.

Please see the section of 1.7: coronary artery disease adverse events for more details about the adverse events related to myocardial infarction and coronary artery diseases.

1.4 Discontinuations due to AEs - Warfarin-comparison Pool

Discontinuations due to AEs (DAE) were slightly higher in the ximelagatran 36-mg group (2.6%) than warfarin (2.0%) as well as in the ximelagatran 24-mg group comparison to warfarin (3.1% versus 2.1%, respectively); this was driven by an excess of bleeding-related AEs. Regardless of treatment group, the most common reason for a DAE was postoperative complication, with a similar incidence between treatment groups.

1.5 Bleeding events in the Warfarin-comparison Pool

Major bleeding events were uncommon overall and higher in ximelagatran groups than warfarin groups during the treatment period (0.9% ximelagatran 36 mg, 0.5% warfarin; 0.9% ximelagatran 24 mg, 0.6% warfarin). In the 36-mg Pool, the difference in the frequencies of major bleeding events between ximelagatran and warfarin was 0.4% (95% CI, –0.1% to1.0%). Similar results were noted for the 24-mg Pool (ximelagatran-warfarin, 0.3%; 95% CI, -0.5% to 1.0%). The proportions of patients with on-treatment major bleeding events in the Warfarin-comparison Pool, for both the 36-mg and 24-mg Pools, are summarized in Table 10.

Table 10 Number (%) of patients with on- treatment adjudicated major bleeding events: Warfarin- comparison Pool (exposed safety population)

Warfarin-comparison Pool	Event rate n/N	%	95% CI	Event rate n/N	%	95% CI	Difference[a] %	95% CI	Nominal p-value[b]
36-mg (EXULT) Pool	**Ximelagatran 36 mg bid**			**Warfarin**					
SH-TPO-0010	6/767	0.8	(0.3; 1.7)	5/752	0.7	(0.2; 1.5)	0.1	(-0.7; 1.0)	0.773
SH-TPO-0012	12/1146	1.0	(0.5; 1.8)	5/1145	0.4	(0.1; 1.0)	0.6	(-0.1; 1.3)	0.086
Pooled	18/1913	0.9	(0.6; 1.5)	10/1897	0.5	(0.3; 1.0)	0.4	(-0.1; 1.0)	0.135
24-mg Pool	**Ximelagatran 24 mg bid**			**Warfarin**					
SH-TPO-0006	5/343	1.5	(0.5; 3.4)	2/329	0.6	(0.1; 2.2)	0.8	(-0.7; 2.4)	0.287
SH-TPO-0010	5/754	0.7	(0.2; 1.5)	5/752	0.7	(0.2; 1.5)	0.0	(-0.8; 0.8)	0.987
Pooled	10/1097	0.9	(0.4; 1.7)	7/1081	0.6	(0.3; 1.3)	0.3	(-0.5; 1.0)	0.498

Data derived from Appendix Tables 2.7.4SP.7.4.1(36)-14 and 2.7.4SP.7.4.1(24)-14.
[a] Difference in event rates (ximelagatran-warfarin).
[b] Cochran-Mantel-Haenszel chi square test.
bid twice daily; CI confidence interval.

Adjudication criteria for major bleeding were medical or surgical intervention for the reported bleeding event and/or bleeding index >2. The distribution of all major bleeding events by adjudication criteria was similar to the distribution of on-treatment events.

In the 36-mg Pool, the most common locations of on-treatment major bleeding events in the ximelagatran group were wound hematoma, gastrointestinal bleeding, and wound bleeding. Events in these locations occurred with comparable frequency in the warfarin group. In the 24-mg Pool, wound hematoma and gastrointestinal bleeding were more frequent in the ximelagatran group than in the warfarin group, while wound bleeding occurred only in the warfarin group. There were no major nasal or urinary bleeding events in any treatment group.

The frequencies of patients with on-treatment major/minor bleeding events were higher in ximelagatran groups than warfarin groups (5.1% ximelagatran 36 mg, 4.1% warfarin; 5.7% ximelagatran 24 mg, 4.7% warfarin).

Two fatal on-treatment major bleeding events occurred in the ximelagatran 36-mg group; both events were coded as GI hemorrhage. None of the on-treatment major bleeding events in the ximelagatran 24-mg group was fatal. There were no fatal on-treatment bleeding events in the warfarin-groups.

Two critical-site on-treatment bleeding events occurred during ximelagatran treatment (0.9%). One patient (SH-TPO-0012-029-10779) treated with ximelagatran 36 mg developed postoperative confusion just after surgery. A CT scan revealed a subdural hematoma. The other patient (SH-TPO-0010-016-2131), who was treated with ximelagatran 24 mg, was found by CT scan to have a left frontal brain hemorrhage after 6 days of postoperative confusion; a biopsy revealed a malignant glioma; the reported AE was coded as cerebral hemorrhage. No

bleeding at other critical sites (intraspinal, intraocular, retroperitoneal, or pericardial) was reported in the ximelagatran groups. None of the major bleeding events reported in warfarin-treated patients occurred at a critical site (intracranial, intraspinal, intraocular, retroperitoneal, or pericardial).

In the ximelagatran groups, on-treatment major bleeding events included GI bleeding in 9 patients (5 in the 36-mg group, 4 in the 24-mg group), with 2 events in the 36-mg group reported as fatal bleeding SAEs as noted above. Additional on-treatment major bleeding events included 12 wound hematomas (7 in the 36-mg group, 5 in the 24-mg group) and 5 wound-bleeding events (all in the 36-mg group). Medical or surgical intervention for the bleeding event was required in 14 ximelagatran-treated patients (11 in the 36-mg group, 3 in the 24-mg group). These interventions included evacuation/aspiration of clot or hematoma, incision and drainage, wound irrigation and debridement, closure of wound, re-operation, endoscopy, laparotomy and gastrostomy for ulcers and evacuation of subdural hematoma.

In the warfarin-treated groups, on-treatment major bleeding events included GI bleeding in 3 patients and haemarthroses in 2 patients. Additional on-treatment major bleeding events included 5 wound hematomas and 2 wound-bleeding events. Medical or surgical intervention for the bleeding event was required in 6 warfarin-treated patients. The interventions included evacuation/aspiration of blood or hematoma, surgical drainage, debridement of wound haematoma, re-operation and removal of blood from knee, and transfusion.

1.5.1 Incidence of reported bleeding events

Fewer than 8% of patients in each treatment group had a reported bleeding event during study treatment. Two patients in the ximelagatran 36-mg group had fatal nonsurgical bleeding events of GI hemorrhage.

In the 36-mg Pool, the frequency of patients with a reported bleeding event was higher in the ximelagatran group than in the warfarin group (7% and 5%, respectively). Overall, the proportions of patients who had at least 1 reported bleeding event were higher in the ximelagatran treatment groups (6.7% and 7.2% respectively) than in the warfarin groups (5.0 and 5.6% respectively), as were the proportions of patients who had an event that led to discontinuation of study treatment (1.1% in ximelagatran group vs. 0.5% in warfarin groups). There was no appreciable difference among groups with respect to SAEs of bleeding.

The overall frequencies of on-treatment reported bleeding events for the 36-mg and 24-mg Pools are shown in Table 11.

Table 11: Number (%) of patients who had an on-treatment reported bleeding event in any category: Warfarin-comparison Pool (exposed safety population)

	Warfarin-comparison Pool							
	36-mg (EXULT) Pool				24-mg Pool			
	Ximelagatran 36 mg bid		Warfarin[a]		Ximelagatran 24 mg bid		Warfarin[a]	
Number of patients	(N=1913)		(N=1897)		(N=1097)		(N=1081)	
Category of AE								
Any AE	129	(6.7)	95	(5.0)	79	(7.2)	61	(5.6)
SAE	15	(0.8)	12	(0.6)	4	(0.4)	7	(0.7)
SAE leading to death	2	(0.1)	0		0		0	
SAE not leading to death	13	(0.7)	12	(0.6)	4	(0.4)	7	(0.7)
Discontinuations of study treatment due to AE	20	(1.1)	9	(0.5)	11	(1.0)	5	(0.5)

Data derived from the AstraZeneca safety database.
[a] Warfarin group includes 752 warfarin-treated patients from SH-TPO-0010.
AE adverse event; bid twice daily; SAE serious adverse event.

The overall incidence of adjudicated bleeding with ximelagatran was low and considered to be clinically acceptable.

1.5.2 Conclusions on bleeding

A numerically higher frequency of bleeding events was observed for ximelagatran in the oral only, post-operative program for TKR when compared with warfarin. The overall incidence of bleeding with ximelagatran was low and considered to be clinically acceptable.

With respect to on-treatment adjudicated events, major bleeding occurred in 0.9% of patients treated with ximelagatran 36 mg, compared with 0.5% of patients treated with warfarin. Major/minor bleeding occurred in 5.1% of patients treated with ximelagatran 36 mg and 4.1% of patients treated with warfarin. Similar results were observed for ximelagatran 24 mg bid compared with warfarin.

Fewer than 8% of patients in any of the ximelagatran or warfarin groups had a reported bleeding event during study treatment, and most events were non-serious. There was no apparent relationship between ximelagatran dose and bleeding risk, as indicated by similar proportions of patients with bleeding events (major and major/minor) in the ximelagatran 36-mg and 24-mg groups in Study SH-TPO-0010.

Subgroup analyses of major/minor bleeding events in the 36-mg and 24-mg comparison groups did not reveal a subgroup with a clinically important difference in bleeding risk from the entire

population (ie, one which might require dose adjustment). In general, treatment differences were consistent across subgroups.

1.6 Analysis of ALAT elevations in the Surgical population

Since ALAT is a more specific marker of liver cell damage than ASAT, and because there was no pattern for an increase in alkaline phosphatase (ALP) or bilirubin in isolation, ALAT forms the basis of the analysis. A threshold of >3x ULN ALAT was used to indicate a signal of potential clinical relevance.

1.6.1 Studies EXULT A (SH-TPO-0010) and EXULT B (SH-TPO-0012)

Changes from baseline in clinical chemistry parameters, including elevations in ALAT, reflected surgical intervention and postoperative recovery and were generally comparable in the ximelagatran and warfarin treatment groups. These changes generally occurred during the immediate postoperative course of treatment and at the time of the end of treatment with a return to near baseline levels at follow-up.

In EXULT A, there were no differences between the ximelagatran groups and the warfarin group for patients who had ALAT elevation >3x ULN at the end of treatment (6/723, 36-mg; 4/706, 24-mg; 12/704 warfarin). During the follow-up period, 4 patients in the ximelagatran 36-mg group, 1 patient in the ximelagatran 24-mg group, and 0 in the warfarin group had their first ALAT elevation >3x ULN. Three of the 4 patients in the ximelagatran 36-mg group had their first ALAT elevation >30 days after receiving their last ximelagatran dose while the fourth patient had their first ALAT elevation 28 days after receiving their last ximelagatran dose.

In EXULT B, there were no differences between the ximelagatran and warfarin groups for patients who had ALAT elevations >3x ULN at end of treatment (7/1095, ximelagatran 36-mg group; 6/1087 warfarin group). During the follow-up period, 4 additional patients had their first ALAT elevation >3x ULN: 3 in the ximelagatran 36-mg group and 1 in the warfarin group. For all 3 ximelagatran 36 mg patients, the elevations were resolved within 30 days of elevation, including one patient (SH-TPO-0012-510-14309) who began a LMWH on postoperative day 11 as treatment for DVT.

Drug effects on liver toxicity beyond 4-6 weeks are unknown. It should be noted that elevation of hepatic enzymes was typically seen between 2nd and 6th month after starting ximelagatran (long-term exposure data).

1.6.2 Hepatobiliary AEs in the Surgical population Warfarin-comparison Pool

Overall frequency of AEs in the liver and biliary system disorder was slightly higher in the ximelagatran 36-mg (EXULT) group compared to warfarin (6.7% vs 5.4%) and in the ximelagatran 24-mg group, 5.5% ximelagatran 24-mg versus 5.1% warfarin. This was due to a higher rate of reported GGT increased (ximelagatran: 5.6% in the 36-mg group, 4.4% in the 24-mg group, versus 4.2% in both warfarin groups).

Incidences of ALAT (SGOT) increased reported as AEs were similar across the groups (36-mg ximelagatran comparison: 2.1% ximelagatran 36-mg, 1.3% warfarin; 24-mg comparison group: 1.4% ximelagatran 24-mg, 1.5% warfarin). There were no hepatobiliary fatal SAEs, non-fatal SAEs or DAEs in either ximelagatran group.

1.6.3 Conclusions of hepatobiliary effects in the Surgical population

There were no differences in the on-treatment incidences of ALAT elevation between ximelagatran and warfarin. However, during the follow-up period (4-6 weeks), 7 patients in the ximelagatran group, and 1 in the warfarin group had their first ALAT elevation >3x ULN. Drug effects on liver toxicity beyond 4-6 weeks are unknown. It should be noted that elevation of hepatic enzymes was typically seen between 2nd and 6th month after starting ximelagatran (long-term exposure data).

1.7 Coronary artery disease adverse events

Serious adverse events on coronary artery disease including MI are summarized in table 12.

Table 12: Summary of CAD adverse events following short-term use of ximelagatram[#]

	Exult A		Exult B##		Exult A and B	
Event: N (%)	Exanta N=1526	Warfarin N=759	Exanta N=1151	Warfarin N=1148	Exanta N=2677	Warfarin N=1907
MI	11 (0.72)	1 (0.13)	5 (0.43)	3 (0.26)	16* (0.60)	4* (0.21)
Other CAD (Angina/ischemia)	3 (0.2)	0	1 (0.17)	1 (0.09)	4 (0.15)	1 (0.05)
Total	14 (0.92)	1 (0.13)	6 (0.7)	4 (0.35)	20** (0.75)	5** (0.26)

*p=0.04951; ** p=0.02800

[#]Excluded 4 patients who did not take study medications, 3 in ximelagatran group (ID: #3206, #7086 and #10944) and 1 in warfarin group (ID: #9089) whose death was also adjudicated by the central adjudication committee as PE.

[##]one case of sudden death (#15016) in the warfarin group was included as MI and two cases of sudden deaths in the Exanta group (ID: #14366 and 12122) were excluded from the analysis.

Summarized from Module 5, vol. 1 Table 54 and vol. 2 Table 11.3.5.1; vol. 3 Table 55 and vol. 4 Table 11.3.5.1

In both Exult A and Exult B, the proportion of patients with coronary artery disease adverse events (MI and angina) was higher in the ximelagatran groups than in the warfarin groups. After combining Exult A and Exult B, proportion of patients with coronary artery disease adverse events was statistically significantly higher in the ximelagatran group (20/2677, 0.75%) than in the warfarin group (5/1907, 0.26%) in the TKR population (p=0.02800). Proportion of patients with MI was also higher in the ximelagatran group (16/2677, 0.60%) than in the warfarin group (4/1907, 0.21%) in the TKR population (p=0.04951). There were no appreciable differences between the treatment groups for underlying diseases including hypertension, diabetes mellitus, hypercholesterolemia, coronary atherosclerosis, as well as age, gender and weight (Table 13).

Table 13: Concomitant medical conditions in studies EXULT A and B

	Ximelagatran N=2225 n (%)	Warfarin N=1575 n (%)
Hypertension	1325 (59.6)	963 (61.1)
hypercholesterolemia	339 (15.2)	243 (15.4)
Diabetes mellitus	290 (13.0)	199 (12.6)
Coronary atherosclerosis	155 (6.9)	99 (6.3)
	N=2677	N=1907
Gender Male	1015 (37.9)	715 (37.5)
Age, years Mean (SD)	67.7 (9.5)	67.5 (9.5)
Weight (kg) Mean (SD)	84.3 (18.1)	84.5 (17.7)

All of events occurred during the first 2 weeks, except 2 cases of MI in the ximelagatran group that occurred at day 28 and day 39, and 1 case in the warfarin group reported at day 21. In the ximelagatran group, 14 cases occurred during the treatment period; 3 cases occurred 1-4 days after last dose of ximelagatran; 2 cases, beyond 1 week after last dose. The relationship between last dose and events in 1 other case is unclear. The diagnoses of MI in 1 patient in the warfarin group is unclear (PE can not be ruled out). One case was reported at day 21. Four other cases were reported during the treatment period. Considering ximelagatran as an anticoagulant with potential to treat MI, these results are worrisome.

2: The non-surgical population who received study drug for > 35 days

2.1 Common adverse events: long-term exposure (LTE) pool

The overall frequencies of AEs, fatal SAEs, non-fatal SAEs and DAEs during active treatment are presented for the LTE pool in Table 14.

Table 14: Number (%) of patients who had an adverse event: LTE pool

Drug:	ximelagatran		comparators	
No. of patients:	(n=6931)		(n=6216)	
Category of adverse events				
Any adverse events	5912	(85.3)	5309	(85.4)
Serious adverse events	1889	(27.3)	1755	(28.2)
Serious adverse events leading to death	112	(1.6)	112	(1.8)
Serious adverse events not leading to death	1821	(26.3)	1686	(27.1)
Discontinuations of study treatment due to adverse events	1189	(17.2)	801	(12.9)

The overall proportion of patients reporting adverse events was high (85%) due to the severity of the underlying diseases in these populations but there was no difference between the treatment groups. The frequency of SAEs (fatal and non-fatal) was similar between the treatment groups. The proportion of patients who discontinued study drug was higher in the ximelagatran group (17.2%) than in the comparator group (12.9%). This was mostly due to discontinuation of study drug due to elevation of hepatic function tests. The most commonly reported AEs in the LTE pool are presented in Table 15. Adverse events reported with a frequency of at least 4.0% in any column are presented. The events are sorted by the ximelagatran column.

Table 15: Number (%) of patients with the most commonly reported AEs: LTE pool

Drug:	ximelagatran		comparators	
No. of patients:	(n=6931)		(n=6216)	
Preferred term	n	(%)	n	(%)
Total no. of patients with AE:	*5912*	*(85.3)*	*5309*	*(85.4)*
Respiratory infection	945	(13.6)	930	(15.0)
Dizziness/vertigo	730	(10.5)	681	(11.0)
Pain	642	(9.3)	659	(10.6)
Accident and/or injury	624	(9.0)	674	(10.8)
Purpura	558	(8.1)	742	(11.9)
Dyspnoea/dyspnoea (aggravated)	551	(7.9)	592	(9.5)
Diarrhoea	528	(7.6)	455	(7.3)
Chest pain	523	(7.5)	494	(7.9)
Headache	480	(6.9)	448	(7.2)
Oedema peripheral/oedema legs	480	(6.9)	500	(8.0)
Back pain	459	(6.6)	473	(7.6)
Fatigue	416	(6.0)	368	(5.9)
Coughing	395	(5.7)	361	(5.8)
Epistaxis	384	(5.5)	594	(9.6)
Angina pectoris/angina pectoris aggravated	378	(5.5)	299	(4.8)
Bronchitis/bronchitis aggravated	375	(5.4)	360	(5.8)
Arthralgia	360	(5.2)	345	(5.6)
Nausea/nausea (aggravated)	351	(5.1)	309	(5.0)
Haematuria	339	(4.9)	290	(4.7)
Abdominal pain	294	(4.2)	262	(4.2)
Cardiac failure/cardiac failure aggravated	292	(4.2)	369	(5.9)
Urinary tract infection	291	(4.2)	269	(4.3)
Hypertension/hypertension aggravated	288	(4.2)	321	(5.2)
Constipation/constipation aggravated	196	(2.8)	252	(4.1)

2.2 Deaths

The overall mortality in the ITT population was 3.9% in the ximelagatran group and 4.4% in the comparator group. AEs that most frequently led to death were myocardial infarction, sudden death, cardiac arrest and cardiac failure, events expected for the 2 populations at risk of cardiovascular events, AF and post ACS.

2.2.1 Deaths: LTE pool

Death was included in the definition of the endpoints in the studies in the LTE pool and all cause mortality is analyzed using the ITT population. Overall mortality was similar between ximelagatran and comparators.

Table 16: Risk of death in the LTE pool, estimated relative risk with 95% CI (ITT population)

Dose	n/N	%	Risk ratio with 95% CI	p-value
Ximelagatran	270/6948	3.9	0.884 (0.750, 1.041)	0.15
Comparator	274/6230	4.4		

Because the comparator was placebo in the VTE-P and Post ACS pools, a higher mortality might have been expected for the comparator group. Therefore, the overall mortality has also been compared between ximelagatran and the active comparator (warfarin). Overall mortality was similar between ximelagatran (6.5%) and warfarin (7.1%).

2.2.2 Fatal SAEs in the safety population

There were 224 fatal cases during active treatment, 112 in the ximelagatran treatment groups and 112 in the comparator groups. A further 331 patients died after stopping study drug (166 in the ximelagatran group and 165 in the comparator group).

The most common fatal SAE was myocardial infarction (MI). During active treatment, the proportion of patients who died due to acute MI was the same for the 2 treatment groups (0.2%). However, after stopping treatment fatal acute MIs occurred more frequently in the ximelagatran group (0.4%) than the comparator group (0.2%).

In the post ACS pool, there was an increased proportion of fatal myocardial infarctions in the post-treatment period (1.1% vs 0.5%). There were 29 fatal cases during active treatment, 15 (1.2%) in the ximelagatran treatment groups and 14 (2.2%) in the placebo group. A further 35 patients died after stopping study drug, 27 (2.2%) in the ximelagatran groups and 8 (1.3%) in the placebo group. All deaths during treatment were reported in terms associated with cardiovascular disease, with the exception of one suicide in the placebo group.

2.2.3 Fatal SAEs considered causally related by the investigator: LTE pool

There were no differences between treatments concerning the number of fatal SAEs considered by the investigators to be causally related to study drug (Table 17).

Table 17: Number (%) of patients with fatal serious adverse event considered causally related by the investigator: LTE pool

	During the treatment		After treatment	
	ximelagatran n=6931	Comparators n=6216	ximelagatran n=6819	Comparators n=6104
	n (%)	n (%)	n (%)	n (%)
Total	14 (0.2)	10 (0.2)	5 (0.1)	8 (0.1)
GI haemorrhage	1			1

Haematemesis	1			1
Hepatitis infectious			1	
Myocardial infarction	1			
Cardiac arrest	1	2		
Cardio-respiratory arrest	1			
Fibrillation ventricular	1			
Cerebral haemorrhage	2	2	1	2
Cerebrovascular disorder	1	1		2
Haemorrhage intracranial		1		1
Subarachnoid haemorrhage	1			
Aspiration pneumonia			1	
Bronchitis aggravated				1
Hypoxia			1	
Resp distress syndrome adult				1
Respiratory disorder		1		
Retroperitoneal haemorrhage		1		
Myeloid metaplasia			2	
Pulmonary carcinoma	1			
Sudden death	3	1		
Sepsis	1			

2.2.4 Comparison of deaths between pools

There was a similar mortality rate in patients taking ximelagatran and those taking comparators in all pools. The most frequent AEs leading to death were driven by the 2 populations at risk of cardiovascular events, AF and post ACS: myocardial infarction, sudden death, cardiac arrest, cardiac failure. There were no obvious differences in the rates of such fatal cardiac events between groups, except for an excess of myocardial infarctions in patients who had discontinued ximelagatran and this was seen in the post ACS pool. Most of these AMIs started during treatment.

2.3 Serious adverse events other than death

There was a higher frequency of SAEs in the hepatobiliary in the ximelagatran groups relative to comparator treatment in all pools.

A higher frequency of SAEs related to coronary artery disease was seen in the ximelagatran groups in all pools with the exception of the Post ACS pool.

Subjects in the safety population who experienced non-fatal SAEs during or after active study treatment are included in the following tables.

Table 18 Number (%) of patients with the most commonly reported non-fatal serious adverse events: LTE pool

Drug:	Before active treatment		ximelagatran		comparators		After ximelagatran		After comparators	
No. of patients:	(n=13147)		(n=6931)		(n=6216)		(n=6819)		(n=6104)	
Preferred term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total no. of patients with non-fatal SAE:	*44*	*(0.3)*	*1821*	*(26.3)*	*1686*	*(27.1)*	*378*	*(5.5)*	*261*	*(4.3)*
Cerebrovascular disorder	3	(<0.1)	128	(1.8)	143	(2.3)	49	(0.7)	28	(0.5)
Angina pectoris/angina pectoris aggravated	2	(<0.1)	136	(2.0)	124	(2.0)	35	(0.5)	14	(0.2)
Cardiac failure/cardiac failure aggravated	5	(<0.1)	145	(2.1)	195	(3.1)	23	(0.3)	15	(0.2)
Myocardial infarction	1	(<0.1)	118	(1.7)	95	(1.5)	26	(0.4)	18	(0.3)
Chest pain	1	(<0.1)	91	(1.3)	91	(1.5)	19	(0.3)	10	(0.2)
Coronary artery disorder	2	(<0.1)	69	(1.0)	35	(0.6)	27	(0.4)	15	(0.2)
Pneumonia	2	(<0.1)	65	(0.9)	95	(1.5)	14	(0.2)	5	(0.1)
Accident and/or injury	0		64	(0.9)	66	(1.1)	6	(0.1)	2	(<0.1)
GI haemorrhage	0		58	(0.8)	46	(0.7)	10	(0.1)	5	(0.1)
Myocardial ischaemia	0		57	(0.8)	34	(0.5)	12	(0.2)	9	(0.1)
Fibrillation atrial	3	(<0.1)	50	(0.7)	42	(0.7)	6	(0.1)	3	(<0.1)
Hepatic enzymes increased NOS	0		49	(0.7)	2	(<0.1)	5	(0.1)	0	
Syncope	0		49	(0.7)	30	(0.5)	5	(0.1)	6	(0.1)
Anaemia	1	(<0.1)	35	(0.5)	40	(0.6)	6	(0.1)	7	(0.1)
Thrombosis deep venous	0		28	(0.4)	74	(1.2)	10	(0.1)	22	(0.4)
Dizziness/vertigo	0		32	(0.5)	33	(0.5)	5	(0.1)	0	
Haematuria	0		32	(0.5)	26	(0.4)	3	(<0.1)	3	(<0.1)
Bronchitis/bronchitis aggravated	1	(<0.1)	33	(0.5)	24	(0.4)	0		1	(<0.1)
Embolism pulmonary	0		18	(0.3)	37	(0.6)	12	(0.2)	12	(0.2)
Cellulitis skin	1	(<0.1)	28	(0.4)	31	(0.5)	1	(<0.1)	6	(0.1)

A total of 26.3% of patients in the ximelagatran group and 27.1% of patients in the comparator group experienced a non-fatal SAE during treatment. A further 5.5% of patients in the ximelagatran group and 4.3% of patients in the comparator group experienced a non-fatal SAE after stopping study drug.

The most common non-fatal SAEs were cardiovascular events which reflect the diseases under study. The most common non-fatal SAEs considered to be causally related to ximelagatran were increases in hepatic enzymes.

The profile of the non-fatal SAEs was consistent with the pattern of all AEs in the pool. There was a higher reporting frequency of SAEs in the hepatobiliary organ system in the ximelagatran groups compared to warfarin or placebo in all pools.

A higher frequency of SAEs related to coronary artery disease was seen in the ximelagatran groups in all pools with the exception of the Post ACS pool.

2.4 **Discontinuation of Study Drug due to an Adverse Event (DAE)**

The most common AEs causing discontinuation of study drug for the LTE pool are presented in Table 19.

Table 19: Number (%) of patients with the most commonly reported DAEs: LTE pool

Drug:	ximelagatran		comparators	
No. of patients:	(n=6931)		(n=6216)	
Preferred term	n	(%)	n	(%)
Total no. of patients with DAE:	*1189*	*(17.2)*	*801*	*(12.9)*
Hepatic enzymes increased NOS	122	(1.8)	6	(0.1)
SGPT increased	84	(1.2)	2	(<0.1)
Cerebrovascular disorder	70	(1.0)	57	(0.9)
Myocardial infarction	70	(1.0)	54	(0.9)
Hepatic function abnormal	57	(0.8)	7	(0.1)
SGOT increased	56	(0.8)	3	(<0.1)
Angina pectoris/angina pectoris aggravated	47	(0.7)	25	(0.4)
Coronary artery disorder	45	(0.6)	17	(0.3)
Haematuria	42	(0.6)	15	(0.2)
GI haemorrhage	41	(0.6)	28	(0.5)
Myocardial ischaemia	34	(0.5)	25	(0.4)
Thrombosis deep venous	27	(0.4)	79	(1.3)
Embolism pulmonary	17	(0.2)	37	(0.6)

The proportion of patients who discontinued study drug was higher in the ximelagatran group (17.2%) than in the comparator group (12.9%). This was mostly due to the discontinuation of study drug due to increased liver function tests (LFTs).

Apart from increases in hepatic enzymes, the most frequent reasons for discontinuations were related to coronary artery disorder in the ximelagatran group (0.6% vs. 0.3%). Thromboembolic events were more common DAEs in the comparators group (1.3% vs. 0.4%), because of placebo control in secondary prevention study.

Other common causes of discontinuations included bleeding events, with no difference between ximelagatran and the comparators, except for hematuria and rectal haemorrhage/melaena, which caused slightly more discontinuations in the ximelagatran group than in the comparators group.

2.5 Bleeding Events

2.5.1 Major bleeding events

The risk of a major bleeding event is summarized by treatment group in Table 20.

Table 20: Risk of a major bleeding event per patient year

Study	Ximelagatran n/N	(%)	Pt-years	Event rate/100 pt-year %	95% CI	Comparators n/N	(%)	Pt-years	Event rate/100 pt-year %	95% CI	Odds ratio with 95% CI and p-value[a]	
	Ximelagatran 36 mg					**Warfarin**						
AF Pooled	94/3851	(2.4)	5115	1.84	(1.47, 2.21)	127/3732	(3.4)	5149	2.47	(2.04, 2.90)	0.74	(0.57, 0.97) p=0.0288
SH-TPA-0002/4	2/187	(1.1)	233	0.86	(-0.33, 2.05)	2/67	(3.0)	77	2.60	(-1.0, 6.2)	0.32	(0.04, 2.34) p=0.2648
SH-TPA-0003	29/1704	(1.7)	2279	1.27	(0.81, 1.74)	41/1703	(2.4)	2347	1.75	(1.21, 2.28)	0.72	(0.43, 1.2) p >0.2
SH-TPA-0005	63/1960	(3.2)	2603	2.42	(1.82, 3.02)	84/1962	(4.3)	2725	3.08	(2.42, 3.74)	0.78	(0.56, 1.09) p=0.1411
	Ximelagatran 36 mg					**Enoxaparin / warfarin**						
VTE-T												(0.28, 1.06)
SH-TPV-0002/5	14/1240	(1.1)	531	2.64	(1.26, 4.02)	26/1249	(2.1)	550	4.72	(2.91, 6.54)	0.55	p=0.0725
	Ximelagatran 24 mg					**Placebo**						
VTE-P												(0.29, 4.81)
SH-TPV-0003	6/612	(1.0)	697	0.86	(0.32, 1.86)	5/611	(0.8)	671	0.75	(0.24, 1.73)	1.16	p>0.2
	Ximelagatran 24-60 mg + ASA					**Placebo + ASA**						
Post ACS												
SH-TPC-0001												(1.15, 20.65)
Pooled doses	21/1245	(1.7)	433	4.85	(3.03, 7.32)	3/638	(0.5)	233	1.29	(0.27, 3.72)	3.91	p=0.0168
24 mg	6/307	(2.0)	113	5.31	(1.97, 11.2)						4.3	(0.89, 26.94) p=0.0635
36 mg	1/303	(0.3)	101	0.99	(0.03, 5.39)						0.77	(0.01, 9.69) p>0.2
48 mg	9/311	(2.9)	109	8.26	(3.85, 15.1)						6.9	(1.67, 40.2) p=0.0023
60 mg	5/324	(1.5)	108	4.63	(1.52, 10.47)						3.72	(0.71, 24.31) p=0.115

ACS Acute coronary syndrome AF Atrial fibrillation ASA Acetylsalicylic acid (aspirin) CI Confidence interval Pt Yr Patient years VTE-P Venous thromboembolism prevention VTE-T Venous thromboembolism treatment
a Nominal p value

In patients with AF, ximelagatran 36 mg was associated with statistically significantly fewer major bleeding events than warfarin (AF pool; 2.4% and 3.4% for the ximelagatran and warfarin group, respectively, p=0.0288). However, there were no significant differences for major bleeding events between the groups in each of 2 pivotal studies (SH-TPA-0003 and STP-0005). In patients with acute VTE, ximelagatran 36 mg (1.1%, 14/1240) was associated with numerically fewer major bleeding events than enoxaparin/warfarin (2.1%, 26/1249).

In patients undergoing extended secondary prophylaxis for VTE, ximelagatran 24 mg was associated with a similar incidence of major bleeding events to placebo (1% and 0.8%, respectively).

2.5.2 Major/minor bleeding events

The risk of a major/minor bleeding event is summarized by treatment group in Table 21.

Table 21: Risk of a major/minor bleeding event per patient year

Study	Ximelagatran n/N	(%)	Pt-years	Event rate/100 pt-year %	95% CI	Comparators n/N	(%)	Pt-years	Event rate/100 pt-year %	95% CI	Odds ratio with 95% CI and p-value[a]
	Ximelagatran 36 mg					**Warfarin**					
AF Pooled	1234/3851	32.0	4055	30.43	(28.73, 32.13)	1459/3732	39.1	3812	38.27	(36.31, 40.23)	0.71 (0.64, 0.77) p<0.0001
SH-TPA-0002/4	19/187	10.2	222	8.56	(4.71, 12.41)	9/67	13.4	69	13.04	(4.52, 21.57)	0.62 (0.27, 1.45) p=0.2733
SH-TPA-0003	478/1704	28.1	1853	25.80	(23.49, 28.11)	547/1703	32.1	1834	29.82	(27.32, 32.32)	0.82 (0.71, 0.94) p=0.0064
SH-TPA-0005	737/1960	37.6	1980	37.22	(34.53, 39.91)	903/1962	46.0	1909	47.30	(44.22, 50.39)	0.66 (0.58, 0.75) p<0.0001
	Ximelagatran 36 mg					**Enoxaparin / warfarin**					
VTE-T											(0.55, 1.08)
SH-TPV-0002/5	68/1240	5.5	517	13.16	(10.03, 16.29)	88/1249	7.0	535	16.46	(13.02, 19.90)	0.77 p=0.1333
	Ximelagatran 24 mg					**Placebo**					
VTE-P											(0.92, 1.66)
SH-TPV-0003	134/612	21.9	596	22.48	(19.19, 26.05)	111/611	18.2	584	19.01	(15.90, 22.43)	1.24 p=0.1513
	Ximelagatran 24-60 mg + ASA					**Placebo + ASA**					
Post ACS											
SH-TPC-0001											(2.63, 5.33)
Pooled doses	247/1245	19.8	379	65.14	(57.02, 73.27)	72/638	11.3	216	33.34	(25.64, 41.04)	3.74 p<0.0001
24 mg	51/307	16.6	103	49.70	(36.06, 63.33)						1.96 (1.22, 3.17) p=0.0058
36 mg	50/303	16.5	88	57.10	(41.27, 72.92)						2.63 (1.58, 4.37) p=0.0002
48 mg	72/311	23.2	96	75.09	(57.74, 92.43)						6 (3.49, 10.31) p<0.0001
60 mg	74/324	22.8	93	79.5	(61.38, 97.61)						7.79 (4.37, 13.88) p<0.0001

ACS Acute coronary syndrome AF Atrial fibrillation ASA Acetylsalicylic acid (aspirin) CI Confidence interval Pt Yr Patient years VTE-P Venous thromboembolism prevention VTE-T Venous thromboembolism treatment

a Nominal p value

In patients with AF, ximelagatran 36 mg was associated with statistically significantly fewer major/minor bleeding events than warfarin (AF pool; 32.0% and 39.1% for the ximelagatran and warfarin groups, respectively, p<0.0001). In patients with acute VTE, ximelagatran 36 mg was associated with numerically fewer major/minor bleeding events than enoxaparin/warfarin (5.5% vs. 7.0%).

In patients undergoing extended secondary prophylaxis for VTE, ximelagatran 24 mg was associated with a numerically more major/minor bleeding events than placebo (21.9% and 18.2% for the ximelagatran and the placebo group, respectively).

In the dose-finding study in post ACS patients, the risk of a major/minor bleeding event with ximelagatran plus ASA increased with increasing dose. Patients who received ximelagatran plus ASA had statistically significantly more major/minor bleeding events than patients who received placebo plus ASA (pooled doses; 19.8% and 11.3% for the ximelagatran plus ASA, and the placebo plus ASA, respectively, p<0.0001).

2.5.3 Fatal bleeding events

The incidence of fatal bleeding events (adjudicated fatal events, and bleeding-related serious adverse events leading to death) is summarized by treatment group in Table 22.

Table 22: Summary of fatal bleeding events, by study

	Adjudicated events (OT approach)		Bleeding-related SAEs[a] (Safety population)	
	Ximelagatran n/N (%)	Comparator n/N (%)	Ximelagatran n/N (%)	Comparator n/N (%)
SH-TPA-0002 SH-TPA-0004[a]	0/187 (0)	0/67 (0)	0/187 (0)	1/67 (1.5)
SH-TPA-0003	6/1704 (0.4)	4/1703 (0.2)	3/1698 (0.2)	2/1699 (0.1)
SH-TPA-0005	7/1960 (0.4)	3/1962 (0.2)	1/1953 (0.1)	2/1953 (0.1)
SH-TPV-0002 SH-TPV-0005	1/1240 (0.1)	4/1249 (0.3)	1/1236 (0.1)	2/1248 (0.2)
SH-TPV-0003	0/612 (0)	0/611 (0)	0/612 (0)	0/611 (0)
SH-TPC-0001	0/1245 (0)	0/638 (0)	0/1245 (0)	1/638 (0.2)
Total	**14/6948 (0.2)**	**11/6230 (0.2)**	**5/6931 (0.1)**	**8/6216 (0.1)**

SAE serious adverse events

a Whilst on treatment. Sixteen patients had a fatal bleeding-related SAE after treatment

OT: on treatment

In addition to the 13 patients with bleeding-related serious adverse events leading to death whilst on treatment in Table 20 (safety population), a further 16 patients had bleeding-related serious adverse events leading to death after stopping treatment. Of these 16 patients, 7 had received ximelagatran and 9 had received warfarin. Thus in total, 29 patients experienced bleeding-related SAEs with a fatal outcome.

Almost all fatal bleeding events were intracranial (17 cases) or gastrointestinal (10 cases), except 1 case of pericardial and 1 case of retroperitoneal bleeding.

Of the 29 patients who experienced bleeding-related SAEs with a fatal outcome, 13 were not included in the "on treatment" analysis of bleeding outcomes. Ten events were intracerebral haemorrhages that were adjudicated as strokes by the adjudication committee.

Patient SH-TPV-0002-701-4723 was not included in the OT-analysis as a fatal bleed. This patient had a "Bleeding per rectum" that started 30 days after last study drug intake and therefore the adjudication committee classified this as "Death not associated with VTE or bleeding".

Conversely, 7 patients in the ximelagatran group and 2 patients in the warfarin group who had a fatal major bleed according to the adjudication committee are not included in the 29 patients who experienced bleeding-related SAEs with a fatal outcome. Eight patients were not captured by the search on bleeding terms because the term used by the investigator to describe the AE leading to death did not match the preferred terms used to identify patients with bleeding events. The remaining patient (SH-TPA-0003-316-2826) in the ximelagatran group died after discontinuing study drug and is therefore not shown in the AE tables.

In summary, a total of 38 patients experienced bleeding-related SAEs with a fatal outcome, 19 cases in each treatment group (ximelagatran or comparator).

2.5.4 Overview of reported bleeding-related adverse events across indication pools

An overview of the incidence of bleeding adverse events is summarized by treatment for the individual pools in Table 23.

Table 23: Number (%) of patients who had bleeding-related adverse events

Drug:	ximelagatran		warfarin		ximelagatran		warfarin/ enoxaparin		ximelagatran		placebo		ximelagatran + ASA		placebo + ASA	
Dosage:	36 mg bid		Individual		36 mg bid		Individual		24 mg bid		-		24, 36, 48 or 60 mg bid		-	
Pool:	AF		AF		VTE-T		VTE-T		VTE-P		VTE-P		Post ACS		Post ACS	
No. of patients:	(n=3838)		(n=3719)		(n=1236)		(n=1248)		(n=612)		(n=611)		(n=1245)		(n=638)	
Category of adverse events																
Any adverse events	1251	(32.6)	1490	(40.1)	226	(18.3)	317	(25.4)	134	(21.9)	108	(17.7)	250	(20.1)	73	(11.4)
Serious adverse events	134	(3.5)	177	(4.8)	27	(2.2)	35	(2.8)	7	(1.1)	3	(0.5)	33	(2.7)	7	(1.1)
Serious adverse events leading to death	4	(0.1)	5	(0.1)	1	(0.1)	2	(0.2)	0		0		0		1	(0.2)
Serious adverse events not leading to death	130	(3.4)	172	(4.6)	26	(2.1)	33	(2.6)	7	(1.1)	3	(0.5)	33	(2.7)	6	(0.9)
Discontinuations of study treatment due to adverse events	102	(2.7)	93	(2.5)	22	(1.8)	31	(2.5)	10	(1.6)	7	(1.2)	56	(4.5)	6	(0.9)

ACS Acute coronary syndrome; AF Atrial fibrillation; ASA Acetylsalicylic acid (aspirin); VTE-P Venous thromboembolism prevention; VTE-T Venous thromboembolism treatment; OT On-treatment

In patients with AF, the incidence of reported bleeding adverse events with ximelagatran 36 mg (32.6%) was less than that observed with warfarin (40.1%). The incidence of serious adverse events and discontinuations due to a bleeding adverse event was low and similar in both treatment groups.

In patients with acute VTE, the incidence of reported bleeding adverse events with ximelagatran 36 mg (18.3%) was less than that observed with enoxaparin/warfarin (25.4%). The incidence of serious adverse events and discontinuations due to a bleeding adverse event was low and similar in both treatment groups.

In patients undergoing extended secondary prophylaxis for VTE, the incidence of reported bleeding adverse events with ximelagatran 24 mg was numerically greater than that observed with placebo. The incidence of serious adverse events and discontinuations due to a bleeding adverse event was low and similar in both treatment groups.

The incidence of reported bleeding adverse events in patients receiving ximelagatran and ASA (20.1%) was higher than that observed with placebo and ASA (11.4%). The incidence of serious adverse events and discontinuations due to a bleeding adverse event with ximelagatran plus ASA was low (2.7% and 4.5% for serious adverse events and discontinuations due to adverse events, respectively), but higher than that observed with placebo and ASA (1.1% and 0.9% for serious adverse events and discontinuations due to adverse events, respectively).

In AF patients, the most commonly reported bleeding related AEs for ximelagatran-treated patients were purpura (which was the preferred term used to code unspecified hematomas, bruises and petechiae) (11.1%), epistaxis (7.2%), haematuria (5.4%) and rectal haemorrhage (2.9%).

In patients with an acute VTE, the most commonly reported bleeding related AEs for ximelagatran-treated patients were purpura (4.6%), epistaxis (3.2%), haematuria (2.8%) and gingival bleeding (2.0%).

In patients undergoing extended secondary prophylaxis for VTE the most commonly reported bleeding related AEs for ximelagatran-treated patients were haematuria (6.0%), purpura (4.7%), melaena (3.6%), and rectal haemorrhage (1.6%).

The most commonly reported bleeding AEs in patients receiving ximelagatran and ASA were epistaxis (4.9%), haematuria (4.9%), melaena (3.7%) and purpura (3.6%).

2.5.5 Relationship between exposure to melagatran and bleeding events

The association between AUC and the cumulative risk of a major/minor bleeding event is summarized for ximelagatran-treated patients in the AF pool in Table 24.

Table 24: Association between AUC and cumulative risk of having a bleeding event (major or minor) after one year in the study

Pool			AUC value	Cumulative Risk[a]	95% CI Lower	95% CI Upper
AF	Major or Minor bleed	P05	2.06	27.3	24.7	29.8
		Q1	2.77	30.5	28.2	32.8
		Median	3.46	33.9	31.7	36.1
		Q3	4.38	39.2	36.6	41.7
		P95	6.19	51.9	46.4	57.4

Cumulative risk at 12 months (Day 366)
AF Atrial fibrillation AUC Area under the curve CI Confidence interval OT On-treatment
a Hazard ratio

The risk of having a major/minor bleeding event with ximelagatran 36 mg increases with increasing AUC values (hazard ratio 1.17, 95% CI: 1.12, 1.21)

There was no statistically significant relationship between the risk of having a major/minor bleeding event with ximelagatran 24 mg and increasing AUC values (hazard ratio 1.08, 95% 0.90, 1.29).

2.5.6 Subgroup analyses of bleeding events:

Within-treatment group comparisons suggested that, for both ximelagatran and warfarin, patients $\geq$75 years old, and those with prior stroke/TIA, were at an increased risk of major/minor bleeding. In the ximelagatran group only, CrCL <80 mL/min, previous CAD and diabetes mellitus were also suggested to be associated with an increased risk of major/minor bleeding events. In the warfarin group, the same conclusion was suggested for patients with paroxysmal AF and those who had previously taken aspirin.

For the majority of subgroups investigated, patients were statistically significantly less likely to have a major/minor bleed with ximelagatran 36 mg than warfarin. Two significant treatment by risk factor interactions were detected, for CrCL <80 mL/min ($p<0.001$) and diabetes mellitus ($p=0.002$). In terms of the key demographic characteristics, the following subgroups were statistically significantly less likely to have a major bleed with ximelagatran 36 mg than warfarin patients with a CrCL ≥80 mL/min, patients less than 75 years old, patients with a BMI ≥25, males and females, patients with a weight ≥50 kg and Caucasians.

There were no subgroups that were statistically significantly less likely to have a major/minor bleed with warfarin compared to ximelagatran.

2.6 Hepatobiliary effects

It should be noted that the following patients have been excluded from the studies:

- Patients with known clinically significant liver disease (as judged by the investigator) or persistent ASAT and/or ALAT > 3 x ULN (defined by central laboratory)
- Patients with continuous treatment with NSAID or Known drug addiction and/or alcohol abuse

In studies with ximelagatran (bid, fixed dose), from June 2000, liver enzymes were monitored at least monthly for the first 6 months and if ALAT increased to >3xULN, were monitored weekly; if ALAT reached >7xULN study drug was stopped. From 2 November 2001, this algorithm was changed. The threshold for beginning weekly monitoring was reduced from 3xULN to 2xULN and the threshold for discontinuation of study drug was revised from 7xULN to 5xULN (or persistent increase >3xULN for up to 4-8 weeks). In the program, 40% of the ximelagatran-treated patients who had an ALAT >3xULN were monitored using the more stringent algorithm.

2.6.1 Patients contributing to ALAT measurement

The number of randomized patients contributing to ALAT testing is shown in Table 25.

Table 25: Number of patients randomized, and contributing ALAT measurements over time in the long-term studies (ITT population) - Central laboratory data only

Study	Total	Ximelagatran only	Number of patients contributing ALAT measurements					
			>0 months	>3 months	>6 months	>12 months	>18 months	>24 months
SH-TPA-0002 SH-TPA-0004	254	187	183	155	119	112	103	94
SH-TPA-0003	3407	1704	1685	1613	1536	1447	824	15
SH-TPA-0005	3922	1960	1927	1738	1595	1425	913	273
SH-TPV-0003	1223	612	612	575	535	495	250	
SH-TPV-0002 SH-TPV-0005	2489	1240	1212	1062	933	0	0	0
SH-TPC-0001	1883	1245	1221	992	810	0	0	0
Total	**13178**	**6948**	**6840**	**6135**	**5528**	**3479**	**2090**	**382**

Of the 6948 patients randomized to ximelagatran, 6840 contributed at least one ALAT measurement and 5528 had an ALAT measurement at the 6-month visit.

2.6.2 Elevations in liver function tests (LFTs)

The distribution of patients with elevated ALAT, ASAT, ALP and total bilirubin, according to various multiples of ULN is shown for the LTE pool in Table 26 (Central laboratory data only).

Table 26: Cumulative incidence of patients with elevated ALAT, bilirubin, ASAT, G-GT and ALP (ITT population): LTE pool - Central laboratory data only

Liver function test	Ximelagatran N=6948	Comparator N=6230
ALAT > ULN	2086 (30%)	945 (15.2%)
ALAT >2 x ULN	838 (12.1%)	178 (2.9%)
ALAT >3 x ULN	531 (7.6%)	68 (1.1%)
ALAT >5 x ULN	299 (4.3%)	26 (0.4%)
ALAT >10 x ULN	106 (1.5%)	4 (0.1%)
ASAT >ULN	1433 (20.6%)	546 (8.8%)
ASAT >2 x ULN	531 (7.6%)	97 (1.6%)
ASAT >3 x ULN	321 (4.6%)	44 (0.7%)
ASAT >5 x ULN	162 (2.3%)	18 (0.3%)
ASAT >10 x ULN	51 (0.7%)	4 (0.1%)
ALP >ULN	1063 (15.3%)	800 (12.8%)
ALP >2 x ULN	131 (1.9%)	64 (1.0%)
ALP >3 x ULN	44 (0.6%)	21 (0.3%)
Bilirubin >1 x ULN	1139 (16.4%)	1008 (16.2%)
Bilirubin >1.5 x ULN	265 (3.8%)	215 (3.5%)
Bilirubin >2 x ULN	78 (1.1%)	67 (1.1%)
Bilirubin >3 x ULN	30 (0.4%)	14 (0.2%)
Bilirubin >5 x ULN	10 (0.1%)	6 (0.1%)
G-GT[a] >3 x ULN	119 (1.7%)	24 (0.4%)

a only measured in study SH-TPC-0001

The pooled data shows a similar pattern to that seen in the individual studies. ALAT showed a significant increase in ximelagatran-treated patients compared to those treated with comparators at all thresholds. ASAT increased in conjunction with ALAT. There was no similar increase for ximelagatran relative to comparators in total bilirubin and ALP.

ALAT is the main marker of a hepatic effect in the ximelagatran group compared to the comparator. There is a strong correlation with ASAT, but ALAT is generally higher and is known to be more specific to the liver. The elevation in the other tests is not as different between groups, and there is no correlation between ALAT and ALP or bilirubin. These features point to a predominantly hepatocellular type of hepatic injury, as opposed to a cholestatic type.

As ALAT is a more specific marker of liver cell damage than ASAT, and there was no pattern for an increase in ALP or bilirubin in isolation, ALAT was used for monitoring and management decisions and forms the basis of the analysis. A threshold of >3xULN ALAT is generally considered to represent a clinically significant elevation. Lower cut-off levels are considered to be less informative due to the commonness of slight elevations in untreated populations. Therefore, ALAT values of >3xULN have been used to indicate a signal of potential clinical relevance.

2.6.3 ALAT elevation according to various thresholds

The distribution of patients with elevated ALAT according to various multiples of the upper limit of the normal range is shown by study for patients treated with ximelagatran in Table 27 and for patients treated with comparator in Table 26. These tables present central laboratory data only.

Table 27 Cumulative incidence of ximelagatran-treated patients with elevated ALAT by study (ITT population) - Central laboratory data only

Study	>ULN	>2 x ULN	>3 x ULN	>5 x ULN	>10 x ULN
SH-TPA-0002 SH-TPA-0004	83 (44.4%)	26 (13.9%)	12 (6.4%)	8 (4.3%)	3 (1.6%)
SH-TPA-0003	457 (26.8%)	170 (10.0%)	107 (6.3%)	57 (3.3%)	15 (0.9%)
SH-TPA-0005	472 (24.1%)	200 (10.2%)	117 (6.0%)	59 (3.0%)	16 (0.8%)
SH-TPV-0002 SH-TPV-0005	419 (33.8%)	180 (14.5%)	119 (9.6%)	69 (5.6%)	24 (1.9%)
SH-TPV-0003	202 (33.0%)	63 (10.3%)	37 (6.0%)	20 (3.3%)	6 (1.0%)
SH-TPC-0001[a]	453 (36.4%)	199 (16.0%)	139 (11.2%)	86 (6.9%)	42 (3.4%)
Total	2086 (30.0%)	838 (12.1%)	531 (7.6%)	299 (4.3%)	106 (1.5%)

a Patients received ASA 160 mg daily in addition to ximelagatran

Table 28 Cumulative incidence of comparator-treated patients with elevated ALAT by study (ITT population) - Central laboratory data only

Study	>ULN	>2 x ULN	>3 x ULN	>5 x ULN	>10 x ULN
SH-TPA-0002 SH-TPA-0004	23 (34.3%)	4 (6.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SH-TPA-0003	232 (13.6%)	37 (2.2%)	14 (0.8%)	7 (0.4%)	0 (0%)
SH-TPA-0005	196 (10.0%)	35 (1.8%)	15 (0.8%)	5 (0.3%)	1 (0.1%)
SH-TPV-0002 SH-TPV-0005	305 (24.4%)	67 (5.4%)	25 (2.0%)	8 (0.6%)	1 (0.1%)
SH-TPV-0003	76 (12.4%)	17 (2.8%)	6 (1.0%)	2 (0.3%)	0 (0.0%)
SH-TPC-0001[a]	113 (17.7%)	19 (3.0%)	8 (1.3%)	4 (0.6%)	2 (0.3%)
Total	945 (15.2%)	179 (2.9%)	68 (1.1%)	26 (0.4%)	4 (0.1%)

a Patients received ASA 160 mg daily in addition to placebo

There was a higher incidence of ALAT elevation in ximelagatran –treated patients regardless of the threshold (xULN) and the effect was consistent across all studies.

Overall, approximately twice as many ximelagatran-treated patients experienced an ALAT elevation >ULN (30.0% vs 15.2%). There were approximately 4 times as many ximelagatran-treated patients who experienced an increase in ALAT >2xULN (12.1% vs 2.9%) and this

difference increased to 7-fold at >3xULN. The additional data obtained from local laboratories did not affect the patterns seen in the Central laboratory data.

2.6.4 Patients with ALAT>3xULN measured at the Central laboratory

The number of patients with an increase in ALAT >3xULN is presented for both ximelagatran and the comparators in Table 29.

Table 29 Elevations of ALAT >3xULN (ITT population) - Central laboratory data only

Study	Dose (mg)	Ximelagatran (%)	Comparator (%)
SH-TPA-0002 SH-TPA-0004 [a]	20,40,60 36	12/187 (6.4)	0/67 (0)
SH-TPA-0003	36	107/1704 (6.3)	14/1703 (0.8)
SH-TPA-0005	36	117/1960 (6.0)	15/1962 (0.8)
SH-TPV-0002 SH-TPV-0005	36	119/1240 (9.6)	25/1249 (2.0)
SH-TPV-0003	24	37/612 (6.0)	6/611 (1.0)
SH-TPC-0001	24	20/307 (6.5)	8/638 (1.3)
	36	39/303 (12.9)	
	48	38/311 (12.2)	
	60	42/324 (13.0)	
Total		**531/6948 (7.6)**	**68/6230 (1.1)**

a Data for doses 20, 40 and 60 mg in SH-TPA-0002 and 36 mg in SH-TPA-0004 are combined

In patients receiving long-term administration of ximelagatran (>35 days) an increase in ALAT >3xULN occurred in 6-13% (average 7.6%, 531/6948) compared to 0-2% (average 1.1%, 68/6230) of patients receiving comparator treatments.

The overall incidence of ALAT > 3xULN in SH-TPA-0002/4 after 2 years of treatment was 6.4% (12/187) in the ximelagatran group and 0% (0/67) in the warfarin group. The incidence was comparable in the other 2 studies in AF patients, SH-TPA-0003 (6.3%) and SH-TPA-0005 (6.0%); the incidence in the warfarin group was 0.8% in both of these studies. The incidence in both the ximelagatran group and the warfarin group was higher in VTE-T patients (9.6% and 2.0%, respectively). The higher incidence in the warfarin group may have been due to the enoxaparin given as part of the treatment regimen in the comparator group. In the post ACS study, SH-TPC-0001, the incidence was notably higher in the ximelagatran 36, 48 and 60 mg dose groups (12 to 13%) but the incidence in the 24 mg group was similar to that seen in AF patients (6.5%).

There were a further 11 patients who had an ALAT elevation >3xULN recorded after study closure and are therefore excluded from the ITT analyses of these data. These 11 patients comprised 9 patients in study SH-TPV-0002/5 (6 in the ximelagatran group and 3 in the

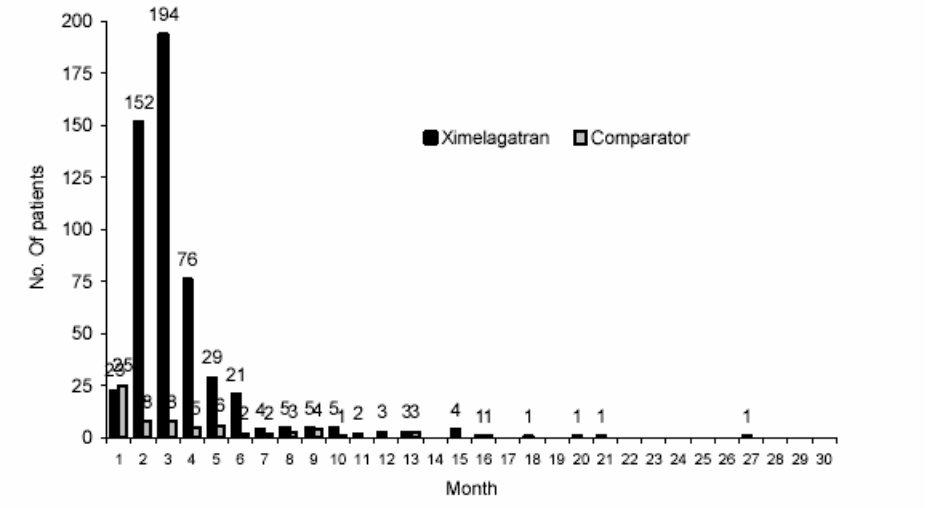
enoxaparin/warfarin group) and 2 patients in study SH-TPC-0001 (1 in the ximelagatran 36 mg group and 1 in the placebo group). Finally, Patient 012-205 in study SH-TPA-0004 had an ALAT elevation >3xULN after 2.5 years of treatment with ximelagatran. This patient is not included in the analysis because only data up to 30 June 2001 (the date of the interim CSR) from this ongoing study have been integrated in the safety database.

2.6.5 Time course of ALAT elevations

As shown in the previous section, 599 patients showed an ALAT elevation >3xULN during the studies, 531 patients in the ximelagatran group (cumulative incidence 7.6%) and 68 patients in the comparator group (cumulative incidence 1.1%). Note that this is the central laboratory data only. Including local laboratory data, 620 patients showed an ALAT elevation >3xULN during the studies, 546 patients in the ximelagatran group (cumulative incidence 7.8%) and 74 patients in the comparator group (cumulative incidence 1.1%).

The time pattern of ALAT elevations was consistent. The increase typically occurred between 1 and 6 months after the initiation of ximelagatran. Before and after this time frame the incidence of ALAT increase was similar to comparators. The divergence occurred largely up to 6 months and thereafter the additional increment was 1.0% for ximelagatran and 0.4% for comparators. Figure 1 shows the number of patients presenting for the first time with an increase in ALAT >3xULN during each month of treatment.

Figure 1: Number of new patients with ALAT >3xULN by month since randomization (ITT population): LTE pool – Central laboratory data only



Of the 6 patients who had a first ALAT >3xULN beyond 15 months, 5 were in the ximelagatran group

The figure shows the number of patients presenting with ALAT >3xULN for the first time and it should be noted that there were 6948 patients in the ximelagatran group and 6230 in the comparator group. In the first month of treatment there was no difference in the incidence of ALAT >3xULN between ximelagatran (23 cases) and comparator-treated patients (25 cases). The difference became significant at 2 months. Of the 531 ximelagatran-treated patients who had ALAT >3xULN, 495 (93.0%) were detected during the first 6 months and 519 (97.7%) were detected within the first 12 months. Beyond 12 months, few new patients presented with ALAT >3xULN.

Regardless of the magnitude of the ALAT increase examined, the time pattern was consistent. In the ximelagatran group, the majority of patients who experienced an elevation in ALAT presented between 2 and 4 months. Beyond 12 months the incidence of increased ALAT was similar to the comparators.

2.6.6 Recovery of elevated ALAT values towards normal

Among the 531 patients in the ximelagatran group who presented with an ALAT >3xULN, 206 (39%) completed the study on study drug. The remaining 325 patients (61%) discontinued study drug prematurely. The analysis of the reduction of elevated ALAT toward normal is presented in Table 30.

Table 30 Number of ximelagatran-treated patients with ALAT>3xULN, measured at the Central laboratory by magnitude of last recorded ALAT measurement (ITT population): LTE pool

	Study drug discontinuation=No				Study drug discontinuation=Yes				
	xULN				xULN				
Max(ALAT)	≤1	(1,2]	(2,3]	>3	≤1	(1,2]	(2,3]	>3	Total
>3xULN	84	10	4	1	101	4	3	4	211
>5xULN	97	5	3	1	76	6	0	4	192
>10xULN	36	3	0	1	73	7	0	8	128
Total	217	18	7	3	250	17	3	16	531

Follow-up ALAT measurements include those made at local laboratories

This table includes ximelagatran-treated patients who had an ALAT >3xULN recorded at the Central laboratory during the studies categorized by their maximal ALAT elevation (>3, >5 or >10xULN). For each category, the number of patients who had a last recorded ALAT value of <1, <2, <3 or >3xULN, is shown. The table is further subdivided into those patients who continued on study drug and those who stopped study drug. For example, from the second column of the table it can be seen that 84 patients who had a maximal ALAT elevation of >3xULN but <5xULN, had returned to an ALAT ≤1xULN at their last recorded measurement, while continuing to take study drug. From the penultimate column in the table it can be seen that 8 patients who had a maximal ALAT elevation of >10xULN, still had ALAT >3xULN at their last recorded measurement, having stopped taking study drug.

Of the 531 ximelagatran-treated patients who had an ALAT elevation >3xULN recorded by the central laboratory, 502 (95%) had their ALAT return to <2xULN by the last measurement taken before the cut-off for this file. So far, it is not possible to identify who the patients are that will not return to baseline. The mean number of days taken for ALAT to return to <2xULN was similar whether the patients continued to take ximelagatran or not (Table 31).

Table 31 Mean number of days between first ALAT elevation >3xULN (measured at the Central laboratory) to normalization for ximelagatran-treated patients (ITT population): LTE pool

	Study drug discontinuation=No				Study drug discontinuation=Yes			
	xULN				xULN			
Max(ALAT)	≤1	(1,2]	(2,3]	>3	≤1	(1,2]	(2,3]	>3
>3xULN	215	118	42	0	218	63	47	12
>5xULN	208	132	75	56	218	79	0	36
>10xULN	168	35	0	24	151	88	0	23

Follow-up ALAT measurements include those made at local laboratories

Most cases show a peak of ALAT within the first 2 to 3 months post-randomization and a decline back towards baseline within about 6 months post-randomization.

The pattern of return to baseline or ULN was similar whether the patient discontinued study drug or not, and only sustained above ULN in a few cases.

A total of 35 patients, 30 in the ximelagatran group and 5 in the comparator group, still had ALAT >2xULN at the last measurement (including local laboratory measurements). Of the 30 ximelagatran-treated patients, 11 died while their ALAT was still elevated; 3 patients had an alternative explanation for the raised LFTs (alcohol); 2 patients were lost to follow-up and one patient had a final ALAT measurement that according to the investigator had "decreased to a medically insignificant level". The remaining 13 patients continued under surveillance at the time of the cut-off for this file.

2.6.7 Re-challenge to ximelagatran after temporary discontinuation of study drug with ALAT elevations

Eighteen patients who discontinued study drug with elevations of ALAT subsequently resumed treatment after ALAT had returned to the normal range. Of these 18 patients, 2 (Patient SH-TPA-0003-017-2619 and Patient SH-TPA-0005-370-5718) again experienced elevations of ALAT after drug was resumed.

2.6.8 Elevated ALAT by dose

Table 32 shows the cumulative incidence of ximelagatran-treated patients with elevated ALAT by dose in study SH-TPC-0001.

Table 32 Cumulative incidence of ximelagatran-treated patients with elevated ALAT by dose in study SH-TPC-0001 (ITT population)

Dose	>1xULN	>2xULN	>3xULN	>5xULN	>10xULN
24 mg	98 (31.9%)	33 (10.8%)	20 (6.5%)	8 (2.6%)	3 (1.0%)
36 mg	103 (34.0%)	53 (17.5%)	39 (12.9%)	27 (8.9%)	13 (4.3%)
48 mg	125 (40.2%)	52 (16.7%)	38 (12.2%)	22 (7.1%)	10 (3.2%)
60 mg	127 (39.2%)	61 (18.8%)	42 (13.0%)	29 (9.0%)	16 (4.9%)

There was not a marked dose response over the dose range 24 mg to 60 mg but there was a noticeably lower incidence of all multiples of ULN at the 24 mg dose compared to the higher doses.

2.6.9 Combination of ALAT and bilirubin elevation

The combination of transaminase and bilirubin elevation has been considered to predict the occurrence of severe injury in some patients. The number of patients in each of the studies that contribute to the LTE pool who had an increase in total bilirubin >2xULN within one month following an increase in ALAT >3xULN are shown in Table 33.

Table 33 Concomitant elevations of ALAT >3xULN and bilirubin >2xULN (ITT population) - Central laboratory data only

Study	Dose (mg)	Ximelagatran (%)	Comparator (%)
SH-TPA-0002 SH-TPA-0004[a]	20,40,60 36	0/187 (0)	0/67 (0)
SH-TPA-0003	36	7/1704 (0.4)	1/1703 (0.1)
SH-TPA-0005	36	9/1960 (0.5)	1/1962 (0.1)
SH-TPV-0002 SH-TPV-0005	36	2/1240 (0.2)	1/1249 (0.1)
SH-TPV-0003	24	0/612 (0)	0/611 (0)
SH-TPC-0001[b]	24, 36, 48, 60	8/1245 (0.6)	1/638 (0.2)
Total		**26/6948 (0.4)**	**4/6230 (0.1)**

a Data for doses 20, 40 and 60 mg in SH-TPA-0002 and 36 mg in SH-TPA-0004 are combined
b All ximelagatran doses combined

ALAT >3xULN was associated with bilirubin >2xULN (within one month following the rise in ALAT) in 0.4% (26/6948) of all patients who were exposed to ximelagatran >35 days as compared to 0.1% (4/6230) of patients exposed to comparators.

Additional ALAT and bilirubin data were obtained from tests performed at local laboratories. These included 11 new cases (10 ximelagatran, 1 comparator) who had an increase in bilirubin >2xULN within one month following an increased ALAT >3xULN. One additional patient

(#7859) described in the section of Deaths in ximelagatran-treated patients with ALAT >3xULN (see below) had bilirubin elevation > 5.6x ULN. This patient was not included in the sponsor's analysis for combination elevation. Therefore, at the cut-off date for this file there were 37 such cases in the ximelagatran group and 5 in the comparator group (0.53% vs 0.08%). The ximelagatran-treated patients who had an increase in total bilirubin >2xULN within one month following an increase in ALAT >3xULN are summarized in Tables below.

Table 34 List of ximelagatran-treated patients with concomitant elevations of ALAT >3xULN and bilirubin >2xULN – Central laboratory data only

Patient ID	Ximelagatran dose (bid)	Age	Sex	Days to ALAT > 3xULN	Max ALAT (xULN)	Max Bilirubin (xULN)	Action with study drug	Outcome	Alternative diagnosis/ Comment
SH-TPA-0003-100-1793	36 mg	69	M	237	3.56	5.00	Discontinued	Death	Hepatic metastases from gastric carcinoma, died from pulmonary embolism
SH-TPA-0003-105-1967	36 mg	71	M	7	8.63	5.77	Disontinued	Recovered	Hospitalised for stroke. Gallstones.
SH-TPA-0003-114-3174	36 mg	85	M	56	12.48	2.23	Discontinued	Recovered	No alternative explanation.
SH-TPA-0003-115-3963	36 mg	45	M	190	4.81	2.77	Continued	Death	Right-sided heart failure, liver steatosis. Died from cardiogenic shock.
SH-TPA-0003-183-2693	36 mg	71	M	218	14.06	2.09	Continued	Recovered	Episode of severe heart failure.
SH-TPA-0003-309-2522	36 mg	73	M	60	4.35	9.23	Temporarily discontinued	Recovered.	Intrahepatic cholestasis due to flucloxacillin. Study medication restarted uneventfully.
SH-TPA-0003-316-2826	36 mg	75	F	94	9.94	2.05	Discontinued	Recovered	No alternative explanation. Died from aortic rupture five months after normalisation.
SH-TPA-0005-200-8434	36 mg	85	M	22	3.75	3.08	Discontinued	Recovered	Dilated bile ducts. Passing gallstone suspected. Sphincterotomy performed.
SH-TPA-0005-490-6221	36 mg	82	M	33	6.69	7.08	Discontinued	Recovered	No alternative diagnosis. Hepatomegaly.
SH-TPA-0005-540-7986	36 mg	81	F	63	19.38	2.08	Discontinued	Recovered	Gallstones on ultrasound.
SH-TPA-0005-620-7259	36 mg	80	M	85	30.00	6.92	Discontinued	Death	No alternative diagnosis to liver failure. Died from bleeding duodenal ulcer.
SH-TPA-0005-690-6546	36 mg	75	M	164	3.58	2.46	Discontinued	Recovered	Concomitant treatment with a statin. Gallstones. Reported as possible acute biliary obstruction.
SH-TPA-0005-0695-5111	36 mg	78	M	821	5.54	3.15	Discontinued	Recovered	No alternative explanation. Abdominal scan revealed renal cell carcinoma.

SH-TPA-0005-1000-6995	36 mg	62	M	619	7.65	2.92	Discontinued	Recovered	Bilirubin elevated throughout the study.
SH-TPA-0005-9390-6560	36 mg	74	M	92	6.98	2.09	Discontinued	Recovered	Bilirubin elevated throughout the study.
SH-TPA-0005-9570-8387	36 mg	80	F	63	15.19	10.82	Discontinued	Recovered	No alternative diagnosis. ASAT higher than ALAT throughout the study.
SH-TPV-0002-302-4105	36 mg	75	F	59	8.77	3.09	Discontinued	Recovered	No alternative diagnosis.
SH-TPV-0002-362-5778	36 mg	63	F	35	4.75	4.55	Continued	Recovered	History of breast cancer. Ultrasound showed "hepatic diffuse disease". Normalized while study drug continued.
SH-TPC-0001-120-0430	24 mg	90	M	132	4.42	2.23	Discontinued	Death	Died from right-sided heart failure.
SH-TPC-0001-259-0007	24 mg	72	M	28	4.06	3.41	Continued	Recovered	No alternative explanation. Renal cyst on ultrasound.
SH-TPC-0001-273-0555	36 mg	72	M	38	6.48	3.09	Discontinued	Recovered	Probably biliary obstruction, according to the investigator.
SH-TPC-0001-290-2630	60 mg	55	M	57	17.85	3.00	Discontinued	Recovered	No alternative explanation.
SH-TPC-0001-299-2324	48 mg	78	M	58	26.63	5.73	Discontinued	Recovered	No alternative explanation.
SH-TPC-0001-306-1234	60 mg	69	F	95	19.0	10.27	Discontinued	Recovered	No alternative explanation. Elevated Alpha-Foeto-Protein, but ultrasound and CT did not reveal any neoplasm.
SH-TPC-0001-338-1440	48 mg	65	F	16	16.06	2.95	Discontinued	Recovered	Right-sided heart failure and alcohol. Study medication taken only two days.
SH-TPC-0001-348-2065	60 mg	51	M	27	11.81	12.86	Discontinued	Death	Died from pancreatic tumour.

Table 35 List of ximelagatran-treated patients with concomitant ALAT >3xULN and bilirubin >2xULN – local laboratory data only

Patient ID	Ximelagatran dose (bid)	Age	Sex	Days to ALAT > 3xULN	Max ALT (xULN)	Max Bilirubin (xULN)	Action with study drug	Outcome	Alternative diagnosis/ Comment
SH-TPA-0003-172-1009	36 mg	76	M	179	50.45	6.68	Temporarily discontinued	Recovered	LFT increase started during exacerbation of psoriasis that was ascribed to concomitant treatment nevbiolol. Soon thereafter suspected spontaneous discharge of choledochus stone. Recovered after ERCP with papillotomy. Serology showed chronic hepatitis B.
SH-TPA-0003-217-2893	36 mg	66	M	285	18.40	2.09	Continued	Died	Hepatic colic and severe heart failure at peak. Died five months later due to abdominal pain causing heart failure.
SH-TPA-0003-309-2452	36 mg	72	M	232	11.86	4.70	Temporarily discontinued	Recovered	Gallstones. ERCP with papillotomy.
SH-TPA-0005-0020-7024	36 mg	74	M	46	9.33	7.20	Discontinued	Recovered (except for ALP)	Carcinoid tumour with metastases to liver. Peak ALAT at the time of a gastrointestinal bleeding.
SH-TPA-0005-0080-6438	36 mg	57	F	228	3.12	2.50	Discontinued	Recovered	Dengue fever and sepsis.
SH-TPA-0005-2160-5402	36 mg	73	F	42	32.96	6.46	Discontinued	Recovered	Haematuria and positive fecal haemoglobin with anemia and hypotension. Hepatic ischemia suspected to have contributed to elevated LFTs.
SH-TPA-0005-2690-8209	36 mg	81	M	115	4.69	7.20	Temporarily discontinued	Recovered	Gallstone pancreatitis. Cholecystectomy performed. Bilirubin elevated throughout the study.
SH-TPV-0002-265-5442	36 mg	73	M	9	14.80	3.64	Discontinued	Died	Acute hepatitis B diagnosed after 18 days on study drug. Elevated LFTs at baseline. Died from fulminant hepatitis.

Table 36 List of ximelagatran-treated patients with concomitant ALAT >3xULN and bilirubin >2xULN – local laboratory data only

Patient ID	Ximelagatran dose (bid)	Age	Sex	Days to ALAT > 3xULN	Max ALT (xULN)	Max Bilirubin (xULN)	Action with study drug	Outcome	Alternative diagnosis/ Comment
SH-TPV-0002-504-4035	36 mg	76	M	144	25.64	3.03	Discontinued	Died	Colon carcinoma with metastases to the right liver lobe. Post-operative multiorgan failure with fatal outcome.
SH-TPC-0001-446-2209	60 mg	59	M	57	16.40	7.59	Discontinued	Recovered	Cyst in caput pancreatis. Biopsy during cholecystectomy showed chronic cholecystitis and indurative pancreatitis.

Concomitant elevations of ALAT >3xULN and bilirubin >2xULN were observed during the first month of ximelagatran therapy in 6 of 37 patients.

Two comparator-treated patients with concomitant ALAT >3xULN and bilirubin >2xULN died and both died from pancreatic cancer.

Nine ximelagatran-treated patients who died are presented here more in detail (including patient # 7859 who was missed by the sponsor for concomitant ALAT and bilirubin elevation analysis).

- Patient 7259, an 80 year old male, began ximelagatran 36 mg bid treatment on 11 June 2001. He experienced elevated liver transaminases with biopsy-demonstrated hepatic necrosis and a fatal bleed due to a duodenal ulcer. The patient had a medical history of hyperlipidemia treated in the past with simvastatin until March 1999, AF since 1996, hydronephrosis probably related to an ectopic ureter insertion, urinary retention, fibromyalgia treated with prednisone in the past, coronary artery disease treated with bypass grafting in 1999, and right colon cancer diagnosed in 1999. Concomitant medications included Lopressor (metoprolol), digoxin, and Flomax (tamsulosin). On 30 May 2001, the patient's baseline liver function tests were normal with ALAT 16 U/L, ASAT 22 U/L, ALP 67 U/L and total bilirubin 0.9 mg/dL . On 6 August 2001, at the Month 2 Visit, his LFTs were mildly elevated, but less than the 3x ULN threshold that required discontinuation of study medication . At the next scheduled visit (4 September 2001) the transaminases were found to be further elevated (ALAT 970 U/L, ASAT 698 U/L, ALP 142 U/L), leading to weekly LFT monitoring and study drug discontinuation on 7 September 2001. Transaminases continued to increase. On 19 September 2001, ALAT and ASAT were 1502 U/L and 1355 U/L, respectively; ALP was 154 U/L; total bilirubin was 2.4 mg/dL (nearly twice the ULN) and direct bilirubin was 0.6 mg/dL. Serologies for hepatitis A, B, and C, cytomegalovirus, Epstein-Barr, and herpes simplex viruses did not show a recent viral infection. Carcino-embryonic antigen and antinuclear antibodies were negative. Abdominal ultrasound showed normal liver, normal gallbladder, normal biliary tree and 2 simple cysts in the right kidney. An abdominal and pelvic CT scan performed on 21 September 2001 showed no significant new findings compared to a prior examination (3 August 2000). Liver transaminases peaked on 27 September 2001 and then decreased on 4 October 2001. ALP peaked at 198 U/L on 3 October 2001 and decreased to 170 U/L on 4 October 2001. Total bilirubin was 10.7 mg/dL

on 3 October 2001 and then decreased to 7.9 mg/dL on 4 October 2001. Prothrombin time (13.6 sec) and INR (1.2), which were close to normal on hospital admission (20 September 2001) started to increase on 1 October 2001, reaching16.3 sec and 1.7 respectively. Conversely, albumin decreased to 2.9 g/dL on 2 October 2001. This laboratory profile suggested impairment of his synthetic liver function. A liver biopsy performed on (27 September 2001) demonstrated "severe active hepatitis with hepatocyte necrosis, areas of collapse and marked bile ductular proliferation consistent with acute submassive necrosis." The hepatologist considered the most likely explanation was medication-induced hepatitis. INR remained elevated (1.8 on 8 October 2001) and serum albumin low (2.5 g/dL on 8 October 2001). platelet count was 65,000/mm^3 (29 October 2001). Profound fatigue continued with no evidence of encephalopathy. However, he had developed ascites, significant lower extremity edema and oliguria. On the morning of 3 November 2001, the patient's wife found him unresponsive at home. Resuscitation failed and the patient was pronounced dead. The cause of death was upper GI bleed due to duodenal ulcer. An autopsy confirmed the presence of atherosclerotic disease, ischemic heart disease with triple CABG and atrial septal defect repair; adenocarcinoma of the colon resected with no evidence of recurrence or metastatic disease, and left hydronephrosis with no evidence of mechanical obstruction. The significant findings were: A large duodenal ulcer (2.5 cm) with erosion into pancreas and peripancreatic soft tissue and hemorrhagic contents through most of the small intestine with intact bowel. A small, friable and diffusely mottled liver suggestive of severe diffuse hepatic necrosis. Microscopically, there was extensive liver necrosis with hepatocyte dropout and bile duct proliferation, similar to that seen in the previous biopsy. A significant amount of hepatic parenchyma remained. Tissue architecture showed early resolution of the inflammation compared to the previous biopsy. There was serous ascites in the abdomen. The spleen was not enlarged. Moderate reduction of megakaryocytes in bone marrow. The cause of death was an acute gastrointestinal bleed from a duodenal ulcer, with a coagulopathic state from hepatic injury contributing to death. Both decreased clotting factors and platelet reduction cause the coagulopathy, the latter related to a decreased number of megakaryocytes in the bone marrow. The autopsy report speculated that prednisone therapy may have caused the duodenal ulcer and decreased synthesis of thrombopoietin by the liver could have played a role in the thrombocytopenia. The investigator assessed the event of liver failure as being related and the event of fatal bleed due to duodenal ulcer as not related to the study medication.

- Patient 5442 was a 73 year old male Caucasian. Relevant medical history included diabetes mellitus, systemic lupus erythematosus, hypertension, heart disease, gastric ulcer, COPD and cardiac arrhythmia. The reason for entering the study was DVT. The patient received 36 mg Ximelagatran b.i.d. Transaminases were slightly increased (ASAT 60 U/l; ALAT 60 U/l; AP 210 U/l), nine days after start of study medication, but this was thought to be due to the known lupus erythematosus which was otherwise not active (titer of antinuclear antibodies > 1:80, i.e. normal). Eighteen days after commencing study medication, the patient experienced hepatitis type B and was hospitalized. Hepatitis serology had been done six days before admission because of rising transaminases and showed HBs antigen, HBc antibody and HBe antigen 2 positive, while HBs antibodies, hepatitis C virus antibodies, HBe antibodies, HAV-

Ak-IgM and HBc-Ak-IgM were all negative. From this constellation with absence of antibodies an acute hepatitis B was diagnosed. With regard to the normal incubation time, infection had probably occurred before inclusion into the study, but a plausible source of infection could not be detected. Transaminases continued to rise. Four days after hospitalization, ASAT was 354 U/l, ALAT 367 U/l, AP 292 U/l and G-GT 54 U/l. LDH had increased to 360 U/l and bilirubin was 1.8 mg/dl. Two days later study medication was withdrawn. The patient's general condition was good, without signs of hepatic encephalopathy or failure. Two days after withdrawal of study medication, ASAT was 593 U/l, ALAT 518 U/l and bilirubin 4 mg/dl. The next day the patient was transferred to an infection treatment unit. The patient began to develop icterus and bilirubin tests taken ten days, 15 days and 19 days after onset, showed a rapid increase to 8 mg/dl, 17.2 mg/dl and 26.8 mg/dl, respectively. Transaminases meanwhile decreased slightly. Eleven days after onset of the event, the patient complained of nausea and pain in his right flank. Five days later, a gastroscopy performed showed multiple gastric ulcers covered with fibrin, but no signs of acute bleeding. Quick value, which had been around 40% before, dropped to 29 % with an international normalized ratio of 2.3. ASAT value was 287 U/l and ALAT was 189 U/l approximately three weeks after onset. Therapy consisted of low molecular heparin, oral iron substitution, pantoprazole, metoclopramide, lactulose, prednisolone, amino acid infusions and amoxicilline + clavulanic acid. The patient's general condition deteriorated. Abdominal computerized tomography performed 18 days after onset, showed beginning formation of ascites. On that day the patient complained of vertigo and nausea and felt very tired. The next day repeated enuresis was reported. Agitation, signs of hepatic encephalopathy and tarry stools appeared three weeks after onset. During the next two days the patient deteriorated dramatically. All therapy was stopped because of poor prognosis. The patient became comatose and died from hepatic failure two days later. Autopsy was not performed. All attending doctors agreed that the cause of death was fulminant hepatitis B, but it seemed debatable whether this was an acute condition or an exacerbation of a chronic disease that had already been present in 2001, but had been masked by the immunosuppressive therapy for lupus erythematosus. Azathioprine induced hepatotoxicity is another aggravating factor under discussion. The investigator considered there was a reasonable possibility that the event may have been caused by study medication.

- Patient 3963 was a 45 year old Caucasian. Relevant medical history included constant atrial fibrillation, left heart failure, congestive cardiomyopathy, chronic bronchitis, paroxysmal ventricular tachycardia and an automatic implantable cardioverter/defibrillator. Pre-study stroke prophylaxis consisted of warfarin. As study treatment the patient was allocated to receive ximelagatran 36 mg b.i.d. Approximately 28 weeks after commencing study medication the patient was hospitalized with dyspepsia, nausea, vomiting, increased weight and girth. In addition the pacemaker had been activated three times for the last few days because of ventricular tachycardia. The condition was consistent with deterioration of congestive heart failure with increased right heart failure, peripheral edema and possible liver enlargement. Blood samples including liver enzymes were taken. An ultrasound of the liver showed severe intra-abdominal obesity and fatty liver. The slightly increased liver enzymes were assessed due to hypoperfusion and liver stasis. The patient's treatment with diuretics

and antiarrhythmics was adjusted after which the condition stabilized. The day before the planned discharge, the condition aggravated acutely with cardiogenic shock. The patient was transferred to another hospital where in spite of maximum inotropic support, the patient died. The patient died approximately nine days after the onset of the event. Cause of death was cardiac failure and shock. An autopsy has not been performed. The investigator considered there was no reasonable possibility that the events may have been caused by study medication. Additional safety surveillance resulted in the following information: Approximately 6 months from start of study drug (day 190), elevated LFTs were noted by the central laboratory: ALT 4.81 x ULN, AST 4.33 x ULN, ALP 1.98 x ULN and Bil 2.77 x ULN. Repeat sampling on day 203 showed ALT 1.31 x ULN, AST 1.17 x ULN, ALP 1.36 x ULN, and Bil 1.77 x ULN. At this time point the patient was re-hospitalized with deterioration of congestive heart failure, as described above.

- Patient 0430 was a 90 year old Caucasian. Relevant medical history included hypertension, myocardial infarction, diabetes, lumbar pain, insomnia and bronchopneumopathy. The reason for entering the study was an acute coronary syndrome with a peak Troponin I value of 0.44 (ULN=0.04). The patient received ximelagatran 24 mg b.i.d. and ASA 160 mg o.d. After four weeks on study drug the patient developed right cardiac failure which was considered non-serious. After 17 days the event was considered medically important and the patient was hospitalized. He presented with bilateral lower leg edema and jugular turgescence. The patient was hospitalized for worsening of right cardiac failure after 16 weeks on study drug. He presented with edema. Study drug was withdrawn (total study drug treatment was 18 weeks) and the patient died from right cardiac failure 3 days after stop of study drug. No autopsy was performed. The investigator considered that there was no reasonable possibility that the events may have been caused by study medication or by other medication. Additional safety surveillance resulted in the following information: Four and a half months from start of study drug (day 132) elevated LFTs were noted by the central laboratory: ALT 4.42 x ULN, AST 6.35 x ULN, ALP 4.30 x ULN, and Bil 2.23 x ULN. ALT had been slightly increased at start of study drug (1.33 x ULN), but was normal from day 8 until day 132. ALP was elevated throughout the study with a peak at the last sampling on day 132. Bil was slightly elevated from day 84. The patient experienced a minor conjunctival bleeding 11 days prior to the ALT elevation and muscular pain 4 days prior to the ALT elevation. As described above, the patient also had hematuria followed by worsening of right cardiac failure with fatal outcome at the time of the ALT elevation.

- Patient 2893 was a 66 year old Caucasian. Medical history included paroxysmal atrial fibrillation, angina pectoris, myocardial infarction, chronic obstructive airways disease, cholelithiasis and hypercholesterolaemia. Pre-study stroke prophylaxis consisted of warfarin. As study treatment the patient was allocated to receive ximelagatran 36 mg b.i.d. Approximately 40 weeks after commencing study medication, the patient experienced abdominal pain and nausea. The patient was hospitalized and hepatic colic was diagnosed. After one week in hospital he also experienced severe heart failure. This event lasted only one day. The patient remained in hospital. One week after the episode with severe heart

failure the patient had symptoms of ventricular tachycardia. He was treated with DC shock and xylocaine. He was discharged from hospital after five weeks, and was recovered from all events at that time. Study drug continued unchanged. Approximately one year and seven weeks after start of study drug the patient suffered from eruption of erysipeloid. He was hospitalized one week later and treated with ciprofloxacin. During the hospitalization stay, approximately one month after he was admitted the patient suffered from abdominal pain due to cholelithiasis. The clinical condition deteriorated and he died the next day. Cause of death was cardiac arrest. The investigator suggested that the abdominal pain surcharged the heart and thereby caused the cardiac insufficiency. There was no action taken regarding study drug prior to the death. The investigator considered there was no reasonable possibility that the events may have been caused by study medication. Additional safety surveillance resulted in the following information: Local ALT peak was 18.4 x ULN at day 287, but ALT never exceeded 3 x ULN in central labs.

- Patient 1793 was a 69 year old Caucasian. Relevant medical history included constant atrial fibrillation and unspecified essential hypertension. Pre-study stroke prophylaxis consisted of warfarin. As study treatment the patient was allocated to receive ximelagatran 36 mg b.i.d. Approximately 34 weeks after commencing study medication, the patient experienced dyspepsia, icterus and weight loss. The patient was hospitalized. Study medication was withdrawn due to the event icterus. Metastases in liver were discovered. During the hospital stay approximately 12 days later malignant neoplasm was discovered in the stomach. Computed tomography, sonogram and laparotomy were performed. The patient was given symptomatic treatment. Nine days after the operation the patient suddenly died. An autopsy was performed which confirmed the cause of death as pulmonary embolism. The investigator considered there was no reasonable possibility that the events may have been caused by study medication. Additional safety surveillance revealed the following information: Approximately eight months from start of study drug (day 237) elevated LFTs were noted by the central laboratory: ALT 3.56 x ULN, AST 2.51 x ULN, ALP 3.54 x ULN, and Bil 5.00 x ULN. No further central labs were obtained for reasons described above.

- Patient 2065 was a 51 year old Caucasian. Relevant medical history included sleep apnoea. The reason for entering the study was an acute coronary syndrome with a peak CKMB value of 331 (ULN=3). The patient received ximelagatran 60 mg b.i.d. and ASA 160 mg o.d. After three weeks and five days on study drug treatment the patient had icterus. A liver ultrasound was performed showing a 4 times 4 cm large tumor in the pancreatic gland. Bilirubin was 141 (normal range 4-21), ALP was 10.2 (normal range 0.8-4.6) and ALAT was 11.2 (normal range < 0.80). Study drug was withdrawn. The patient was discharged after two weeks and six days. Six weeks after stop of study drug the patient had visual field loss. A CT-scan of the brain was done. Treatment with heparin fraction was given. According to available information the event was still present when the patient died. Two weeks and six days later the patient was again hospitalized due to worsening symptoms of his pancreatic tumor with liver metastasis. Ultrasound showed ascites, which was evacuated. No chemotherapy was given during this hospitalization. He was discharged after one week and four days. The

patient died at home three days later because of his cancer. The investigator considered that there was no reasonable possibility that the events had been caused by the study medication. Additional safety surveillance resulted in the following information: Expressed as multiples of ULN, ALT peak value was 11.81 x ULN at day 34, which was 8 days after study drug had been stopped. At day 40 ALT was 4.79 x ULN, AST 2.02 x ULN, ALP 2.35 x ULN, and Bil 12.45 x ULN. No further central labs were obtained before death.

- Patient 4035 was a 76 year old Caucasian. Relevant medical history included previous VTE event, hypertension, parkinsonism, pyeloglomerulonephritis and coronary disease. The reason for entering the study was DVT. The patient received ximelagatran 36 mg b.i.d. Fifteen weeks after start of study drug the patient was hospitalized due to melaena, decreased haemoglobin and anaemia. HB was 8.6. Bleeding from the digestive tract was suspected. Study drug was permanently stopped. Blood transfusion (two units of blood) was given. Gastroscopy was normal. The patient recovered from the bleeding and was discharged from hospital one week after start of event. Hb was now 12.0 (normal for this patient). Two weeks after discharge from hospital colonoscopy and ultrasonography were done that revealed adenocarcinoma of colon. Four weeks after stop of study drug the patient was hospitalized for operation of colon adenocarcinoma and liver metastases in the right liver lobe. Resection of sigmoideum and right liver lobe were done. After six days X-ray of abdomen showed fluid levels. An abscess of the anastomosis was diagnosed and he was re-operated. Four days later a multiorgan failure developed diagnosed with abdominal ultrasound and x-ray. The patient was treated with antibiotics, fluid, enoxaparin, blood, plasma and digoxin. He died the same day and the probable cause of death was the multiorgan failure. The investigator considered there was a reasonable possibility that the event bleeding from digestive tract may have been caused by study medication, but that there was no reasonable possibility that the events adenocarcinoma, liver metastases, abscess of anastomosis and multiorganic failure may have been caused by study medication.

- Patient 7859 (not included in the sponsor's concomitant ALAT and bilirubin elevation analysis) was a 77 year old Caucasian and initiated on ximelagatran 36 mg bid treatment on 13 August 2001. Past medical history included a cholecystectomy, duodenal ulcer, sick sinus syndrome, pacemaker insertion, hypertension, carotid stenosis, abdominal aortic aneurysm repair (13 April 2001), and coronary artery disease. On 15 October 2001 (day 63), safety laboratory results demonstrated elevated liver transaminases: ALAT 216 U/L, ASAT 154 U/L; ALP was 156 U/L and total bilirubin 1.3 (baseline 1.1) mg/dL. He took his last dose of study medication in the evening on day 80. The next day (on 2 November 2001), the patient awoke with stomach pain and light-headedness. Bowel movements produced bloody stools. He was admitted to hospital that same morning. At admission, he had pallor, blood pressure 76/45 mm Hg, and heart rate 103/min. Laboratory tests showed hemoglobin of 7 g/dL, hematocrit 20%, prothrombin time 37 sec, INR 3.4, aPTT 69 sec, albumin 2 g/dL, ASAT 629 U/L, ALAT 569 U/L, ALP 173 U/L and plasma melagatran was 0.25 μM (therapeutic range). During hospitalization, he received vitamin K, packed red blood cells (19 units), fresh frozen plasma (15 units), cryoprecipitate (30 units) and fluids. On 03 Nov laboratory tests showed hemoglobin of 9.6 g/L, hematocrit of 27.3%, prothrombin time 14.5 secs, aPTT 53 secs and

INR 1.1. Liver enzymes also decreased: ALAT 134 U/L, ASAT 236 U/L and ALP 49U/L, but bilirubin was 6.2 (5.6x ULN). The patient underwent a gastroscopy that revealed a Bilroth II anastomosis. There was bleeding in the pre-anastomotic area and epinephrine was injected to attempt to decrease the bleeding. The same day (3 November 2001) he presented with signs of respiratory failure. Echocardiogram showed 55% left ventricular function and no major cardiac abnormalities. However, heart rate was 130 to 140/min. Vasopressors were necessary to sustain blood pressure and diltiazem was given to decrease the heart rate. Synchronized cardioversion failed 4 times to establish sinus rhythm. Shock persisted despite resuscitation with fluids, 2 units of packed RBC, 10 units of fresh frozen plasma and 1 unit of platelets. Profound coagulopathy occurred. A consulting surgeon deemed operation futile. Support was subsequently withdrawn and the patient died on 3 November 2001. No autopsy was conducted but the cause of death was considered to be hemorrhage. The investigator assessed the event as possibly related to the study medications and concluded that the liver problems contributed to the bleeding.

2.6.10 Deaths in ximelagatran-treated patients with ALAT >3xULN

The number of deaths in ximelagatran-treated patients having maximum ALAT >3xULN is 19 (3.6%, 19/531) and in patients having maximum ALAT $\leq$3xULN is 251 (251/6417, 3.9%) for central laboratory ITT population. There was no apparent difference in the incidence of death between ximelagatran-treated patients who experienced an increase in ALAT >3xULN (3.6%) and those who did not (3.9%).

In addition to the 19 patients (19/531, 3.6%) who had ALAT >3xULN measured at the Central laboratory subsequently died, an additional patient died after study closure and is therefore not counted in the ITT analysis and a further 3 patients who had ALAT >3xULN measured at a local laboratory subsequently died. Therefore, a total of 23 patients who had ALAT >3xULN subsequently died. The one individual who had an hepatic SAE leading to death was Patient SH-TPV-0002-265-5442 (see details above). ALAT was elevated 12 days after starting study medication and he died 6 days thereafter from an acute hepatitis B rapidly evolving to fulminant hepatitis. This pattern of ALAT elevation was not consistent with the previously observed pattern of elevations in patients exposed to ximelagatran. Although ximelagatran was not the cause of the infectious hepatitis, the investigator could not rule out the possibility that it aggravated the outcome. Two other patients who died due to GI hemorrhage with severe coagulopathy had elevated hepatic enzymes prior to death; both cases (patient 7259 and 7859) were described above. Clearly, coagulopathy was due to ximelagatran and it aggravated and contributed to these 2 patients' deaths.

Patients who had ALAT >3xULN measured at the Central laboratory and subsequently died are presented in Table 37.

Table 37: List of ximelagatran-treated patients who had ALAT >3xULN measured at the Central laboratory and subsequently died

			No of days post-randomization		Cause of death
Patient	Age	Sex	ALAT >3xULN	Patient died	
SH-TPA-0003-100-1793	69	M	240	240	Embolism Pulmonary
SH-TPA-0003-104-2978	78	F	62	140	Myocardial Infarction
SH-TPA-0003-115-3963	45	M	190	209	Cardiac failure
SH-TPA-0003-118-1685	74	M	70	556	Sudden death
SH-TPA-0003-258-3276	75	F	91	99	Cerebrovascular disorder
SH-TPA-0003-316-2826	75	F	94	146	*(No fatal SAE[a])*
SH-TPA-0005-0230-6977	63	M	155	169	Aneurysm
SH-TPA-0005-0610-6082	81	M	122	125	Cardiomyopathy - Sudden death
SH-TPA-0005-0620-7259	80	M	85	145	GI haemorrhage
SH-TPA-0005-0760-7438	64	M	58	469	Cardiac arrest
SH-TPA-0005-1860-5022	88	M	101	124	Sepsis
SH-TPA-0005-2990-6603	85	M	94	94	Death
SH-TPA-0005-3030-7859	77	M	63	82	GI haemorrhage
SH-TPV-0002-265-5442	73	M	12	18	Hepatitis infectious
SH-TPC-0001-120-0430	90	M	132	132	Cardiac failure
SH-TPC-0001-150-0733	65	M	140	140	Renal failure NOS - Sepsis
SH-TPC-0001-278-2524	62	M	61	89	Sudden death
SH-TPC-0001-310-2946	54	M	139	139	Myocardial infarction
SH-TPC-0001-348-2065	51	M	27	40	Pancreas neoplasm

a AE not recorded after discontinuation in this study. Cause of death was recorded as rupture of aorta ascendense

An additional patient died after study closure and is therefore not counted in the ITT analysis. Patient SH-TPC-0001-062-0286, an 82 year old female, died from AMI 2 weeks after stopping study drug (ximelagatran 36 mg bid) due to a previous AMI.

A further 3 patients who had ALAT >3xULN measured at a local laboratory subsequently died. These were as follows:

Patient SH-TPA-0005-0050-8357, a 74-year-old female, died from sepsis while taking ximelagatran 36 mg bid, and the temporary ALAT elevation was found during a previous hospitalization for pneumonia.

Patient SH-TPA-0003-217-2893, a 67-year-old male, died while taking ximelagatran 36 mg bid due to acute cholecystitis and cardiac arrest. The reported SAE term was abdominal colic.

Patient SH-TPV-0002-504-4035, a 76-year-old male, died due to multiorgan failure. The patient had been hospitalized for operation of colon adenocarcinoma and liver metastases in the right liver lobe, 4 weeks after stop of study drug (ximelagatran 36 mg bid).

Seven of 19 cases (#1793, 3963, 7259, 7859, 5442, 0430 and 2065) have been discussed above in detail. Patient 2826 died from rupture of aorta and patient 6603 died 16 months after discontinuing study drug.

2.6.11 Potential prognostic factors related to ALAT >3xULN.

The multivariate analysis of potential prognostic factors for the risk of ALAT>3xULN was performed using a logistic regression model with a stepwise selection algorithm. The following factors were tested for inclusion; sex (female vs male), age, (>=75 vs <75 years), weight (>=75 vs <75 kg), BMI (>=27 vs <27 kg/m2), CrCL (>=80 vs <80 mL/min), ethnic origin (Asian vs rest, i.e. all others), concomitant aspirin use (yes vs no), concomitant statin use (yes vs no), and patient population (VTE-T vs rest, VTE-P vs rest and Post ACS vs rest, AF was used as "baseline"). Stepwise analyses are presented in Table 38 (for patients in the ximelagatran group only).

Table 38: ALAT >3xULN, analysis of potential prognostic factor, stepwise model selection algorithm, (ximelagatran group only) (ITT population): LTE pool

	Odds Ratio	95% Confidence Interval		p-value
		Lower limit	Upper limit	
Post ACS	1.53	1.19	1.96	0.0009
HMG Co-A reductase inhibitors use	1.31	1.05	1.65	0.0190
VTE-T	1.53	1.22	1.93	0.0003
BMI>=27 kg/m^2	0.57	0.47	0.68	<.0001
Asian	0.35	0.17	0.71	0.0038
Female Sex	1.41	1.18	1.70	0.0002

From these analyses 6 risk factors were statistically significant for the ximelagatran group: Post ACS population (p=0.0009), VTE-T population (p=0.0003), use of statins (p=0.019), BMI <27 kg/m2 (p<0.0001), non-Asian race (p=0.0038) and female sex (p=0.0002, 9.4% vs. 6.7%).

2.6.12 Relationship between exposure to melagatran and ALAT elevation.

Exposure to melagatran has been evaluated in patients in the non-surgical long-term studies. Individual melagatran AUCs were estimated by population PK modeling. The distribution of melagatran AUC in patients with an event is largely within the melagatran AUC range in patients without an event. These data suggest that for the patient population and doses studied exposure is not predictive of ALAT >3xULN in individual patients.

The calculated cumulative risk (hazard ratio) of an increase in ALAT for each unit increment of AUC, in each pool, is shown in Table 39. Except for the VTE-P and post ACS pools, there is a

statistically significant relationship between exposure and the risk of an ALAT elevation above 3xULN in each pool.

Table 39 Relationship of melagatran AUC to occurrence of ALAT elevation >3xULN

Endpoint	Events	Patients	Hazard Ratio[a]	95% CI Lower	95% CI Upper	Pr > Chi-Square
LTE pool[b]	491	6687	1.07	1.03	1.12	0.0004
AF[b]	217	3606	1.13	1.03	1.24	0.0084
VTE-T	112	1240	1.17	1.07	1.29	0.0011
VTE-P	36	596	1.26	0.95	1.69	0.1125
Post ACS	126	1245	1.03	0.98	1.09	0.2763

a Hazard ratio corresponds to the increase in cumulative risk with one unit increase of AUC
b Excluding SH-TPA-0002 and SH-TPA-0004
Data derived from PK exposure response statistical analysis report version 6.2, Table 47

2.6.13 Summary of hepatobiliary toxicity

In patients receiving long-term administration of ximelagatran (>35 days) an increase in ALAT >3xULN occurred in 6-13% (total: 531/6948, 7.6%) compared to 0-2% (total: 68/6230, 1.1%) of patients receiving comparator treatments. ASAT increased in conjunction with ALAT. The time pattern of ALAT elevations was consistent and typically occurred between 1 and 6 months after the initiation of ximelagatran. Prior to and after this time frame the incidence of ALAT increase was similar to comparators. These data are based on ALAT sampling in 6840 patients.

Among the 531 patients in the ximelagatran group who presented with an ALAT >3xULN, 206 (39%) completed the study on study drug. The remaining 325 patients (61%) discontinued study drug prematurely. The hepatic transaminases returned to <2xULN in the majority of patients (95%), whether the patient continued treatment with ximelagatran or not.

An evaluation of potential risk factors for increase in ALAT indicated an increased risk in the Post ACS (p=0.0009), and VTE-T (p=0.0003) populations and also in female patients (p=0.0002) patients with low BMI (<27 kg/m2) (p<0.0001) and patients receiving concomitant treatment with statins (p=0.019); Asian patients were found to have a decreased risk (p=0.0038). Although any single factor identified above may not be strong enough to justify to excluding the subgroup population, the patients who have 2 or more risk factors should not be given ximelagatran, such as, female patients with low body weight or who are taking statin.

ALAT >3xULN was associated with bilirubin >2xULN (within one month following the rise in ALAT) in 0.53% (37/6948) of all patients who were exposed to ximelagatran >35 days as compared to 0.08% (5/6230) of patients exposed to comparators (including 10 ximelagatran and 1 comparator by local laboratory measurement). A total of 14 ximelagatran-treated patients (14/37, 35.1%) have no alternative explanation for concomitant ALAT and bilirubin elevation. Concomitant elevations of ALAT >3xULN and bilirubin >2xULN were observed during the first month of ximelagatran therapy in 6 of 37 patients. Nine of the ximelagatran-treated patients who had ALAT >3xULN and bilirubin >2xULN (24.3%, 9/37) died with these elevations. Among

them, 3 died from heart failure; 3 died from carcinomas with hepatic matastases; 2 (ID# 7259, and 7859) died from GI bleeding with coagulopathy and 1 (ID# 5442) died from hepatitis B. One patient developed biopsy documented hepatic necrosis with coagulopathy with a fatal outcome from a duodenal ulcer (#7259). Liver failure/toxicity by ximelagatran might have caused or at least contributed to these deaths.

In conclusion, safety data on hepatobiliary toxicity does not support the safe use of ximelagatran for long-term (>35 days) treatment of patients with AF or DVT for either 36 mg bid or 24 mg bid dosing.

2.7 Analysis of adverse events of pancreatic effects

Pancreatic hyperplasia has been observed in pre clinical studies in rats. A "pancreas sub-study" was performed as part of study SH-TPA-0005 to determine if there was a safety concern for ximelagatran regarding pancreatic hyperplasia. CCK plasma concentrations were measured after approximately 3 months of receiving study drug in a subset of patients. The objective of this assessment was to determine whether ximelagatran was associated with elevations in plasma CCK after a standard meal because this is the mechanism by which rats undergo pancreatic trophic stimulation, possibly leading to pancreatic adenomas and occasionally, pancreatic carcinoma. In addition, special abdominal CT scans were performed, which were designed to measure pancreas volume, obtained prior to drug exposure and then again after 12 months' exposure to study drug. The objective of this assessment was to determine whether long-term administration of ximelagatran was associated with increased pancreas volume because a trophic effect on pancreas would yield increased volume of pancreatic tissue.

2.7.1 CCK in plasma – laboratory findings

A total of 130 patients (62 ximelagatran, 68 warfarin) were enrolled in the CCK subset, of whom 119 (56 ximelagatran, 63 warfarin) provided CCK plasma data at 3 months. Mean (SD) CCK plasma concentration was 14.97±18.32 picomolar for the ximelagatran-treated patients and 11.39±16.51 picomolar for the warfarin-treated patients. Median CCK plasma concentration was 6.63 (range 2.00 to 62.50) picomolar for the ximelagatran-treated patients and 4.50 (range 2.00 to 62.50) picomolar for the warfarin-treated patients. There was no statistically significant difference in the plasma concentrations between the 2 groups, p=0.225 (Mann-Whitney test). The data were not normally distributed and no transformations were applied and hence the Mann-Whitney test was used.

2.7.2 Pancreas volume – laboratory findings

Complete sets of pancreatic CT scans were available for a subset of 34 patients in the ximelagatran group and 28 patients from the warfarin group. The mean ±SD change from baseline in pancreatic volume was -10.85±13.63 for the ximelagatran group and -10.49±13.85 for the warfarin group and was statistically significant for both treatment groups (p=0.0001 and 0.0004, respectively). However, the between group comparison was not statistically significant, p=0.92 (Student's t-test). Pancreatic volume change over one year did not correlate with CCK

plasma concentration at 3 months. Treatment, CCK, and treatment-CCK interaction did not affect pancreatic volume.

2.7.3 Analysis of AEs affecting the pancreas: long-term exposure (LTE) pool

During the program, 13 patients (2 ximelagatran, 11 comparator) were diagnosed with a pancreatic cancer. Fifteen patients developed pancreatitis during active treatment in the program (6 ximelagatran, 9 comparator). A further 2 patients had an AE of pancreatitis in the follow-up period, one after treatment with ximelagatran (SH-TPA-0003-096-2960) and one after treatment with warfarin (SH-TPA-0005-2690-7288).

Taking into account both the AE profile and the sub study data, there is no safety concern for ximelagatran regarding pancreatic events.

2.8 Analysis of adverse events of coronary artery disease

Patients with coronary artery disease (CAD) adverse events are summarized in Table 40.

Table 40: Summary of patients with adverse events of coronary artery diseases (safety population)

Population with CAD AE		Ximelagatran (AF, n= 3836) (VTE-T, n=1236) (VTE-P, n=612) n	%	Warfarin (AF, n= 3719) (VTE-T, n=1248) (VTE-P, n=611 placebo) n	%	p-value
AF:	Total CAD	268	7.0	248	6.7	P=0.584
	MI	62	1.6	52	1.4	
VTE-T	Total CAD	16	1.3	1	0.1	P=0.00024
	MI	3	0.2	0	0	
VTE-P	Total CAD	16	2.6	12	2.0	P=0.447
	MI	10	1.6	3	0.5	P=0.05131
VTE	Total CAD	32	1.7	13	0.7	P=0.00411
	MI	13	0.7	3	0.16	P=0.01183

VTE=VTE-T + VTE-P

In all study populations except the post ACS, the proportion of patients with coronary artery disease adverse events was higher in the ximelagatran groups than in the comparator groups (7.0% and 6.7% for the AF pool, 1.3% and 0.1% for the VTE-T pool and 2.6% and 2.0% for the VTE-P pool, for the ximelagatran and comparator groups, respectively). This trend was consistent across the pools for myocardial infarction; however, the difference in event rates (%/patient year) was small (0.9% and 0.6% for the AF pool, 0.6% and 0% for the VTE-T pool and 1.1% and 0.2% for the VTE-P pool, for the ximelagatran and comparator groups, respectively). Proportion of patients with coronary artery disease adverse events was statistically significantly higher in the ximelagatran group (32/1848, 1.7%) than in the warfarin/placebo

group (12/1859, 0.7%) in VTE (VTE-T + VTE-P) population (p=0.00411). Proportion of patients with MI was also significantly higher in the ximelagatran group (13/1848, 0.7%) than in the warfarin/placebo group (3/1859, 0.16%) in VTE population (p=0.01183). There were no appreciable differences between the treatment groups for underlying diseases including hypertension, hypercholesterolemia, diabetes mellitus, coronary atherosclerosis, as well as age, gender and weight. Considering ximelagatran as an anticoagulant with potential to treat MI, these results are worrisome.

2.9 Clinical Laboratory Evaluations

The analyses of clinical laboratory data in the individual studies in this application have not identified any adverse findings with the exception of increases in LFTs.

Microscopic hematuria was more common in the ximelagatran group than in the placebo group in the post ACS pool; however, in the warfarin comparison pools there was no difference.

A reduction in triglycerides, cholesterol and LDL was seen in the ximelagatran group in the AF pool.

2.10 ECG analysis in patient studies

There have been no signals of any relevant effect on QT intervals in patients exposed to ximelagatran (24 mg bid) in studies investigating prophylactic treatment after hip and knee replacement operations.

ECG measurements were performed in 2 studies carried out on the prophylactic effect of ximelagatran on postoperative thrombo-embolism in patients undergoing total hip or total knee replacement. In these studies (SH-TPO-0005 and SH-TPO-0006, n=2491) ECG was recorded at baseline and at the time of venography (6-12 days postoperatively).

The most common ECG abnormality on the day of venography was atrial arrhythmia and the incidence of this abnormality was comparable in the ximelagatran and enoxaparin groups. No clinically meaningful differences between treatment groups were observed in changes from baseline in any of the ECG parameters during this study.

At the time of venography, heart rate and the QTc interval calculated using Bazett's formula were increased relative to baseline, while the PR and QT intervals were reduced. There was little change in the QTc interval when calculated using Fridericia's formula and the study specific formula. The mean changes in these ECG parameters were small and comparable in both treatment groups.

The proportion of subjects with a large increase in QTc ($\geq$60 ms) from baseline to last day on study drug was numerically lower among subjects receiving ximelagatran (3.1% - 4.0%).

In SH-TPV-0003 ECG recordings were done at the randomization visit (Visit 2, before first intake of study drug) and the visits at 2 weeks (Visit 3) and 9 and 18 months (Visit 6 and 9) after randomization. ECGs from approximately 250 patients were sent for central reading and evaluation by one cardiologist. The following ECG variables were measured: RR interval, PQ interval, QRS duration and QT interval. T-wave abnormalities and U-waves were to be noted.

There were minor changes in the distribution of T-U fusion and U-wave abnormalities from baseline to last visit on treatment, but to a similar extent in the ximelagatran and placebo groups. There was no effect of ximelagatran on QTc time.

2.11 Safety in Special Groups and Situations

2.11.1 Gender, long-term exposure (LTE) pool

In the ximelagatran treatment group, increased hepatic enzymes were more commonly reported for women than for men.

In both treatment groups, coronary artery disorders were more commonly reported for men than for women (female 8.4% vs male 11.4% in the ximelagatran group and female 7.7% vs male 9.8% in the comparator group). In general, bleeding events were more frequently reported for women than men. For example purpura was reported for 10.7% of females vs 6.6% of males in the ximelagatran group and 16.3% of females vs 9.5% of males in the comparator group.

2.11.2 Age, long-term exposure (LTE) pool

To evaluate the frequency of AEs in older vs younger patients, patients were grouped into 3 age categories: below 65 years, 65 to 74 years and 75 years and above.

Irrespective of treatment group, the overall frequency of reported AEs was higher amongst the elderly. Patients aged ≥75 years reported fewer non-fatal SAEs in the ximelagatran treatment group compared to the comparator group (30.3% vs 36.3%), while more patients in the ximelagatran treatment group discontinued study treatment due to AEs in this age group (20.5% vs 16.1%).

In both treatment groups, the overall AE reporting rate was higher with increasing age, with the exception of elevated hepatic enzymes which was reported with a similar frequency in all age groups.

2.11.3 Race, long-term exposure (LTE) pool

To evaluate the frequency of AEs in different race groups, the patients were grouped into four categories: Caucasian, Black, Asian and Other.

In the ximelagatran treatment group, less than 10% of the population were non-Caucasian races. There was no indication of a different AE profile in these sub-groups.

2.11.4 Body weight, LTE pool

To evaluate the frequency of AEs in different body weight groups, patients were grouped into 3 weight categories: less than 50 kg, 50 to 100 kg and above 100 kg.

The AE profile was similar in all weight categories. Fewer than 2% of patients in each treatment group weighed less than 50 kg. The AE profile was not different in this sub-group.

In the ximelagatran treatment group, elevated hepatic enzymes and bleeding events were less frequently reported in patients above 100 kg.

2.11.5 Body mass index (BMI), LTE pool

To evaluate the frequency of AEs in groups with different BMI, patients were grouped into 3 BMI categories: less than 25, 25 to 30 and above 30.

For patients in the lowest BMI category, the reporting frequency of non-fatal SAEs was lower in the ximelagatran treatment group (24.8% vs 28.0%). There was a higher frequency of reported AEs leading to drug discontinuation in the ximelagatran treatment group compared to comparators group (19.3% vs 14.9%).

In the BMI category 25-30, there was a higher reporting frequency of drug discontinuations due to AE in the ximelagatran treatment group compared to comparators treatment group (18.3% vs 13.2%).

For the ximelagatran treatment group in the BMI category >30, there was a higher reporting frequency of AEs leading to drug discontinuations compared to comparators group (13.8% vs 10.7%).

In the ximelagatran treatment group, reporting frequency of elevated hepatic enzymes and bleeding events increased with decreasing BMI.

2.11.6 Influence of renal function, LTE pool

To evaluate if renal function had any influence on the frequency and pattern of reported AEs, the patients were grouped into 4 categories: calculated creatinine clearance below 30, between 30 (inclusive) and 50 (non-inclusive), between 50 (inclusive) and 80 (non-inclusive) or above 80 (inclusive).

Apart from elevated hepatic enzymes, no difference was seen in the overall AE profile between ximelagatran and comparators for any category of calculated CrCL.

Patients with calculated creatinine clearance below 30 mL/min were to be excluded from the clinical studies. Although a few patients (<1%) in this category were recruited and the pattern of AEs was not different from that in other CrCL categories. There was a trend towards an increased frequency of bleeding-related AEs by decreasing calculated creatinine clearance in both treatment groups.

There was no indication of an increased frequency of elevated hepatic enzymes reported as AEs in any calculated CrCL group.

2.11.7 Subjects with renal impairment

Melagatran, the active metabolite of ximelagatran, is eliminated primarily via renal excretion. Renal function decreases with age and, as the target patient population is of older age (median age about 65 years), patients with severe renal impairment (creatinine clearance of less than 30 mL/min) have been excluded in the patient studies with melagatran/ximelagatran. Study SH-TP1-0026 was conducted to investigate the pharmacokinetics of oral ximelagatran and subcutaneous melagatran in subjects with severe renal impairment (CrCL 10 to 30 mL/min, n=12). Subjects with normal renal function (CrCL $\geq$50 mL/min, n=12) were included as a control group.

As expected, subjects with severe renal impairment had higher plasma concentrations of melagatran both after subcutaneous administration of melagatran and oral dosing of ximelagatran. The renally impaired subjects had about 4 times higher AUC after subcutaneous melagatran and about 5 times higher AUC after oral ximelagatran, compared to the control subjects. The mean (SD) half-lives of melagatran were 6.8 (2.0) h and 9.3 (3.5) h after sc melagatran and oral ximelagatran dosing, respectively, in the subjects with renal impairment. These half-lives were about 3-fold higher than for control subjects. The clearance and the renal clearance of melagatran were lower in the renally impaired subjects and were linearly correlated to renal function measured with iohexol clearance (mean (SD) of 12.5 (5.2) mL/min and 86.5 (9.7) mL/min for subjects with renal impairment and normal controls).

Study SH-TP1-0027 investigated the effect of melagatran given via dialysate, compared to dalteparin, in 11 uraemic patients (GFR <8 mL/min). The frequency of clot formation in tubings and in the dialysis filter, the iohexol clearance and the filter pressure were comparable between treatments. The half-life of melagatran was longer when melagatran was administered between dialyses compared to during hemodialysis. The clearance of melagatran was increased by about 7-fold and comparable to the iohexol clearance during haemodialysis.

2.11.8 Subjects with hepatic impairment

Study SH-TP1-0013 investigated the influence of hepatic impairment on the absorption, metabolic biotransformation of ximelagatran to the active form and excretion in subjects with mild to moderate hepatic impairment (as defined by Child Pugh score). Age, weight and gender-matched subjects with normal hepatic function were included as a control group. After adjusting

for differences in creatinine clearance between the 2 groups, the AUC estimates were comparable. The results support that the absorption of ximelagatran and the metabolic biotransformation to its active form melagatran are not influenced for subjects with mild and moderate hepatic impairment. However, because of liver toxicity risk, patients who have abnormal liver function or history of liver diseases have been excluded from the studies.

2.11.9 Drug/drug interaction

Concomitant administration of an anticoagulant and an antiplatelet agent may result in increased bleeding risk, therefore co-administration should be undertaken with caution.

The AUC and Cmax of melagatran was increased by approximately 82% and 74%, respectively, after co-administration of a single dose of ximelagatran and multiple doses of erythromycin (500 mg tid) compared with ximelagatran alone. The mechanism of this interaction is not known. Therefore, caution should be exercised in patients who have increased exposure already, such as patients with moderate renal impairment.

There were no P450-mediated interactions with ximelagatran, in vitro.

2.11.10 Use in pregnancy and lactation

Three cases, all from the VTE-T and VTE-P pools, of ximelagatran exposure during pregnancy have been reported from studies in the present application. In 2 of the ximelagatran cases the pregnancies were completed and full-term babies were delivered. For one of these (study SH-TPV-0002 Subject 063-5395), it was estimated that the maximal exposure to drug could have been 3 weeks from estimated conception. No complications were present during the pregnancy and a completely healthy girl was born. In the other case (study SH-TPV-0003, Subject 653-1285) the maximal exposure to drug was estimated to be up to 2 months from estimated conception. A full-term baby was delivered after an uneventful pregnancy. The boy was found to have a hypospadia that needed surgical correction. Otherwise the baby was healthy.

The third pregnancy reported on ximelagatran, both pregnancies reported on warfarin and 3 of the pregnancies on placebo were terminated through elective abortion, none due to medical reasons.

A study, SH-TP1-0029, was performed with the primary objective to assess the excretion of ximelagatran and its metabolites into breast milk after administration of ximelagatran (single 36 mg dose) to breast-feeding women. Ximelagatran and its 2 intermediates were not detectable in breast milk. Only trace amounts of melagatran (mean 0.00091% of given dose ximelagatran 36 mg) were excreted into breast milk. The exposure of melagatran to a breast-fed child is therefore not believed to be of concern.

2.11.11 Overdose

One case of overdose on melagatran/ximelagatran has been reported in the present program. For a period of 11 days Patient SH-TPV-0002-231-4935, received oral ximelagatran 144 mg daily by mistake, instead of 72 mg daily. No adverse effect was reported.

Ximelagatran doses above the recommended regimen may lead to an increased risk of bleeding. Overdose associated with bleeding complications should lead to temporary treatment discontinuation. There is no antidote but ximelagatran is mainly renally excreted with a short half life. Therefore, satisfactory diuresis should be maintained. Melagatran is efficiently eliminated by dialysis. Plasma and blood products can be administered as needed in case of bleeding.

2.11.12 Drug abuse

Based on its pharmacological properties, ximelagatran is not likely to have a potential for drug abuse. No findings during the clinical study program indicate that ximelagatran induces drug abuse.

2.11.13 Withdrawal and rebound

In Study SH-TPA-0003 (AF population), 11 patients had a stroke after stopping ximelagatran. Of these 11 patients, 2 had primary events within 30 days of stopping study drug; one was being treated with aspirin and LMWH (nadroparin), the other was being treated with clopidogrel. The remaining 9 patients had primary events more than 30 days after stopping drug. The treatments taken by these 9 patients after stopping study drug were: Vitamin K antagonists (3 patients), aspirin (2), clopidogrel (2), LMWH (1) and no treatment (1). There is therefore no indication of a rebound effect in this study.

A follow-up visit was performed in study SH-TPV-0002/5 (VTE-T population) at approximately 2 weeks after completing the randomized treatment period to allow for the observation of any rapid rebound effect. No patient in the ximelagatran treatment group experienced VTE events during the 2-week follow-up period.

For post ACS pool, the total frequency of AMIs after stopping treatment was similar for ximelagatran (1.5%) and placebo (1.4%), and the total mortality was similar between the treatments. However, after stopping treatment fatal AMIs occurred more frequently in the ximelagatran group (0.4%) than the comparator group (0.2%). In the post ACS pool, there was an increased proportion of fatal myocardial infarctions in the post-treatment period (1.1% vs 0.5%).

3 SAFETY UPDATE

The sponsor submitted a 4-months safety update report on April 23, 2004. This safety update report included safety information between 27 June 2003 and 23 March 2004. Safety information included in this report consists of new and follow-up data from recent Phase I studies and studies

in patients. No other safety data are available, as ximelagatran has not been marketed in any country as of 23 March 2004.

A summary of new safety data associated with the SH-TPA-0004 (SPORTIF IV) study is included in this section. SH-TPA-0004 (SPORTIF IV) is an ongoing, open-label, 5-year (recently amended to 10-year) continuation study of the dose guiding study SH-TPA-0002 (SPORTIF II) in patients with AF. The 187 patients in the ximelagatran group received 20, 40, or 60 mg (double-blind, SPORTIF II) for 12 weeks. Those patients (n=125) who continued into the long term study (SPORTIF IV) transferred to a 36 mg bid dose. The warfarin group (67 patients) in SH-TPA-0002 received open-label warfarin (INR 2-3) and continued into SH-TPA-0004 without change. The primary objective of SH-TPA-0004 is to evaluate the safety and tolerability of long-term treatment with fixed oral dose ximelagatran compared to warfarin.

There were 17 deaths (9.1%) by March 23, 2004 in the ximelagatran group and 4 deaths (6.0%) in the warfarin group. The breakdown of these numbers is presented in Table 41.

Table 41 Total Deaths in Long Term Studies SH-TPA-0002 and SH-TPA-0004

	Ximelagatran (N=187)	Warfarin (N=67)
Deaths in interim 2-year report (up to 30 June 2001)	3	2
Deaths from 30 June 2001 to 27 June 2003	9	2
Deaths from 28 June 2003 to 23 March 2004	5	0
Total, n (%)	17 (9.1%)	4 (6.0%)

Although proportion of total deaths was not statistically significantly higher in the ximelagatran group (17/187, 9.1%) than in the warfarin group (4/67, 6.0%) (p=0.426), there were numerically more deaths in the ximelagatran group than in the warfarin group. The reasons for the 5 deaths during this safety update period are listed below.

Treatment	Center: Patient ID	Sex (M/F)	Age (years)	Adverse event (verbatim term)	Causality (as assessed by the investigator)
Ximelagatran	001:268[a]	M	67	Subdural haematoma	Not related
Ximelagatran	012:187	M	67	Sudden death—cardiac arrest	Not related
Ximelagatran	014:192[b]	M	81	Death	Not related
Ximelagatran	014:373[a]	M	92	Heart failure	Not related
Ximelagatran	071:073	M	60	Intracerebral haemorrhage	Not related

For detailed evaluation for this study report, please see Medical Officer's Review dated July 22, 2004 by Dr. Mehul Desai from the Division of Cardio-renal Drug products.

D. Adequacy of Safety Testing

Safety testing regarding liver toxicity in patients taking Exanta ≤ 35 days is not adequate. In both study EXULT A and EXULT B, the patients were only followed up for 4 weeks after operation. Based on the long-term clinical data, liver enzymes elevations in patients who taken Exanta were found typically between 2nd month and 6th month after initiation of Exanta. Liver toxicity was not seen typically during first 4 weeks, even in the patients who had severe liver failure and died from liver failure. Therefore, it is inadequate to monitor liver toxicity for only 4-6 weeks. Clinical data with 6 month follow-up may be needed for adequately assessing liver toxicity following short term use of Exanta.

E. Summary of Critical Safety Findings and Limitations of Data

Safety testing regarding liver toxicity in patients taking Exanta ≤ 35 days is not adequate. In both study EXULT A and EXULT B, the patients were only followed up for 4 weeks after operation. Clinical data with 6 month follow-up are needed to assess liver toxicity following short term use of Exanta.

In patients receiving long-term administration of ximelagatran (>35 days) an increase in ALAT >3xULN occurred in 6-13% (total: 531/6948, 7.6%) compared to 0-2% (total: 68/6230, 1.1%) of patients receiving comparator treatments. ASAT increased in conjunction with ALAT. The time pattern of ALAT elevations was consistent and typically occurred between 1 and 6 months after the initiation of ximelagatran.

ALAT >3xULN was associated with bilirubin >2xULN (within one month following the rise in ALAT) in 0.53% (37/6948) of all patients who were exposed to ximelagatran >35 days as compared to 0.08% (5/6230) of patients exposed to comparators (including 10 ximelagatran, 1 comparator by local laboratory measurement). A total of 14 ximelagatran-treated patients (14/37, 35.1%) have no alternative explanation for concomitant ALAT and bilirubin elevation. Nine ximelagatran-treated patients with concomitant ALAT >3xULN and bilirubin >2xULN died (24.3%, 9/37). Among these, 3 died from heart failure; 3 died from carcinomas with hepatic matastases; 2 (ID# 7259, and 7859) died from GI bleeding and 1 (ID# 5442) died from hepatitis B. One patient developed biopsy documented hepatic necrosis with coagulopathy with a fatal outcome from a duodenal ulcer (#7259). Liver failure/toxicity due to ximelagatran might have caused or at least contributed to these deaths.

The proportion of patients with coronary artery disease adverse events (MI or ischemia/angina) was significantly higher in the ximelagatran groups than in the warfarin/placebo groups for both short-term (7-12 days) and long-term (>35 days) use. In the patients undergoing TKR surgery (Exult A and Exult B), proportion of patients with coronary artery disease adverse events was statistically significantly higher in the ximelagatran group (20/2677, 0.75%) than in the warfarin group (5/1907, 0.26%) (p=0.02800). Proportion of patients with MI was also higher in the

ximelagatran group (16/2677, 0.60%) than in the warfarin group (4/1907, 0.21%) in TKR population (p=0.07308). There were no appreciable differences between the treatment groups for underline diseases including hypertension, hypercholesterolemia, diabetes mellitus, coronary atherosclerosis, as well as age, gender and weight.

The proportion of patients with coronary artery disease adverse events was statistically significantly higher in the ximelagatran group (32/1848, 1.7%) than in the warfarin/placebo group (12/1859, 0.7%) in the VTE (VTE-T + VTE-P) population (p=0.00411). The proportion of patients with MI was also significantly higher in the ximelagatran group (13/1848, 0.7%) than in the warfarin/placebo group (3/1859, 0.16%) in the VTE population (p=0.01183). In all study populations except the post ACS, the proportion of patients with coronary artery disease adverse events was higher in the ximelagatran groups than in the comparator groups (7.0% and 6.7% for the AF pool, 1.3% and 0.1% for the VTE-T pool and 2.6% and 2.0% for the VTE-P pool, for the ximelagatran and comparator groups, respectively). This trend was consistent across the pools for myocardial infarction.

VIII. Dosing, Regimen, and Administration Issues

EXANTA should be taken twice daily, with or without food. Patients should be advised that if they miss their scheduled dose they should not double the next dose.

Following are dosage regimens supported by the submitted studies:

Knee Replacement Surgery
The treatment is initiated with EXANTA at a dose of 36 mg twice-daily for a treatment period of 7 to 12 days. Provided hemostasis has been established, the first dose should be given the morning after surgery, but no sooner than 12 hours from the time of surgery.

Long Term Secondary Prevention of Venous Thromboembolic Events
Patients who have received standard anticoagulant treatment for DVT or PE are to be treated with EXANTA 24 mg twice-daily.

Patients with Renal Impairment: No dosage adjustment is necessary with EXANTA in patients with a creatinine clearance $\geq$30 mL/min. Usage of EXANTA in patients with severe (CrCL <30 mL/min) renal impairment is not recommended.

Patients with Hepatic Impairment: The use of EXANTA in patients with hepatic disease and/or ALT >2 times the upper limit of normal at the start of therapy is contraindicated.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender and Age Effects Analyses and Adequacy of Investigation

In study EXULT A and B for prevention of DVT in patients undergoing elective knee replacement surgery, the incidence of VTE and/or all-cause mortality was higher in females and older patients and summarized in table below.

Table 42 Incidence of total VTE and/or all-cause mortality for selected subgroups (efficacy ITT population; blinded ICAC assessment) – Pooled 36 mg bid

Subgroup factor		Ximelagatran 36 mg (n=1611)		Warfarin (n=1575)	
Category	p-value[a]	%	(n/N)	%	(n/N)
Sex	<0.001				
Male		18.9	(119/628)	24.9	(149/599)
Female		23.4	(230/983)	33.5	(327/976)
Age	0.001				
<65 years		19.7	(110/559)	25.6	(137/536)
65 to 74 years		22.1	(148/671)	33.3	(230/691)
≥75 years		23.9	(91/381)	31.3	(109/348)

Female sex, older age, and a prior history of VTE are known risk factors for VTE. The reasons for the increased incidence of total VTE and/or all-cause mortality in females versus males are unclear. The incidence of proximal DVT, PE, and/or all-cause mortality was also examined as a function of these same pre-specified subgroups. The results for the subgroup comparisons were in agreement with those for total VTE and/or all-cause mortality; however, there were too few events to perform a logistic regression analysis involving proximal DVT, PE, and/or all-cause mortality.

An evaluation of potential risk factors for increase in ALAT indicated an increased risk in female patients (p=0.0002) patients with low BMI (<27 kg/m2) (p<0.0001) and patients receiving concomitant treatment with statins (p=0.019).

B. Evaluation of Evidence for Race, or Ethnicity Effects on Safety or Efficacy

The subgroup factors that had no significant impact on the incidence of total VTE and/or all cause mortality in patients undergoing elective knee replacement surgery were: race, body mass index, estimated CrCL, general anaesthesia (yes/no), time to first dose, and time to ambulation.

An evaluation of potential risk factors for increase in ALAT indicated an increased risk in the Post ACS (p=0.0009), and VTE-T (p=0.0003) populations and also in female patients (p=0.0002) patients with low BMI (<27 kg/m2) (p<0.0001) and patients receiving concomitant treatment with statins (p=0.019); Asian patients were found to have a decreased risk (p=0.0038).

C. Evaluation of Pediatric Program

There are no pediatric data in this submission. AstraZeneca requests that the requirements to conduct pediatric studies as per the Pediatric Research Equity Act be waived for the indications claimed in this application.

It is unlikely that a substantial number of pediatric patients will be treated with EXANTA for the claimed indications. The estimated number of pediatric patients diagnosed with atrial fibrillation in the US in 2002 is less than 1,500 children (Mattson Jack Group). The estimated total number of pediatric patients treated for venous thromboembolism (of which prevention of recurrent events, the indication claimed in this application, is a subset of patients) in the US in 2002 is less than 3,000 children (Solucient). The estimated cumulative number of pediatric patients diagnosed with conditions for which EXANTA will be indicated is less than 5,000 children. Therefore, the number of pediatric patients likely to be treated with EXANTA for the claimed indications is well below the number defined as a substantial number in the Pediatric Final Rule. Therefore, I recommend that request for waiver of pediatric study for the indications claimed in this application be granted.

D. Comments on Data Available or Needed in Other Populations

The sponsor has adequately conducted studies to assess the influence of renal function, subjects with renal impairment. There are no adequate data to assess the safety in pregnant women. Ximelagatran is contraindicated for patients with liver impairment, because of high risk of liver toxicity. Some findings are summarized below.

Influence of renal function
Apart from raised hepatic enzymes, no difference was seen in the overall AE profile between ximelagatran and comparators for any category of calculated CrCL.

Patients with calculated creatinine clearance below 30 mL/min were to be excluded from the clinical studies. Nevertheless, a few patients (<1%) in this category were recruited and the pattern of AEs was not different from that in other CrCL categories. There was a trend towards an increased frequency of bleeding-related AEs by decreasing calculated creatinine clearance in both treatment groups.

Melagatran, the active metabolite of ximelagatran, is eliminated primarily via renal excretion. Renal function decreases with age and, as the target patient population is of older age (median age about 65 years), patients with severe renal impairment (creatinine clearance of less than 30 mL/min) have been excluded in the patient studies with melagatran/ximelagatran. Study SH-TP1-0026 was conducted to investigate the pharmacokinetics of oral ximelagatran and subcutaneous melagatran in subjects with severe renal impairment (CrCL 10 to 30 mL/min, n=12). Subjects with normal renal function (CrCL $\geq$50 mL/min, n=12) were included as a control group.

As expected, subjects with severe renal impairment had higher plasma concentrations of melagatran both after subcutaneous administration of melagatran and oral dosing of

ximelagatran. The renally impaired subjects had about 4 times higher AUC after subcutaneous melagatran and about 5 times higher AUC after oral ximelagatran, compared to the control subjects. The mean (SD) half-lives of melagatran were 6.8 (2.0) h and 9.3 (3.5) h after sc melagatran and oral ximelagatran dosing, respectively, in the subjects with renal impairment. These half-lives were about 3-fold higher than for control subjects. The clearance and the renal clearance of melagatran were lower in the renally impaired subjects and were linearly correlated to renal function measured with iohexol clearance (mean (SD) of 12.5 (5.2) mL/min and 86.5 (9.7) mL/min for subjects with renal impairment and normal controls).

Study SH-TP1-0027 investigated the effect of melagatran given via dialysate, compared to dalteparin, in 11 uraemic patients (GFR <8 mL/min). The frequency of clot formation in tubings and in the dialysis filter, the iohexol clearance and the filter pressure were comparable between treatments. The half-life of melagatran was longer when melagatran was administered between dialyses compared to during hemodialysis. The clearance of melagatran was increased by about 7-fold and comparable to the iohexol clearance during haemodialysis.

Safety in pregnancy

Three cases, all from the VTE-T and VTE-P pools, of ximelagatran exposure during pregnancy have been reported from studies in the present application. In 2 of the ximelagatran cases the pregnancies were completed and full-term babies were delivered. For one of these (study SH-TPV-0002 Subject 063-5395), it was estimated that the maximal exposure to drug could have been 3 weeks from estimated conception. No complications were present during the pregnancy and a completely healthy girl was born. In the other case (study SH-TPV-0003, Subject 653-1285) the maximal exposure to drug was estimated to be up to 2 months from estimated conception. A full-term baby was delivered after an uneventful pregnancy. The boy was found to have a hypospadia that needed surgical correction. Otherwise the baby was healthy.

The third pregnancy reported on ximelagatran, both pregnancies reported on warfarin and 3 of the pregnancies on placebo were terminated through elective abortion, none due to medical reasons.

Ximelagatran and its 2 intermediates were not detectable in breast milk. Only trace amounts of melagatran (mean 0.00091% of given dose ximelagatran 36 mg) were excreted into breast milk. The exposure of melagatran to a breast-fed child is therefore not believed to be of concern.

XI. Appendix

A. Other Relevant Materials --- List of abbreviations

ABBREVIATIONS AND CONVENTIONS

Term	Abbreviation
ACS	**Acute coronary syndrome**
ACT	**Activated coagulation time**
AE	**Adverse event**
AF	**Nonvalvular atrial fibrillation**
ALAT	**(ALT) alanine aminotransferase**
ALP	**Alkaline phosphatase**
AMI	**Acute myocardial infarction**
APTT	**Activated partial thromboplastin time**
ASA	**Acetylsalicylic acid**
ASAT	**(AST) aspartate aminotransferase**
AUC	**Area under the curve**
bid	**Twice daily**
BMI	**Body mass index**
CBT	**Capillary bleeding time**
CCK	**Cholecystokinin**
CEAC	**Clinical event adjudication committee**
CFR	**Code of Federal Regulations**
CI	**Confidence interval**
Cmax	**Maximum plasma concentration**
CrCL	**Estimated creatinine clearance**
CSR	**Clinical study report**
CT	**Computerized tomography**
CV	**Coefficient of variation**
CYP	**Cytochrome P450**
DAE	**Discontinuation of study drug due to an adverse event**
DTI	**Direct thrombin inhibitor**
DVT	**Deep vein thrombosis**
ECG	**Electrocardiogram**
EU	**European Union**
EXULT	**EXanta Used to Lessen Thrombosis**
EXULT A	**SH-TPO-0010 (290A)**
EXULT B	**SH-TPO-0012 (290B)**
GCP	**Good Clinical Practice**
H 319/68	**Melagatran**
H 376/95	**Ximelagatran**

Term	Abbreviation
ICAC	Independent central adjudication committee
ICH	International Conference on Harmonization
INR	International normalized ratio (prothrombin time)
ITT	Intention-to-treat
LMWH	Low molecular weight heparin
LFT	Liver function test
LTE	Long-term exposure pool
MAA	Marketing Authorization Application
NNT	Number needed to treat
NOS	Non-specific
NSAID	Nonsteroidal anti-inflammatory drug
OS	Orthopedic surgery
OT	On-treatment
PD	Pharmacodynamics
PE	Pulmonary embolism
PK	Pharmacokinetics
PT	Prothrombin time
SAE	Serious adverse event
sc	Subcutaneous
SEE	Systemic embolic event
SPORTIF	Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation
SPORTIF II	SH-TPA-0002
SPORTIF III	SH-TPA-0003
SPORTIF IV	SH-TPA-0004
SPORTIF V	SH-TPA-0005
TIA	Transient ischemic attack
THRIVE	THRombin Inhibitor in Venous thromboEmbolism
THRIVE III	SH-TPV-0003
THR	Total hip replacement
TKR	Total knee replacement
tmax	Time to reach maximum plasma concentration
UFH	Unfractionated heparin
ULN	Upper limit of normal
VKA	Vitamin K antagonist
VTE	Venous thromboembolism (includes both distal and proximal deep vein thrombosis, plus pulmonary embolism)
VTE-P	Long-term secondary prevention after treatment of VTE
VTE-T	Treatment of VTE

B. Individual More Detailed Study Reviews

1 STUDY SH-TPO-0010 (EXULT A)

Exult A was studied between May 2001 and April 2002. Title of the protocol was "Optimization of Dose of H 376/95 (Oral Direct Thrombin Inhibitor) Compared to Warfarin (COUMADIN) for the Prevention of Venous Thromboembolism Following Total Knee Arthroplasty.

1.1 Objectives:

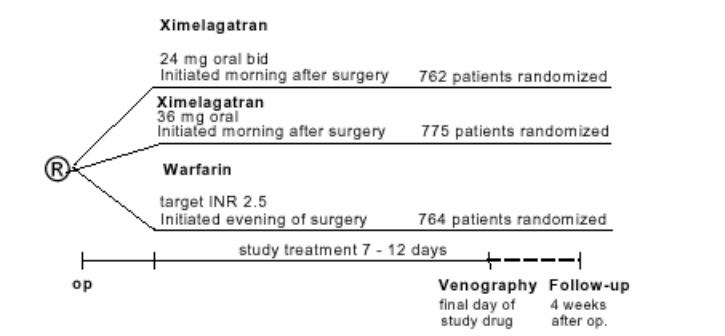
The primary objective was to determine the more effective dose of oral ximelagatran using 2 doses (24 and 36 mg) compared with warfarin for the prevention of total VTE and/or all-cause mortality in TKR patients after unilateral or bilateral TKR.

Secondary objectives were to compare ximelagatran with warfarin for the incidence of proximal DVT and/or PE and/or all-cause mortality, and total VTE and/or all-cause mortality according to on-site evaluations, and to compare the incidence of bleeding between treatments.

Efficacy was assessed by the number of patients with confirmed distal and/or proximal DVT and/or symptomatic PE and/or all-cause mortality during the treatment period and safety was assessed by standard means with a focus on bleeding complications.

1.2 Design:

A randomized, double-blind, double-dummy, parallel-group multicentre study designed to determine the more effective dose of oral ximelagatran at 24 and 36 mg bid begun at least 12 hours after surgery versus oral warfarin begun the evening of surgery and titrated to a target INR of 2.5 (INR range 1.8 to 3.0) in preventing VTE in patients undergoing TKR. Treatment duration was 7 to 12 days, with follow-up at 4 to 6 weeks after surgery.



1.3 Selection of study population

Inclusion criteria

For inclusion in the study, patients had to fulfill all of the following criteria:

1. Be scheduled for elective primary unilateral or bilateral TKR

2. Be at least 18 years old
3. Weigh between 88 lbs (40 kg) and 300 lbs (136 kg)
4. Be a male, or a female that is using a reliable form of contraception.
5. Provide written informed consent

Exclusion criteria

Any of the following was regarded as a criterion for exclusion from the study:

1. Be scheduled for hemiarthroplasty or surface repair or revisionary surgery
2. Have had a traumatic epidural/spinal puncture for this surgery (> 3 attempts or gross bleeding)
3. Have any condition resulting in immobilization for $\geq$ 3 days
4. Have treatment with anticoagulant or antiplatelet drugs within 7 days prior to surgery. Aspirin up to 500 mg daily and non-steroidal anti-inflammatory drugs (NSAIDs) were allowed.
5. Have a known disorder associated with an increased risk of bleeding
6. Have had an ischemic stroke or myocardial infarction within the 30 days prior to surgery
7. Have had any major surgical procedure within 30 days prior to surgery
8. Have significant renal impairment (an estimated creatinine clearance or CrCL <30 mL/min)
9. Have abused drugs and/or alcohol within the last 6 months
10. Have malignancy currently under active cytotoxic treatment, or being the reason for joint replacement surgery
11. Have a known clinically significant liver disorder, or aspartate aminotransferase (ASAT) and/or alanine aminotransferase (ALAT) above 2 times the upper limit of normal (ULN)
12. Have thrombocytopenia (platelet count <100 x 10^9 /L)
13. Have a known allergy to contrast media or iodine
14. Have any condition that would preclude venography
15. Have been previously randomized into this study or any other study of melagatran or ximelagatran
16. Be mentally or legally incapacitated
17. Have any condition that may interfere with full participation in the study or produce a significant risk to the patient
18. Have received any investigational agent (drug or device) for any therapeutic reason
19. Have planned use of intermittent pneumatic compression or foot pump device.
20. Have a contraindication to warfarin

1.4 Doses and treatment regimens

Patients were randomized to 1 of 3 treatment groups:

(1) ximelagatran 24 mg tablet with a 36 mg placebo tablet given twice a day in the morning and evening with doses taken at intervals as close to 12 hours as possible and placebo capsule(s) matching warfarin given in the evening, **or**

(2) ximelagatran 36 mg tablet with a 24 mg placebo tablet given twice a day in the morning and evening with doses taken at intervals as close to 12 hours as possible and placebo capsule(s) matching warfarin given in the evening, **or**

(3) warfarin 2.5 mg capsule(s) given once a day in the evening and titrated to a target INR of 2.5 (range 1.8 to 3.0) and two placebo tablets matching ximelagatran 24 mg and 36 mg given twice a day in the morning and evening,

Patients were permitted to take study medication with or without meals. The first dose of warfarin or placebo was to be administered in the evening of the day of surgery. The first dose of ximelagatran 24 mg or placebo and ximelagatran 36 mg or placebo was to be administered the morning after surgery (no sooner than 12 hours postoperatively). If adequate hemostasis was not achieved at the scheduled start times or if the patient was unable to take oral medication, study therapy was to begin as soon as adequate hemostasis had been achieved or oral intake was possible. All anticoagulant or antiplatelet medications, except for aspirin ‹500 mg/day and short-acting NSAIDs were discontinued at least 7 days prior to surgery.

1.5 Efficacy variable

Primary variable
The primary efficacy variable in this study was the number of patients with VTE (objectively confirmed DVT and/or PE) and/or all-cause mortality.

Secondary variables
The secondary efficacy variables in this study include incidence of proximal VTE (venographic assessment of the proximal veins + symptomatic, objectively confirmed proximal DVT and/or symptomatic PE, with objective site evaluations, during the treatment period) and/or all-cause mortality during the treatment period (ITT population), and incidence of total venous thromboembolism and/or all-cause mortality (local assessment).

1.6 Statistical Analyses of efficacy variables

All efficacy parameters were evaluated using centrally adjudicated events and presented for the efficacy ITT population. The primary analysis was also presented for patients without any major protocol violations (per-protocol population).

To address the primary objective of this study, the ximelagatran 36 mg treatment group was compared to the warfarin treatment group. As part of this comparison, the incidence of VTE was estimated for each treatment group by the type of surgery performed (unilateral/bilateral) using the observed proportions with 95% confidence interval (CI). An estimate of the between-treatment group difference was also provided with 95% CI. Treatment differences were tested using the CMH chi-square test, stratified by type of surgery. If this comparison was statistically significant ($p<0.05$), then the ximelagatran 24 mg treatment group was to be compared to the warfarin-treatment group, also at a significance level of 0.05. If the initial comparison of ximelagatran 36 mg and warfarin was not statistically significant ($p>0.05$), then no further statistical testing was performed. For a complete assessment of efficacy results, the ximelagatran 24 mg and 36 mg treatment groups were also compared. All secondary objectives were assessed at a significance level of 0.05.

1.7 Protocol deviations

The numbers of patients with protocol deviations that resulted in data being excluded from analyses are summarized by treatment group in Table A1.

Table A1: Number (%) of patients with major protocol deviations (randomized population)

Population Protocol deviation	Ximelag 24 mg N=762		Ximelag 36 mg N=775		Warfarin N=764	
Total randomized	762	(100)	775	(100)	764	(100)
• Did not receive study drug	5	(0.7)	6	(0.8)	5	(0.7)
Safety population	757	(99.3)	769	(99.2)	759	(99.3)
• Venogram unavailable or indeterminate and venous thromboembolism not confirmed during treatment period	143	(18.8)	140	(18.1)	151	(19.8)
Efficacy intention-to-treat population[a]	614	(80.6)	629	(81.2)	608	(79.6)
• Not compliant with study drug[a]	9	(1.2)	10	(1.3)	20	(2.6)
• Did not receive first dose of study drug on schedule[b]	9	(1.2)	11	(1.4)	22	(2.9)
• Venogram not performed within 6 to 13 days after surgery	3	(0.4)	5	(0.6)	1	(0.1)
• Received prohibited concomitant therapy with anticoagulants or thrombolytics	5	(0.7)	6	(0.8)	5	(0.7)
Per-protocol population	590	(77.4)	602	(77.7)	562	(73.6)

Data derived from Table 11.1.3, Section 11.1.

[a] Patients randomized to ximelagatran who took less than 10 doses, or who missed more than two doses of active study drug were not compliant. Patients randomized to warfarin who did not have a minimum international normalized prothrombin time ratio ≥1.5 were not compliant.

[b] First doses of active ximelagatran were scheduled for administration on the morning after surgery; warfarin on the evening of the day of surgery.

Number (%) of patients with major protocol deviations is similar between the treatment groups.

1.8 Disposition

Of 2656 patients enrolled in 116 centers, 2301 were randomized to receive double-blind treatment with ximelagatran 24 mg (n=762), ximelagatran 36 mg (n=775), or warfarin (n=764) at 114 centers located throughout the United States, Canada, Israel, Mexico, and Brazil.

Sixteen randomized patients were excluded from the safety analysis population because they did not receive study drug; 5 patients were excluded from the ximelagatran 24 mg treatment group, 6 from the ximelagatran 36 mg treatment group, and 5 from the warfarin treatment group.

Approximately 92% of patients from each treatment group completed the study. The proportion of early discontinuations from treatment for any reason were not appreciably different among treatment groups; 5.4% (41) patients discontinued from treatment with ximelagatran 24 mg, 6.8% (53) patients from ximelagatran 36 mg, and 5.6% (43) patients

from warfarin. More patients discontinued treatment because of adverse events in ximelagatran groups (23 patients in each group, 3%) than warfarin group (13 patients, 1.7%).

1.9 Demographic and other patient characteristics

The demographic characteristics of study patients are summarized in Table A2.

Table A2: Summary of demographic characteristics of study patients

Demographic or baseline characteristic[a]		Ximelag 24 mg N=757	Ximelag 36 mg N=769	Warfarin N=759
Gender, % (n/N)	Male	38.6 (292/757)	36.0 (277/769)	39.5 (300/759)
	Female	61.4 (465/757)	64.0 (492/769)	60.5 (459/759)
Age, % (n/N)	≤70 years	55.4 (419/757)	56.0 (431/769)	55.7 (423/759)
	>70 years	44.6 (338/757)	44.0 (338/769)	44.3 (336/759)
	Mean (SD)	67.7 (9.7)	68.5 (9.5)	67.8 (9.6)
	Range	32.0 to 87.0	33.0 to 89.0	33.0 to 89.0
Race, % (n/N)	Caucasian	95.6 (724/757)	95.7 (736/769)	95.7 (726/759)
	Black	3.8 (29/757)	3.4 (26/769)	4.0 (30/759)
	Oriental	0.3 (2/757)	0.5 (4/769)	0.4 (3/759)
	Other	0.3 (2/757)	0.4 (3/769)	0 (0/759)
Country, % (n/N)	United States	41.7 (316/757)	41.5 (319/769)	41.4 (314/759)
	Canada	36.5 (276/757)	37.5 (288/769)	37.0 (281/759)
	Israel	10.0 (76/757)	9.4 (72/769)	9.9 (75/759)
	Mexico	8.1 (61/757)	8.2 (63/769)	7.9 (60/759)
	Brazil	3.7 (28/757)	3.5 (27/769)	3.8 (29/759)
Weight (kg),	≤85	55.4 (419/757)	57.1 (439/769)	55.6 (422/759)
% (n/N)	>85	44.6 (338/757)	42.8 (329/769)	44.4 (337/759)
	Mean (SD)	84.7 (18.0)	83.9 (17.6)	84.8 (17.8)
	Range	40.0 to 133.0	44.0 to 159.0	41.0 to 139.0
BMI, % (n/N)	≤30 kg/m^2	51.1 (387/757)	52.4 (403/769)	51.6 (392/759)
	>30 kg/m^2	48.9 (370/757)	47.3 (364/769)	48.1 (365/759)
	Mean (SD)	30.8 (5.7)	30.5 (5.6)	30.6 (5.5)

	Range	18.5 to 57.0	18.6 to 49.2	14.5 to 61.8
Estimated	<30	0.1 (1/757)	0 (0/769)	0.5 (4/759)
creatinine	30 to 50	4.5 (34/757)	5.1 (39/769)	5.3 (40/759)
clearance	>50 to 80	30.3 (229/757)	33.0 (254/769)	30.4 (231/759)
(mL/min),	>80	61.6 (466/757)	58.5 (450/769)	61.3 (465/759)
% (n/N)	Mean (SD)	99.1 (37.8)	96.1 (36.5)	97.8 (39.2)
	Range	18.9 to 369.4	31.6 to 305.5	16.3 to 289.6
Nicotine use,	Nonsmoker	59.2 (448/757)	59.7 (459/769)	60.2 (457/759)
% (n/N)	Previous smoker	30.9 (234/757)	30.8 (237/769)	29.5 (224/759)
	Occasional smoker	1.2 (9/757)	2.7 (21/769)	2.6 (20/759)
	Daily smoker	8.7 (66/757)	6.8 (52/769)	7.6 (58/759)
Alcohol use	None	62.0 (469/757)	64.6 (497/769)	65.5 (497/759)
(drinks per week)	1 to 7	28.4 (215/757)	26.8 (206/769)	25.2 (191/759)
% (n/N)	8 to 14	3.2 (24/757)	4.0 (31/769)	4.5 (34/759)
	>14	2.9 (22/757)	1.6 (12/769)	1.3 (10/759)
	Mean (SD)	5.6 (7.0)	5.0 (7.5)	5.1 (6.2)
	Range	1.0 to 49.0	1.0 to 84.0	0.0 to 56.0

Data derived from Tables 11.1.4.1 and 11.1.5.1, Section 11.1.
a Only major protocol deviations were excluded from the safety population analysis
SD standard deviation, BMI Body mass index

Of the 2285 patients included in the safety population, slightly more than 60% were female in each treatment group (from 60.5% to 64.0%), 96% of all patients were Caucasian in each treatment group. At baseline, approximately 60% of patients were non-smokers in each treatment group and slightly more than 60% of patients did not consume alcohol in each treatment group (from 62.0% to 65.5%).

The mean age of patients in each treatment group was approximately 68 years and approximately 56% were 70 years of age or younger in each treatment group. Approximately 56% of patients had a maximum body weight of 85 kg and approximately 52% had a maximum body mass index of 30 kg/m^2. The reasons for total knee replacement surgery are summarized in Table A3.

Table A3: Summary of the reasons for knee surgery

	Ximelag 24 mg N=614		Ximelag 36 mg N=629		Warfarin N=608	
Reason	**%**	**(n/N)**	**%**	**(n/N)**	**%**	**(n/N)**
Osteoarthrosis	94.6	(581/614)	94.4	(594/629)	94.7	(576/608)
Rheumatoid arthritis	4.4	(27/614)	4.0	(25/629)	3.0	(18/608)
Septic arthritis sequelae	0	(0/614)	0.2	(1/629)	0	(0/608)
Hip/knee fracture sequelae	0.3	(2/614)	0.6	(4/629)	0.3	(2/608)
Other	0.7	(4/614)	0.8	(5/629)	2.0	(12/608)

Over 95% of patients in each treatment group had unilateral knee surgery, predominately from a medial parapatellar approach (more than 88% in each treatment group). A total of 15% of patients (278 patients out of a total 1851) underwent epidural catheter placement and approximately one-third of this number (96 patients out of the total 278) had a catheter in place for more than 12 hours. No epidural bleeding was reported. Prostheses were cemented in place in approximately 90% of the patients in each treatment group and tibial osteotomies were seldom performed. Mean tourniquet use approximated 75 minutes in each treatment group; mean operating times were approximately 95 minutes.

In each treatment group, the mean time to the first dose of study drug was approximately 20 hours, the mean time to ambulation was 1.6 days, and the mean hospital stay was approximately 6 days. Approximately 60% of patients in each treatment group were ambulatory within 1 day, and the majority of patients in each treatment group were fully weight-bearing when discharged from the hospital. Approximately 40% of patients in each treatment group had maximum hospital stays of 4 days. More than 60% of patients in each treatment group used passive embolism stockings following surgery. More than 95% of patients in each treatment group were discharged following surgery to their home (from 57.4% to 59.3%) or to a rehabilitation center (from 36.6% to 38.2%).

1.10 Efficacy Results

1.10.1 Primary variable: Incidence of total venous thromboembolism and/or all-cause mortality

The frequency of total VTE and/or all-cause mortality among patients undergoing knee replacement was 24.9% for patients randomized to ximelagatran 24 mg, 20.3% for patients randomized to ximelagatran 36 mg, and 27.6% for patients randomized to warfarin (see Table below).

Table A4: Frequency of total VTE and/or all-cause mortality (efficacy intention-to-treat population)

				Ximelag vs warfarin		
Treatment group	%	(n/N)	Exact 95% CI	%	95% CI	CMH p-value[a]
Ximelag 24 mg	24.9	(153/614)	(21.5, 28.5)	–2.7	(–7.6, 2.2)	0.282
Ximelag 36 mg	20.3	(128/629)	(17.3, 23.7)	–7.3	(–12.0, –2.5)	0.003
Warfarin	27.6	(168/608)	(24.1, 31.4)			

Data derived from Table 11.2.1.1, Section 11.2.

[a] Treatment differences were tested using the Cochran-Mantel-Haenszel (CMH) test, adjusted for the type of surgery performed (unilateral/bilateral).

Note: Total venous thromboembolism includes pulmonary embolism.

CI Confidence interval.

Ximelagatran 36 mg was superior compared to warfarin (p=0.003) in reducing total VTE and/or all-cause mortality among patients with TKR according to blinded ICAC assessment. The reduction in the frequency of total VTE and/or all-cause mortality in patients randomized to ximelagatran 36 mg was 7.3% relative to patients randomized to warfarin (p=0.003). The corresponding absolute reduction for patients in the ximelagatran 24 mg treatment group was 2.7% (p=0.282).

According to blinded ICAC assessment, the absolute reduction in the frequency of total VTE and/or all-cause mortality was 7.3% with ximelagatran 36 mg compared to warfarin (27.6% warfarin vs 20.3% ximelagatran 36 mg), providing a relative risk reduction of 26.4% and the number needed to treat (1/ARR) was 14 (95% CI 8-39). In those patients who received oral 24 mg ximelagatran twice daily, the rate of total VTE and/or all-cause mortality was 24.9%; the relative risk reduction was 9.8% and the absolute risk reduction was 2.7%. However, the difference between the rate of 24.9% (ximelagatran 24 mg) and the warfarin rate of 27.6% was not significant.

For patients with unilateral TKR, the reduction in total VTE and/or all-cause mortality was 2.2% in the ximelagatran 24 mg treatment group and 7.1% in the ximelagatran 36 mg treatment group relative to warfarin. Corresponding reductions in total VTE and/or all-cause mortality for patients with bilateral TKR were 15.7% and 12.6%, respectively. As approximately 96% of patients in each treatment group had unilateral surgery, the reductions in total VTE and/or all-cause mortality for the combined surgeries approximate the reductions for patients with unilateral surgery.

The reduction in the frequency of total VTE and/or all-cause mortality among patients randomized to ximelagatran 36 mg was 4.6% relative to patients randomized to ximelagatran 24 mg, but this difference was not statistically significant (p=0.055).

1.10.2 Secondary variables

Incidence of proximal deep vein thrombosis, pulmonary embolism, and/or all-cause mortality (blinded ICAC assessment)

The frequency of proximal DVT, PE, and/or all-cause mortality among patients undergoing total knee replacement was 2.5% for patients randomized to ximelagatran 24 mg, 2.7% for patients randomized to ximelagatran 36 mg, and 4.1% for patients randomized to warfarin (Table A5).

Table A5 Frequency of proximal DVT, PE, and/or all-cause mortality (efficacy intention-to-treat population; blinded ICAC assessment)

Treatment group	%	(n/N)	Exact 95% CI	Ximelag vs warfarin %	95% CI	CMH p-value[a]
Ximelag 24 mg	2.5	(15/606)	(1.4, 4.0)	–1.7	(–3.7, 0.3)	0.104
Ximelag 36 mg	2.7	(17/629)	(1.6, 4.3)	–1.4	(–3.5, 0.6)	0.171
Warfarin	4.1	(25/603)	(2.7, 6.1)			

Data derived from Table 11.2.1.1, Section 11.2.
[a] Treatment differences were tested using the Cochran-Mantel-Haenszel (CMH) test, adjusted for the type of surgery performed (unilateral/bilateral).
CI Confidence interval.

Reductions in the frequency of proximal DVT, PE, and/or all-cause mortality was 1.4% for patients randomized to ximelagatran 36 mg relative to patients randomized to warfarin (p=0.171) and 1.7% for patients randomized to ximelagatran 24 mg (p=0.104). There was no statistically significant difference between the treatment groups for the frequency of composite endpoint of proximal DVT, PE, and/or all-cause mortality that is a clinically meaningful endpoint.

Incidence of total venous thromboembolism and/or all-cause mortality (local assessment)

The frequency of total VTE and/or all-cause mortality assessed locally at study centers was approximately 10% higher than assessed centrally by the ICAC. The locally assessed frequency of total VTE and/or all-cause mortality among patients undergoing knee replacement was 33.4% for patients randomized to ximelagatran 24 mg, 29.6% for patients randomized to ximelagatran 36 mg, and 37.7% for patients randomized to warfarin (Table A6).

Table A6 Frequency of total VTE and/or all-cause mortality according to local assessments (safety population with evaluable local assessments)

Treatment group	%	(n/N)[a]	Exact 95% CI	Ximelag vs Warfarin %	95% CI	CMH p-value[b]
Ximelag 24 mg	33.4	(211/631)	(29.8, 37.3)	–4.3	(–9.6, 1.0)	0.108
Ximelag 36 mg	29.6	(188/636)	(26.0, 33.3)	–8.2	(–13.3, –3.0)	0.002
Warfarin	37.7	(240/636)	(34.0, 41.6)			

Data derived from Table 11.2.12, Section 11.2.
[a] Patient population based on patient evaluations using venographic assessments at the individual study sites.
[b] Treatment differences were tested using the Cochran-Mantel-Haenszel (CMH) test, adjusted for the type of surgery performed (unilateral/bilateral).
Total venous thromboembolism includes pulmonary embolism.
CI Confidence interval.

Corresponding frequencies according to central assessment were 24.9%, 20.3% and 27.6%. Ximelagatran 36 mg was superior to warfarin in reducing total VTE and/or all-cause mortality among patients with TKR according to local assessments. The absolute reduction in the frequency of total VTE and/or all-cause mortality in patients randomized to ximelagatran 36 mg was 8.2% relative to patients randomized to warfarin (p=0.002) according to local assessments versus 7.3% according to central assessments. Corresponding reductions for patients in the ximelagatran 24 mg treatment group were 4.3% (p=0.108) according to local assessments versus 2.7% according to central assessments.

The reduction in the locally assessed frequency of total VTE and/or all-cause mortality among patients randomized to ximelagatran 36 mg was 3.9% relative to patients randomized to ximelagatran 24 mg, according to local assessments, but this difference was not statistically significant (p=0.138).

Although the rates of total VTE and/or all-cause mortality assessed by local study centers tended to be greater than those assessed centrally, analyses based on the local assessments were consistent with central assessments.

Symptomatic and asymptomatic thromboembolic events

There were 34 symptomatic thromboembolic events over the entire study period, 10 (1.6%) in the ximelagatran 24 mg treatment group, 13 (2.1%) in the ximelagatran 36 mg treatment group, and 11 (1.8%) in the warfarin treatment group (Table A7).

Table A7 Symptomatic and asymptomatic thromboembolic events over the entire study (efficacy intention-to-treat population)

	Ximelag 24 mg N=614		Ximelag 36 mg N=629		Warfarin N=608	
Event	**%**	**(n/N)**	**%**	**(n/N)**	**%**	**(n/N)**
Asymptomatic DVT	24.6	(151/614)	19.7	(124/629)	27.3	(166/608)
Proximal DVT	2.0	(12/614)	2.1	(13/629)	3.8	(23/608)
Distal DVT[a]	22.6	(139/614)	17.6	(111/629)	23.5	(143/608)
Symptomatic DVT[b]	1.0	(6/614)	1.3	(8/629)	1.5	(9/608)
Proximal DVT	0.3	(2/614)	0.5	(3/629)	0.7	(4/608)
Distal DVT	0.7	(4/614)	0.8	(5/629)	0.8	(5/608)
Pulmonary embolism	0.5	(3/614)	0.3	(2/629)	0.2	(1/608)
Death	0.2	(1/614)	0.5	(3/629)	0.2	(1/608)

Data derived from Tables 11.2.7.2 and 11.2.8.2, Section 11.2.
[a] Distal DVT = Total DVT minus proximal DVT
[b] Each patient is counted only once within the categories of Asymptomatic DVT and Symptomatic DVT using the worst case principle.
DVT deep vein thrombosis.

There were no appreciable differences among treatment groups in the incidences of syptomatic DVT, PE, or death. The main difference between the treatment groups is the incidence of asyptomatic distal DVT which is not clinically meaningful.

1.10.3 Subgroup analyses

The frequency of total VTE and/or all-cause mortality was examined by subgroup factors relating to prespecified demographic and other patient characteristics. The results of the subgroup analysis were consistent with the overall pattern of results seen for all patients, with the incidence of total VTE and/or all-cause mortality consistently lower in the ximelagatran 36 mg group and comparable to or slightly lower in the ximelagatran 24 mg group, in comparison to the warfarin group, for a majority of subgroups examined.

Table A8 Frequency of total VTE and/or all-cause mortality by selected subgroup (efficacy intention-to-treat population; blinded ICAC assessment)

Subgroup factor	Ximelag 24 mg N=614		Ximelag 36 mg N=629		Warfarin N=608		p-value[a]
	%	(n/N)	%	(n/N)	%	(n/N)	
Gender							0.043
Male	23.8	(58/244)	19.8	(47/237)	22.8	(55/241)	
Female	25.7	(95/370)	20.7	(81/392)	30.8	(113/367)	
Age							0.009
≤70 years	20.8	(69/331)	19.5	(71/364)	27.2	(94/345)	
>70 years	29.7	(84/283)	21.5	(57/265)	28.1	(74/263)	
Country							<0.001
United States	22.0	(56/255)	14.5	(37/255)	22.1	(54/244)	
Canada	32.0	(71/222)	26.4	(64/242)	36.0	(85/236)	
Israel	17.5	(10/57)	25.0	(14/56)	19.2	(10/52)	
Mexico	18.2	(10/55)	18.5	(10/54)	22.6	(12/53)	
Brazil	24.0	(6/25)	13.6	(3/22)	30.4	(7/23)	
Renal function							0.175
Severe (CrCL <30 mL/min)	0	(0/0)	0	(0/0)	0	(0/3)	
Moderate (CrCL 30 to 50 mL/min)	17.2	(5/29)	9.4	(3/32)	29.0	(9/31)	
Mild (CrCL >50 to 80 mL/min)	26.4	(51/193)	19.5	(39/200)	31.4	(58/185)	
Normal (CrCL >80 mL/min)	25.2	(93/369)	22.2	(84/378)	26.3	(98/373)	

Data derived from Tables 11.2.3, 11.2.4, and 11.2.18, Section 11.2.
Note: Total venous thromboembolism includes pulmonary embolism.
[a] 67 patients were excluded from the logistic regression analysis due to missing data.
CrCl Creatinine clearance

Results of the logistic regression analysis showed that the majority of subgroups factors analyzed had no significant impact on the incidence of total VTE and/or all-cause mortality. However,

female patients, older patients and patients enrolled at sites in Canada were associated with higher rates of VTE ($p = 0.043$, 0.009 and < 0.001, respectively). The interaction of each subgroup factor with treatment was also analyzed and indicated no statistically significant interactions between treatment and any examined subgroup ($p \geq 0.1$).

1.10.4 INR in the warfarin treatment arm

At the time of venography, only 58.3% of patients in the warfarin treatment group had INR values within the therapeutic range of 1.8 to 3.0 (Table A9).

Table A9 Proportion of patients in the warfarin treatment group with INR within the therapeutic range (efficacy intention-to-treat population)

	International normalized ratios[a]		
	<1.8	1.8 to 3.0	>3.0
Visit	% (n/N)	% (n/N)	% (n/N)
Postoperative Day 1	99.2 (597/602)	0.8 (5/602)	0 (0/602)
Postoperative Day 2	60.9 (369/606)	32.2 (195/606)	6.9 (42/606)
Postoperative Day 3	35.2 (210/597)	46.9 (280/597)	17.9 (107/597)
Venography	23.8 (141/592)	58.3 (345/592)	17.9 (106/592)

Data derived from Table 11.1.18.2, Section 11.1.
a The therapeutic range of the international normalized ratio is 1.8 to 3.0. There were 608 patients in the efficacy intention-to-treat population who were randomized to warfarin treatment.
Note: Venography refers to the End of Treatment Period Study Visit

There was no appreciable difference in mean INR between patients with confirmed VTE and with no confirmed VTE at the postoperative Day 3 and End of Treatment Period study visits, although the patients with confirmed events had a mean INR slightly less than patients without confirmed events (2.30 and 2.36, respectively for patients at postoperative Day 3; 2.31 and 2.43, respectively for patient at the End of Treatment Period study visit).

There were no appreciable differences between the distribution of INR values in patients with and without confirmed VTE.

There are several major problems in this study using warfarin as a comparator:

- Warfarin is not suitable for short-term therapy for prevention of VTE in patients with TKR surgery. Warfarin is not approved for this indication.
- The comparison is unfair, because warfarin will take about 3-5 days to reach therapeutic level, while Exanta reaches therapeutic levels within hours.
- The results show that 35.2% of patients receiving warfarin had an INR less than 1.8 by postoperative day 3 and 24% by end of treatment (day 7 – 12).

Therefore, it is unacceptable to claim that ximelagatran 36 mg bid is superior to warfarin.

1.10.5 Conclusions on efficacy results

In this study (EXULT 290A), ximelagatran 36 mg bid showed greater efficacy than warfarin in preventing total VTE and/or all-cause mortality in patients undergoing primary elective TKR. The absolute reduction in the frequency of total VTE and/or all-cause mortality was 7.3% with warfarin (27.6% warfarin vs. 20.3% ximelagatran 36 mg), providing a relative risk reduction of 26.4% and a number needed to treat (1/ARR) of 14 (95% C.I. 8-39). The 36 mg dose was superior to "warfarin group"(p=0.003). The benefit was mainly due to a reduction in asymptomatic distal DVT diagnosed by venography which is not clinically meaningful. There were no clinically or statistically significant differences between ximelagatran and warfarin in reducing the frequency of proximal DVT, PE, and/or all-cause mortality in this population. Ximelagatran 24 mg bid was effective in achieving a rate of total VTE and/or all-cause mortality numerically better than "warfarin" (27.6% warfarin vs 24.9% ximelagatran 24 mg), but this difference did not reach statistical significance. The female patients, older patients and patients enrolled at sites in Canada were associated with higher rates of VTE.

There are several major problems for comparison of ximelagatran with warfarin in this study. Warfarin is not suitable for short-term therapy for prevention of VTE in patients with TKR surgery. Warfarin is not approved for this indication. The comparison is unfair, because warfarin will take about 3-5 days to reach therapeutic level, while Exanta reaches therapeutic levels within hours. The results show that 35.2% of patients receiving warfarin had an INR less than 1.8 by postoperative day 3, and 24% by end of treatment (day 7 – 12). Therefore, although the study demonstrated that the 36 mg dose of ximelagatran was superior to "warfarin group" (p=0.003) for primary endpoints, it is unacceptable to claim that ximelagatran is better than warfarin for this indication.

1.11 Safety Results

1.11.1 Extent of exposure

The duration of treatment received is summarized in Table A10. The mean number of days on treatment was approximately 8 days for each treatment group. There were no appreciable differences in exposure to study drug among treatment groups from Day 10 onwards, although overall warfarin administration may have been reduced relative to ximelagatran because warfarin is often withheld if INR is elevated. The minimum number of days on study drug was 1 day for patients in each treatment group; the maximum was 13 days for patients in the ximelagatran 24 mg treatment group and 14 days for patients in the ximelagatran 36 mg and warfarin treatment groups.

Table A10 Overview of exposure in the safety population

Days on treatment	Ximelag 24 mg N=757	Ximelag 36 mg N=769	Warfarin N=759
1 to 6 (n, [%])	39 (5.2)	58 (7.5)	130 (17.1)
7 to 9 (n, [%])	570 (75.3)	567 (73.7)	485 (63.9)
10 to 12 (n, [%])	138 (18.2)	140 (18.2)	136 (17.9)
13 to 14 (n, [%])	6 (0.8)	3 (0.4)	7 (0.9)
Mean (SD)	8.0 (1.8)	7.9 (1.9)	7.6 (2.3)
n	753	768	758

Data derived from Tables 11.3.1.1 and 11.3.1.2, Section 11.3.
SD Standard deviation

1.11.2 Adverse events

A summary of adverse events in each category of seriousness is presented in Table A11.

Table A11 Number (%) of patients with treatment-emergent adverse events (safety population, follow-up included)

	Ximelag 24 mg N=757		Ximelag 36 mg N=769		Warfarin N=759	
Category	n	(%)	n	(%)	n	(%)
At least 1 adverse event	482	(63.7)	493	(64.1)	469	(61.8)
Drug-related adverse event	83	(11.0)	98	(12.7)	85	(11.2)
Serious adverse event	45	(5.9)	44	(5.7)	33	(4.3)
Discontinued due to adverse event	23	(3.0)	23	(3.0)	13	(1.7)
Death	2	(0.3)	4	(0.5)	2	(0.3)

Data derived from Table 11.3.3.1, Section 11.3.

More than 60% of patients in each treatment group experienced at least one adverse event. There were no appreciable differences among treatment groups in the proportions of patients with at least one adverse event or with drug-related adverse events. The incidence of serious adverse events and discontinuations attributed to adverse events was higher in the ximelagatran treatment groups than in the warfarin group. Eight patients died who had undergone surgery and were randomized to study drug; 4 received ximelagatran 36 mg and 2 each received ximelagatran 24 mg and warfarin.

The most common treatment-emergent adverse events experienced by at least 5% of patients in any treatment group are shown in Table A12 listed by preferred term in order of decreasing total incidence.

Table A12 Number (%) of patients with adverse events occurring with a minimum incidence of 5% of all patients (safety population)

Adverse event Preferred term	Ximelag 24 mg N = 757		Ximelag 36 mg N = 769		Warfarin N = 759	
	n	(%)	n	(%)	n	(%)
At least 1 adverse event	482	(63.7)	493	(64.1)	469	(61.8)
Postoperative complications[a]	157	(20.7)	164	(21.3)	145	(19.1)
Fever	59	(7.8)	48	(6.2)	54	(7.1)
Nausea	45	(5.9)	63	(8.2)	49	(6.5)
Gamma glutamyl transferase increased	46	(6.1)	53	(6.9)	47	(6.2)
Constipation	31	(4.1)	42	(5.5)	41	(5.4)

Data derived from Table 11.3.3.3, Section 11.3.
[a] Expanded in Table 38, Section 8.3.3.

The most common adverse event was postoperative complications (for events such as anemia; pain; wound infection; bleeding and delayed wound healing) as experienced by 20.4% of all patients. The remaining common adverse events experienced by at least 5% of the patients were fever (7.0%), nausea (6.9%), increased serum levels of gamma glutamyl transferase (6.4%) and constipation (5.0%). There were no appreciable differences among treatment groups in the incidence of adverse events.

The common treatment-emergent adverse events attributed to study drug by the investigator were increased serum levels of gamma glutamyl transferase (4.3%), postoperative complications (3.1%), alkaline phosphatase (2.8%), ALAT (2.6%) and ASAT (1.7%).

Bleeding events

Bleeding events were categorized as major/minor/no bleeding. The most common treatment-emergent reported bleeding events were coded under postoperative complications (5.1%). Treatment-emergent bleeding complications reported by at least 1% of patients in any treatment group are summarized in Table A13. Hemoptysis was experienced by 5 patients (0.7%) randomized to ximelagatran, all on the 36 mg dose, and by 1 patient (0.1%) randomized to warfarin.

Table A13 Number (%) of patients with reported bleeding events occurring with a minimum incidence of 1% of all patients (safety population)

Adverse event Preferred term	Ximelag 24 mg N = 757		Ximelag 36 mg N = 769		Warfarin N = 759	
	n	(%)	n	(%)	n	(%)
At least 1 bleeding-related adverse event[a]	73	(9.6)	77	(10.0)	62	(8.2)
Postoperative complications[b]	38	(5.0)	44	(5.7)	34	(4.5)
Purpura	7	(0.9)	8	(1.0)	12	(1.6)
Hematuria	6	(0.8)	8	(1.0)	8	(1.1)

Data derived from Table 11.3.3.5, Section 11.3.
[a] Bleeding events identified as adverse events by the investigators were categorized by the Independent Central Adjudication Committee.
[b] Postoperative complications are expanded in Table 38.

The frequencies of adjudicated bleeding events on treatment are summarized by event type in Table A14.

Table A14 Frequency of ICAC adjudicated on-treatment bleeding events by event type (safety population)

Event type Treatment group	%	(n/N)	Exact 95% CI	Ximelag vs warfarin %	95% CI	CMH p-value[a]
Major bleeding events						
Ximelag 24 mg	0.8	(6/757)	(0.3, 1.7)	0.1	(–0.7, 1.0)	0.765
Ximelag 36 mg	0.8	(6/769)	(0.3, 1.7)	0.1	(–0.7, 1.0)	0.766
Warfarin	0.7	(5/759)	(0.2, 1.5)			
Minor bleeding events						
Ximelag 24 mg	4.0	(30/757)	(2.7, 5.6)	0.0	(–2.0, 2.0)	0.994
Ximelag 36 mg	4.7	(36/769)	(3.3, 6.4)	0.7	(–1.3, 2.8)	0.510
Warfarin	4.0	(30/759)	(2.7, 5.6)			
Major/minor bleeding events						
Ximelag 24 mg	4.8	(36/757)	(3.4, 6.5)	0.3	(–1.8, 2.4)	0.803
Ximelag 36 mg	5.3	(41/769)	(3.9, 7.2)	0.9	(–1.3, 3.0)	0.461
Warfarin	4.5	(34/759)	(3.1, 6.2)			

Data derived from Table 11.3.2.11, Section 11.3.
a Treatment differences were tested using the Cochran-Mantel-Haenszel (CMH) test, adjusted for the type of surgery performed (unilateral/bilateral).
ICAC Independent Central Adjudication Committee CI Confidence interval

Approximately 5% of patients in each treatment group had major or minor bleeding events while receiving study medication; approximately 1% of patients in each treatment group had major

bleeding events, 0.8% in each of the ximelagatran treatment groups and 0.7% in the warfarin treatment group. Approximately 5% to 6% of patients in each treatment group had major or minor bleeding events during the entire study, including the period from the last administration of study medication until the follow-up visit. Most bleeding events occurred while the patients were receiving study medication. There were no statistically significant differences between the ximelagatran and warfarin treatment groups in the frequency of major, minor, or combined major or minor bleeding events while receiving study medication ($p \geq 0.461$). Similarly, there were no statistically significant differences between ximelagatran 24 mg and 36 mg in the frequencies of these bleeding events while receiving study medication ($p \geq 0.490$).

The frequency of on-treatment bleeding events for patients treated with warfarin by INR range is summarized in Table A14.

Table A14 Frequency of on-treatment bleeding events for patients treated with warfarin by international normalized ratios (safety population)

Visit / Event type	International normalized ratios					
	<1.8		1.8 to 3.0		>3.0	
	%	(n/N)	%	(n/N)	%	(n/N)
Postoperative Day 3						
No confirmed bleeding	36.0	(252/700)	45.9	(321/700)	18.1	(127/700)
Major/minor bleeding	57.6	(19/33)	36.4	(12/33)	6.1	(2/33)
Venography						
No confirmed bleeding	25.1	(170/678)	56.2	(381/678)	18.7	(127/678)
Major/minor bleeding	30.3	(10/33)	60.6	(20/33)	9.1	(3/33)

Data derived from Table 11.3.2.18, Section 11.3.
Note: Venography refers to the End of Treatment Period Study Visit

The frequency of bleeding events increased from postoperative Day 3 to the End of Treatment Period Study Visit for patients within the therapeutic INR range, from 36.4% to 60.6%, and decreased from postoperative Day 3 to End of Treatment Period Study Visit for patients below the therapeutic INR, from 57.6% to 30.3%.

For all warfarin treated patients with INR values within the therapeutic range (1.8 to 3.0), 37.1% had confirmed bleeding events at postoperative Day 3 versus 58.8% at End of Treatment Period Study Visit. Mean INRs of warfarin treated patients with bleeding events were lower at postoperative Day 3 and the day of the End of Treatment Period Study Visit than for patients with no confirmed bleeding (1.9 versus 2.3, and 2.1 versus 2.4, respectively).

There were no appreciable differences in mean melagatran levels between patients with confirmed on-treatment major/minor bleeding events and with no confirmed bleeding at the postoperative Day 3 and End of Treatment Period study visits suggesting that the bleeding events occurred independently of melagatran plasma concentrations.

Subgroup analyses of adjudicated bleeding events

For the majority of subgroups examined, the pattern of results was consistent with that of the overall population and the incidences of bleeding events in the ximelagatran groups were comparable to or slightly higher than those in the warfarin group. A logistic regression analysis examining on-treatment bleeding events found that there was a statistically significant effect of gender and location of the study site on the incidence of major/minor bleeding events, with male patients and patients enrolled at sites in Canada associated with an increased risk of bleeding ($p \leq 0.001$). The interaction of each subgroup factor with treatment was also analyzed and indicated no statistically significant interactions between treatment and any examined subgroup ($p \geq 0.096$). The frequency of on-treatment major/minor bleeding events by selected subgroup factors is summarized in Table A15.

Table A15 Frequency of on-treatment bleeding events by selected subgroup

Subgroup factor	Ximelag 24 mg N=757 %	(n/N)	Ximelag 36 mg N=769 %	(n/N)	Warfarin N=759 %	(n/N)	p-value[a]
Gender							0.001
Male	5.8	(17/292)	9.0	(25/277)	6.0	(18/300)	
Female	4.1	(19/465)	3.3	(16/492)	3.5	(16/459)	
Country							<0.001
United States	3.8	(12/316)	4.1	(13/319)	4.5	(14/314)	
Canada	7.2	(20/276)	8.3	(24/288)	6.0	(17/281)	
Israel	1.3	(1/76)	1.4	(1/72)	0	(0/75)	
Mexico	0	(0/61)	4.8	(3/63)	0	(0/60)	
Brazil	10.7	(3/28)	0	(0/27)	10.3	(3/29)	
Renal function							0.71
Severe (CrCL <30 mL/min)	0	(0/1)	0	(0/0)	0	(0/4)	
Moderate (CrCL 30 to 50 mL/min)	0	(0/34)	0	(0/39)	5.0	(2/40)	
Mild (CrCL >50 to 80 mL/min)	3.1	(7/229)	6.7	(17/254)	4.8	(11/231)	
Normal (CrCL >80 mL)	5.8	(27/466)	4.9	(22/450)	4.3	(20/465)	

Data derived from Tables 11.3.2.13, 11.3.2.14, and 11.3.2.19, Section 11.3.

[a] Treatment differences based upon subgroup factors were tested using logistic regression techniques, excluding data from 94 patients with missing data.

CrCL Creatinine clearance

Deaths

Eight patients died who had undergone surgery and were randomized to treatment; 4 patients had received ximelagatran 36 mg, 2 patients had received ximelagatran 24 mg, and 2 patients had received warfarin. Of the eight deaths, 1 occurred in each treatment group during the study

treatment period; none of these was adjudicated as due to fatal PE or fatal bleeding (2 MIs and 1 ischemic bowel with perforation). The other five deaths occurred after study treatment was discontinued and up until the end of the study.

The 2 warfarin treated patients died as a result of myocardial infarction. Deaths of patients who received ximelagatran 36 mg resulted from PE (Patients 93/144 and 217/3259), myocardial infarction (Patient 112/154), and hypotension, gastrointestinal bleeding, and multiorgan failure (Patient 401/7037). Patient 46/2236, who received ximelagatran 24 mg, died as a result of intestinal perforation. The cause of death for Patient 215/3776, who also received ximelagatran 24 mg, was unknown.

Narratives for patient 401/7037, Patient 46/2236 and Patient 215/3776 are listed below.

- Patient 401/7037 was a 79 yeas old female Caucasian. The subject had a history of hypertension, deafness, congestive obstructive pulmonary disease, appendectomy, and renal lithotripsy. She underwent left TKR for osteoarthritis. Operative blood loss was 130 mL, and postoperative drainage was 100 mL. The subject received the first dose of warfarin placebo approximately 10 hours after surgery. She received 1 day of treatment with ximelagatran 36 mg for a total of 2 doses. On postoperative day 1 at 17: 50 hour, the subject experienced paleness, nausea, and vomiting. She was found to have hypotension (80/ 50 mm Hg), a respiratory rate of 20/ min, and a temperature of 35.8 ^{o}C. Therapy with the study drug was discontinued, and the patient was transferred to intensive care. She was evaluated again at 00: 30 hour and diagnosed with arrhythmia, seizures, disorientation, paleness, and hypotension (90/ 60 mm Hg). The subject's hemoglobin was low, and she had bleeding via her nasogastric tube. Hemodynamic instability, hydroelectrolytic and acid- base disorder, and upper gastrointestinal bleeding were diagnosed. She was intubated, and mechanical ventilation was necessary. Acute renal failure was diagnosed. The subject was treated with intravenous plasma, two units of blood, and potassium chloride. On postoperative day 3, the subject's upper gastrointestinal bleeding continued with hypotension and tachycardia. Her central venous pressure was 10.5 to 23 mm Hg. On postoperative day 5, the subject became unstable and underwent exploratory laparotomy for the upper gastrointestinal bleeding. During the procedure, multiple gastric ulcers were found. Her condition worsened, and she died on postoperative day 46. The probable cause of death was acquired hospital pneumonia and multiple organ failure. An autopsy was not performed. The mandatory venography was not performed for this subject because she was in intensive care. The study investigator assessed the acute renal failure as medically significant and assessed all of the events as not related to the study drug. The upper gastrointestinal bleeding was adjudicated as a major bleeding event.

- Patient 46/2236 was a 79 years old female Caucasian. The subject's medical history included anemia, hypertension, depression, left bundle branch block, hyperlipidemia, colonic stricture and arteriovenous malformations of the cecum, and left eye cataract removal. The subject underwent left TKR for osteoarthritis. Operative blood loss was 250 mL, and postoperative drainage was 500 mL. The subject received the first dose of warfarin placebo approximately 11 hours after surgery. She received 7 days of treatment with ximelagatran 24 mg for a total

of 13 doses. On postoperative day 5, she complained of constipation. On postoperative day 6, a flat plate of the abdomen revealed a possible early ileus. The subject was put on enteral nutrition and started on Reglan (metoclopramide) therapy. On the morning of postoperative day 7, she had cold clammy skin with gray pallor. The subject was tachypneic, and her abdomen was distended. A nasogastric tube was inserted. Study drug was discontinued. Laboratory results showed an increased white blood cell count. On postoperative day 8, abdominal obstruction series results were consistent with a bowel perforation. The subject was taken to surgery, and a subtotal colectomy was performed. She remained in critical condition following surgery and expired on postoperative day 9 due to multiple complications of sepsis. The mandatory venography was not performed for this subject. The study investigator assessed the event as not related to the study drug.

- Patient 215/3776 was a 70 years old male Caucasian. The subject had a history of asthma, cancer of the prostate, fractured wrist, influenza, and tonsillectomy. The subject underwent left TKR for osteoarthritis. Operative blood loss was not reported, and postoperative drainage was 365 mL. The subject received the first dose of warfarin placebo approximately 8 hours after surgery. He received 2 days of treatment with ximelagatran 24 mg for a total of 4 doses. On postoperative day 2, the subject became diaphoretic, pale, and tachycardic. An EKG revealed atrial fibrillation, and a chest x- ray revealed pulmonary edema. Cardiac enzymes were subsequently negative. He was treated with digoxin, nitro- paste, and oxygen. At 02: 00 on postoperative day 3, the subject vomited coffee ground material and had bright red stools. The subject was transferred to the intensive care unit, and therapy with the study drug was discontinued and unblinded. He was diagnosed with a gastrointestinal bleed. He was treated with pantaloc, fresh frozen plasma, and packed red blood cells. On postoperative day 7, the subject was started on Fragmin (dalteparin). He was discharged to home recovered on postoperative day 12. The mandatory venography was not performed for this subject because he withdrew from the study due to the adverse event. The subject was re- hospitalized on postoperative day 18 with shortness of breath. On postoperative day 21, he was transferred to another hospital and was lost to follow- up. The subject died secondary to an unknown cause on postoperative day 25. The study investigator assessed the upper and lower gastrointestinal bleed as related to the study drug and the shortness of breath and death as not related to the study drug. The Adjudication Committee classified this cause of death as pulmonary embolism, due to lack of information to the contrary and based on the pre- specified Adjudication Committee charter. The gastrointestinal bleed was adjudicated as a major bleeding event.

Serious adverse events

The frequency of serious adverse events experienced by at least two patients who were treated with ximelagatran or with warfarin is summarized in Table A16.

Table A16 Number (%) of patients with serious adverse events occurring in at least 2 patients treated with either ximelagatran or warfarin (safety population)

Serious adverse event Preferred term	Ximelag 24 mg N=757		Ximelag 36 mg N=769		Warfarin N=759	
	n	(%)	n	(%)	n	(%)
At least 1 serious adverse event	45	(5.9)	44	(5.7)	33	(4.3)
Postoperative complications	7	(0.9)	6	(0.8)	5	(0.7)
Myocardial infarction	7	(0.9)	4	(0.5)	2	(0.3)
Atrial fibrillation	0		3	(0.4)	3	(0.4)
Gastrointestinal hemorrhage	4	(0.5)	1	(0.1)	0	
Ileus	1	(0.1)	2	(0.3)	1	(0.1)
Cerebrovascular disorder	1	(0.1)	1	(0.1)	1	(0.1)
Dyspnea	3	(0.4)	0		1	(0.1)
Purpura	1	(0.1)	2	(0.3)	1	(0.1)
Syncope	1	(0.1)	0		2	(0.3)
Arthropathy	0		2	(0.3)	0	
Confusion	1	(0.1)	0		2	(0.3)
Hemarthrosis	0		0		2	(0.3)
Hematemesis	0		2	(0.3)	0	
Hematuria	0		0		2	(0.3)
Pneumonia	0		0		2	(0.3)
Pulmonary embolism	0		2	(0.3)	1	(0.1)
Urosepsis	2	(0.3)	0		0	
Duodenal ulcer hemorrhagic	2	(0.3)	0		1	(0.1)
Intestinal perforation	2	(0.3)	0		0	
Angina pectoris	1	(0.1)	2	(0.3)	0	
Hyponatremia	2	(0.3)	0		0	

Data derived from Table 11.3.5.1, Section 11.3.

The most common serious adverse events experienced by at least 0.5% of patients were postoperative complications (0.8%) and myocardial infarction (0.6%).

Eleven randomized patients underwent surgery and dosing with study medication (warfarin or placebo) on Day 0 but discontinued before dosing with active study drug (ximelagatran or placebo) on Day 1. Of these 11 patients, 7 patients were randomized to warfarin, 3 patients to ximelagatran 24 mg and one patient to ximelagatran 36 mg. Therefore, four patients did not

receive active study drug before discontinuing from the study. All 11 patients have been included in the safety analyses.

Serious postoperative complications were experienced by 18 patients, 13 (0.9%) randomized to ximelagatran and 5 (0.7%) to warfarin. Serious myocardial infarctions were experienced by 13 patients, 11 (0.7%) randomized to ximelagatran and 2 (0.3%) to warfarin.

Five patients experienced serious gastrointestinal hemorrhage; all five were randomized to ximelagatran, 4 (0.5%) to the 24 mg dose and 1 (0.1%) to the 36 mg dose. One patient in the ximelagatran 24 mg dose group, experiencing a serious gastrointestinal hemorrhage, discontinued study medication prior to receiving an active dose of study medication on postoperative Day 1. This patient was one of the eleven patients described in the previous paragraph. There were no other appreciable differences in the incidence of serious adverse events among treatment groups.

1.11.3 Discontinuations due to adverse events

The frequency of discontinuations of study drug attributed to adverse events experienced by at least 0.2% patients is summarized in Table A17.

Table A17 Number (%) of patients who discontinued from study drug because of adverse events (greater than or equal to 0.2% of patients) (safety population)

Adverse event leading to discontinuation of study drug	Ximelag 24 mg N=757		Ximelag 36 mg N=769		Warfarin N=759	
Preferred term	n	(%)	n	(%)	n	(%)
At least 1 adverse event leading to discontinuation	23	(3.0)	23	(3.0)	13	(1.7)
Postoperative complications	2	(0.3)	3	(0.4)	2	(0.3)
Myocardial infarction	3	(0.4)	2	(0.3)	1	(0.1)
Atrial fibrillation	1	(0.1)	3	(0.4)	1	(0.1)
Nausea	2	(0.3)	2	(0.3)	1	(0.1)
Gastrointestinal hemorrhage	2	(0.3)	1	(0.1)	1	(0.1)
Vomiting	2	(0.3)	2	(0.3)	0	

Data derived from Table 11.3.6.1, Section 11.3.

The two most common adverse events leading to discontinuation of study drug were postoperative complications (7 patients [0.3%]) and myocardial infarction (6 patients [0.3%]). Other adverse events that led to discontinuation of study drug by at least 0.2% of all patients were atrial fibrillation, nausea, gastrointestinal hemorrhage, and vomiting. The incidence of discontinuations attributed to adverse events was higher in the ximelagatran treatment groups than in the warfarin group.

1.11.4 Clinical laboratory evaluation

Hematology
Changes from baseline in hemoglobin levels were greatest within the first 3 days following surgery and returned to near baseline levels by the end of the follow-up period. Changes from baseline in platelet counts were greatest between baseline and End of Treatment Period Study Visit and returned to above baseline levels by the end of the follow-up period. There were no appreciable differences in changes from baseline in hemoglobin levels or platelet counts among treatment groups at any evaluation. Changes from baseline in other hematology parameters tended to be smaller at follow-up than at End of Treatment Period Study Visit, but no appreciable differences were seen over time or among treatment groups.

Clinical chemistry

Changes from baseline in liver enzymes and total bilirubin were greater at End of Treatment Period Study Visit than at follow-up. There were no appreciable differences in mean baseline values or in changes from baseline in liver enzymes and total bilirubin among treatment groups at any evaluation.

Changes in individual patients over time in selected liver function parameters

The frequencies of measures of liver function outside the extended reference ranges for liver enzymes (ASAT, ALAT, and alkaline phosphatase) and total bilirubin are summarized in Table A18. The only hepatic parameter with values at least 3X ULN with an incidence exceeding 1% in any treatment group was ALAT (ranging to 1.7%) at venography. There were no appreciable differences in the frequency of the measures of liver function at least 3X ULN among treatment groups for any hepatic parameter. It should be noted that there were 5 additional patients with ALT elevation ($\geq$ 3ULN) in the ximelagatran groups (1 patient in 24 mg group and 4 patients in 36 mg group) and none in the warfarin group during the following up period. This may indicate that ximelagatran may cause late occurrence of liver toxicity and 4-6 weeks of follow-up may not be adequate to assess the safety for short-term use of ximelagatran.

Table A18 Frequency of selected liver function test values elevated above upper limits of normal (safety population)

Laboratory test	Level	Ximelag 24 mg N = 757		Ximelag 36 mg N = 769		Warfarin N = 759	
Visit	(xULN)	%	(n/N)	%	(n/N)	%	(n/N)
Alanine aminotransferase							
Baseline	≥3	0.1	(1/731)	0	(0/746)	0	(0/742)
Venography	≥3	0.6	(4/697)	0.8	(6/718)	1.7	(12/697)
Follow-up	≥3	0.1	(1/693)	0.6	(4/700)	0	(0/700)
Aspartate aminotransferase							
Baseline	≥3	0.3	(2/731)	0	(0/746)	0	(0/742)
Venography	≥3	0.1	(1/697)	0.3	(2/718)	0.9	(6/697)
Follow-up	≥3	0	(0/694)	0	(0/700)	0	(0/700)
Alkaline phosphatase							
Baseline	≥3	0.1	(1/731)	0.1	(1/745)	0	(0/742)
Venography	≥3	1.0	(7/697)	0.8	(6/717)	0.7	(5/697)
Follow-up	≥3	0.1	(1/693)	0.4	(3/700)	0	(0/700)
Total bilirubin							
Baseline	≥2	0	(0/730)	0	(0/745)	0.1	(1/742)
Venography	≥2	0	(0/697)	0.1	(1/718)	0.1	(1/697)
Follow-up	≥2	0	(0/693)	0.1	(1/700)	0.1	(1/700)

Data from Table 11.3.8.7, Section 11.3.
ULN Upper limit of normal
Note: Venography refers to the End of Treatment Period Study Visit

Expected postoperative changes were observed: elevations were seen in measures of hepatic function (ASAT, ALAT, GGT, alkaline phosphatase, and LDH) and white blood cell counts, and reductions in RBCs, all at the time of venography, which generally returned to near baseline values at the follow-up visit. Hemoglobin levels diminished in all treatment groups following surgery and returned to near baseline at the follow-up visit. Platelet counts diminished in all treatment groups following surgery and returned to above baseline at the follow-up visit. There were few appreciable differences in clinical laboratory values among treatment groups. These changes are consistent with surgical intervention and postoperative recovery.

1.11.5 Conclusions on safety results

There were no statistically significant differences between either the ximelagatran treatment group and warfarin in the frequency of major bleeding events, the frequency of minor bleeding events, or the frequency of any (major and minor) bleeding events on treatment or over the entire study. Five patients experienced serious gastrointestinal hemorrhage; all five were randomized to

ximelagatran, 4 (0.5%) to the 24 mg dose and 1 (0.1%) to the 36 mg dose (One patient discontinued study medication prior to receiving an active dose of study medication on postoperative Day 1).

No appreciable differences were detected among the treated groups in regard to adverse events. The incidences of serious adverse events (5.7-5.9% vs. 4.3%), deaths (6 vs. 2) and discontinuations attributed to adverse events (3% vs. 1.7%) were numerically higher in the ximelagatran treatment groups than in the warfarin group. There was a statistically significant effect of gender and location of the study site on the incidence of major/minor bleeding events, with male patients and patients enrolled at sites in Canada associated with an increased risk of bleeding ($p \leq 0.001$).

Serious myocardial infarctions were experienced by 13 patients, 11 (0.7%) randomized to ximelagatran and 2 (0.3%) to warfarin. Three additional patients in ximelagatran group reported angina.

There were no appreciable differences in the frequency of the measures of liver function at least 3X ULN among treatment groups for any hepatic parameter. However, it should be noted that there were 5 additional patients with ALT elevation ($\geq$ 3ULN) in ximelagatran groups and none in the warfarin group during the following up period. This may indicate that ximelagatran may cause late occurrence of liver toxicity and 4-6 weeks of follow-up may not be adequate to assess the safety for short-term use of ximelagatran. A study incorporating at least 6 months of follow-up will be needed to assess liver toxicity following short-term use of ximelagatran.

2: STUDY SH-TPO-0012 (EXULT B)

Exult B was studied between June 2002 and April 2003. Title of the protocol was "Safety and Efficacy of H 376/95 (Oral Direct Thrombin Inhibitor) Compared to Warfarin (COUMADIN) for the Prevention of Venous Thromboembolism Following Total Knee Arthroplasty.

2.1 Study objectives

Primary objectives
The purpose of this study was to confirm the superior efficacy of ximelagatran compared to warfarin for the prevention of VTE in patients after TKR. The primary analysis was to focus on the primary composite endpoint of proximal and distal DVT and/or PE and/or all-cause mortality, according to independent central adjudication.

Secondary objectives
The secondary objectives of this study were to compare ximelagatran with warfarin for the incidence of:

- the secondary composite endpoint of proximal DVT and/or PE and/or all-cause mortality during the study drug treatment period
- the secondary composite endpoint of total DVT and/or PE and/or all-cause

mortality according to local on-site evaluations during the study drug treatment period
- major and any bleeding during the study drug treatment period.

2.2 Study design

This (EXULT B) was a multi-center, randomized, double-blind, double-dummy, parallel-group active comparator study in patients who had undergone primary elective TKR. Patients were randomized to 1 of 2 treatment groups: ximelagatran 36 mg twice daily (bid) (initiated as early as possible on the morning after surgery) or warfarin once daily (initiated the evening of surgery), administered for 7 to 12 days. Independent Central Adjudication Committee (ICAC) evaluation of mandatory bilateral venography (performed at the End of Treatment Period Study Visit) in conjunction with objectively confirmed, symptomatic VTE events and/or all-cause mortality were used to determine the primary endpoint. Symptomatic events or deaths occurring within 2 days following mandatory venography or up to Day 12, if no mandatory venography was done, were included in the primary analysis of efficacy.

2.3 Selection of study population

Inclusion criteria
For inclusion in the study, patients had to fulfill all of the following criteria:
1. Be scheduled for elective primary unilateral or bilateral TKR
2. Be at least 18 years old
3. Weigh between 88 lbs (40 kg) and 300 lbs (136 kg)
4. Be a male, or a female that was either a) surgically sterile, b) at least 2 years postmenopausal, or c) using a reliable form of contraception.
5. Provide written informed consent.

Exclusion criteria
Any of the following was regarded as a criterion for exclusion from the study:
1. Be scheduled for hemiarthroplasty or surface repair or revisionary surgery
2. Have had a traumatic epidural/spinal puncture for this surgery (> 3 attempts or gross bleeding)
3. Have any condition resulting in immobilization for $\geq$ days within the 30 days prior to surgery
4. Have treatment with anticoagulant or antiplatelet drugs within 7 days prior to surgery. Acetylsalicylic acid up to 500 mg daily and non-steroidal anti-inflammatory drugs (NSAIDs) were allowed.
5. Have a known disorder associated with an increased risk of bleeding
6. Have had an ischemic stroke or MI within the 30 days prior to surgery
7. Have had any major surgical procedure within 30 days prior to surgery
8. Have significant renal impairment (CrCL<30 mL/min)
9. Have abused drugs and/or alcohol within the last 6 months
10. Have malignancy currently under active cytotoxic treatment, or being the reason for joint replacement surgery
11. Have a known clinically significant liver disorder, or ASAT and/or ALAT > 2 times ULN.
12. Have thrombocytopenia (platelet count <100 x 10^9 /L)

13. Have a known allergy to contrast media or iodine
14. Have any condition that would preclude venography
15. Have been previously randomized into this study or any other study of melagatran or ximelagatran
16. Be mentally or legally incapacitated
17. Be in a situation or condition that, in the opinion of the investigator, may interfere with full participation in the study or produce a significant risk to the patient
18. Have received any investigational agent (drug or device) for any therapeutic reason within 30 days prior to surgery
19. Have planned use of intermittent pneumatic compression or foot pump device (Passive anti-embolism stockings and continuous passive motion devices are acceptable.)
20. Have a contraindication to warfarin.

2.4 Doses and treatment regimens

Patients were randomized in a double-dummy fashion to 1 of 2 treatment groups:

- Ximelagatran 36-mg tablet given twice daily in the morning and evening with doses taken at intervals as close to 12 hours as possible and placebo capsule(s) matching warfarin given in the evening,
  or
- Warfarin 2.5 mg capsule(s) given once daily in the evening and titrated to a target INR of 2.5 (range: 1.8 to 3.0) and 1 placebo tablet matching ximelagatran 36 mg given twice daily in the morning and evening.

2.5 Criteria for evaluation (main variables)

Efficacy

- Primary endpoint: The number of patients with verified distal and/or proximal DVT, and/or symptomatic PE with objective confirmation, and/or all-cause mortality during the treatment period according to central evaluations.
- Secondary endpoints: The number of patients with proximal DVT/PE (venographic assessment of the proximal veins + symptomatic, objectively confirmed proximal DVT and/or PE during the treatment period) + all-cause mortality during the treatment period.

  And

  The number of patients with verified distal and/or proximal DVT, and/or symptomatic PE with objective confirmation, and/or all-cause mortality during the treatment period according to local on-site evaluations.

Safety

Safety assessments included bleeding complications occurring after TKR; surgical site evaluations; adverse event (AE) reports; clinical laboratory data (hematology and clinical chemistry) and vital signs. An independent Data Safety Monitoring Board was in place during the performance of the study.

2.6 Statistical methods

The presence or absence of DVT, PE, and all-cause mortality was assessed locally at each investigative site and by the ICAC. The primary statistical analysis was performed using central evaluations. To address the primary objective of this study, ximelagatran 36 mg was compared to warfarin. Treatment differences were tested using the Cochran-Mantel-Haenszel (CMH) chi-square test, stratified by type of surgery (unilateral and bilateral). All objectives were assessed at a significance level of 0.05. A secondary analysis, in which the local venography assessments were substituted for the central venography assessments and analyzed, was also performed. Sub-group analyses were also performed on the frequency of thromboembolic events (total VTE and proximal VTE). The main analysis of efficacy was performed on the efficacy intention-to-treat (ITT) population, ie, all randomized and treated patients with a venogram adequate for evaluation or objectively confirmed, symptomatic DVT/PE and/or all-cause mortality while on treatment.

The frequency of adjudicated bleeding events (major and/or minor) was determined for each treatment group by the type of surgery performed. Differences among treatment groups were tested using the CMH chi-square test, stratified by type of surgery (unilateral/bilateral). Liver function test results (alanine aminotransferase [ALAT], aspartate aminotransferase [ASAT], alkaline phosphatase, total bilirubin) were summarized according to the proportion of patients with results greater than 2, 3, 5, and 7 times the upper limit of normal (ULN). Analyses of AEs, laboratory parameters (including hemoglobin and platelet count), and vital signs were summarized descriptively.

2.7 Summary of patients

Of 2813 patients enrolled in 115 centers, 2303 were randomized to study drug at 113 centers. Four randomized patients were excluded from the safety analysis population because they did not receive study drug. Of the 2299 patients included in the safety population, data from 982 and 967 patients in the ximelagatran and warfarin groups, respectively, were analyzed for efficacy in the ITT population while data from 941 and 883 patients, respectively, were included in the PP population. The discrepancy in the number of patients in each treatment group evaluable for the PP population was primarily due to a higher proportion of patients in the warfarin group compared with the ximelagatran group who were noncompliant (did not have a minimum INR of 1.5) with study drug or who did not receive their first dose of study drug on schedule.

Approximately 94% of patients in each treatment group completed the study (ie, completed the 4- to 6-week follow-up visit). The proportion of patients who discontinued study drug early for any reason was comparable in the ximelagatran group (n=53, 4.6%) and the warfarin group (n=52, 4.5%). The most common reason for early discontinuation of study drug in the ximelagatran and warfarin groups was AEs (29 and 34 patients, respectively). Other reasons for discontinuation of treatment across both treatment groups included consent withdrawn (17 patients), confirmed VTE event (14 patients), other (10 patients), and eligibility criteria not fulfilled (1 patient).

An additional 19 patients (9 ximelagatran; 10 warfarin) discontinued the study during the 4- to 6-week follow-up period. The reason for discontinuation of the study following completion of treatment was consent withdrawn (6 patients in each treatment group), AE (2 ximelagatran; 1 warfarin), and other (1 ximelagatran; 3 warfarin).

2.8 Protocol deviations

The numbers of patients with protocol deviations that resulted in data being excluded from the analyses are provided in Table B1.

Table B1 Number (%) of patients with protocol deviations (randomized population)

Protocol deviation[a]	Number (%) of randomized patients	
	Ximelagatran 36 mg (n=1152)	Warfarin (n=1151)
Total randomised	1152 (100.0)	1151 (100.0)
Did not receive study drug	1 (0.1)	3 (0.3)
Safety population	1151 (99.9)	1148 (99.7)
Venogram unavailable or indeterminate and no confirmed death or symptomatic VTE during treatment period	169 (14.7)	181 (15.7)
Efficacy intention-to-treat population	982 (85.2)	967 (84.0)
Not compliant with study drug[b]	15 (1.3)	29 (2.5)
Did not receive first dose of study drug on schedule[c]	11 (1.0)	44 (3.8)
Venogram not performed within 6 to 13 days after surgery	2 (0.2)	5 (0.4)
Received prohibited concomitant therapy with anticoagulants or thrombolytics	15 (1.3)	8 (0.7)
Per-protocol population	941 (81.7)	883 (76.7)

Data derived from Table 11.1.3, Section 11.1.

[a] All protocol deviations are listed for each patient and therefore patients can be counted in more than 1 category.

[b] Patients randomized to ximelagatran who took less than 10 doses and who missed more than 2 doses of active study drug were not compliant. Patients randomized to warfarin who did not have a minimum international normalized prothrombin time ratio of 1.5 were not compliant.

[c] The first dose of warfarin was scheduled for administration on the evening of the day of surgery; first dose of ximelagatran was scheduled for administration on the morning after surgery.

VTE venous thromboembolism.

Three primary patient populations were analyzed in this study, the safety population, the efficacy ITT population, and the PP population.

More patients (44, 3.8%) in warfarin group than ximelagatran group (11, 1.0%) did not receive first dose of study drug on schedule.

2.9 Summary of demographic and baseline characteristics

The demographic and key baseline characteristics of patients included in the safety population are summarized in Table B2.

Table B2 Demographic and baseline characteristics (safety population)

Demographic or baseline characteristic		Ximelagatran 36 mg (n=1151)	Warfarin (n=1148)
Gender, n (%)	Male	446 (38.7)	415 (36.1)
	Female	705 (61.3)	733 (63.9)
Age in years, n (%)	<65	427 (37.1)	395 (34.4)
	65 to 74	469 (40.7)	500 (43.6)
	≥75	255 (22.2)	253 (22.0)
Age, years	Mean (SD)	66.9 (9.4)	67.1 (9.4)
	Range	26 to 91	32 to 89
Race, n (%)	Caucasian	1081 (93.9)	1087 (94.7)
	Black	62 (5.4)	50 (4.4)
	Oriental	3 (0.3)	6 (0.5)
	Other	5 (0.4)	5 (0.4)
Alcohol use in drinks per week, n (%)	None	766 (66.6)	767 (66.8)
	1 to 7	308 (26.8)	307 (26.7)
	8 to 14	46 (4.0)	35 (3.0)
	>14	10 (0.9)	17 (1.5)
	Missing	21 (1.8)	22 (1.9)
Alcohol use, drinks per week	Mean (SD)	4.5 (4.9)	5.0 (6.2)
	Range	0.0 to 28.0	1.0 to 49.0

Data derived from Tables 11.1.4.1 and 11.1.5.1, Section 11.1.
CrCL creatinine clearance; SD standard deviation.

Demographic or baseline characteristic		Ximelagatran 36 mg (n=1151)	Warfarin (n=1148)
Country, n (%)	United States	464 (40.3)	467 (40.7)
	Canada	312 (27.1)	306 (26.7)
	Israel	43 (3.7)	40 (3.5)
	Mexico	144 (12.5)	141 (12.3)
	Brazil	188 (16.3)	194 (16.9)
Weight in kg, n (%)	<50	5 (0.4)	13 (1.1)
	50 to 100	934 (81.1)	930 (81.0)
	>100	212 (18.4)	203 (17.7)
	Missing	0	2 (0.2)
Weight, kg	Mean (SD)	84.3 (18.6)	84.1 (17.6)
	Range	45.0 to 150.0	42.0 to 151.0
Body mass index in kg/m^2, n (%)	<25	144 (12.5)	130 (11.3)
	25 to 30	433 (37.6)	417 (36.3)
	>30	569 (49.4)	594 (51.7)
	Missing	5 (0.4)	7 (0.6)
Body mass index, kg/m^2	Mean (SD)	30.8 (5.7)	30.9 (5.5)
	Range	17.3 to 56.2	17.3 to 56.5
Estimated CrCL in mL/min, n (%)	<30	4 (0.3)	1 (0.1)
	30 to <50	48 (4.2)	74 (6.4)
	50 to <80	324 (28.1)	320 (27.9)
	≥80	753 (65.4)	721 (62.8)
	Missing	22 (1.9)	32 (2.8)
Estimated CrCL, mL/min	Mean (SD)	99.2 (37.7)	99.4 (38.9)
	Range	24.4 to 284.5	27.5 to 363.4
Nicotine use, n (%)	Non-smoker	720 (62.6)	703 (61.2)
	Previous smoker	331 (28.8)	331 (28.8)
	Occasional smoker	19 (1.7)	21 (1.8)
	Daily smoker	81 (7.0)	92 (8.0)
	Missing	0	1 (0.1)

The 2 treatment groups were well matched with respect to demographic and baseline characteristics. Of the 2299 patients included in the safety population, slightly more than 60% in each treatment group were female, approximately 94% in each treatment group were Caucasian, and approximately two-thirds of the patients were enrolled at centers in the United States or Canada. At baseline, slightly more than 60% of patients in the ximelagatran and warfarin groups were non-smokers and approximately 67% of patients in each treatment group did not consume alcohol.

The mean age of patients in the ximelagatran and warfarin groups was approximately 67 years and between 41% and 44% of patients in both groups were between 65 and 74 years of age. The estimated creatinine clearance was normal (≥80 mL/min) for comparable proportions of patients in the ximelagatran (65.4%) and warfarin (62.8%) groups.

The proportions of patients included in the efficacy ITT population who entered the study with risk factors for DVT were generally comparable in the 2 treatment groups. More patients in the ximelagatran group (n=11, 1.1%) compared with the warfarin group (n=6, 0.6%) entered the study with a known history of PE, while comparable proportions of patients in the 2 groups had a history of DVT (n=35, 3.6% and n=29, 3.0%, respectively). Approximately one-quarter of patients in both the ximelagatran and warfarin groups (24.2% and 25.9%, respectively) had a history of varicose veins. No patient in either treatment group was reported to have known APC resistance, protein-C, protein-S, or antithrombin III deficiencies. Three patients (2 ximelagatran, 1 warfarin) entered the study with another known coagulation disorder.

In the efficacy ITT population, the most common reason for TKR was osteoarthrosis, with comparable percentages of patients in the ximelagatran and warfarin groups (94.2% and 95.4%, respectively) presenting with this reason.

Approximately 95% of patients in each treatment group underwent unilateral knee surgery, most (>94%) for osteoarthrosis. Prostheses were cemented in place in approximately 90% of the patients in each treatment group. There were no appreciable differences between treatment groups in the use of prior, concomitant, or follow-up therapies or in the proportion of patients using an anticoagulant for extended prophylaxis. The population of patients studied was suitable for the purpose of this study and representative of the general TKR population.

2.10 Efficacy results

2.10.1 Primary variable: Incidence of total venous thromboembolism and/or all-cause mortality (blinded ICAC assessment)

In this study, frequency rates of total VTE included patients with a confirmed DVT of the distal or proximal veins by mandatory venography as well as any patient who had clinical signs/symptoms of DVT or PE that were objectively confirmed and centrally adjudicated by the ICAC. Frequency rates of proximal VTE included patients with a confirmed DVT of the proximal veins by mandatory venography as well as any patient with objectively confirmed and adjudicated signs/symptoms of proximal DVT or PE. All-cause mortality included all deaths occurring during treatment or within 2 days following venography or up to postoperative Day 12, if mandatory venography was not performed. Symptomatic events occurring within 2 days following mandatory venography or up to Day 12, if no mandatory venography was done, were included in this analysis. Patients adequate for evaluation for the presence of total VTE may not have been adequate for evaluation for the presence of proximal DVT/PE.

The frequency of total VTE and/or all-cause mortality among patients undergoing TKR was 22.5% for patients in the ximelagatran group and 31.9% for patients in the warfarin group (Table B3).

Table B3 Frequency of total venous thromboembolism and/or all-cause mortality (efficacy ITT population; blinded ICAC assessment)

				Ximelagatran vs Warfarin		
Treatment Group	**%**	**(n/N)**	**Exact 95% CI**	**%**	**95% CI**	**CMH p-value[a]**
Ximelagatran 36 mg	22.5	(221/982)	(19.9, 25.2)	-9.3	(-13.3, -5.4)	<0.001
Warfarin	31.9	(308/967)	(28.9, 34.9)			

Data derived from Table 11.2.1.1, Section 11.2.
[a] Treatment differences were tested using the Cochran-Mantel-Haenszel (CMH) chi-square test, adjusted for the type of surgery performed (unilateral/bilateral).
Note: Total venous thromboembolism includes distal DVT, proximal DVT, and pulmonary embolism.
CI confidence interval; DVT deep vein thrombosis; ICAC Independent Central Adjudication Committee
ITT intention-to-treat.

Ximelagatran 36 mg was superior to warfarin group ($p<0.001$) in reducing total VTE and/or all-cause mortality among patients with TKR according to blinded ICAC assessment. The absolute reduction in the frequency of total VTE and/or all-cause mortality was 9.3% with ximelagatran (31.9% warfarin vs 22.5% ximelagatran 36 mg) ($p<0.001$); the number needed to treat to obtain benefit (1/ARR) was 11 (95% CI: 8 to 19).

Results obtained from data in the efficacy ITT population were confirmed by analyses of data from patients in the PP population. The frequency rates of total VTE and/or all-cause mortality in the PP population were 22.6% and 33.3% among patients in the ximelagatran and warfarin groups, respectively ($p<0.001$).

2.10.2 Secondary variables

Incidence of proximal deep vein thrombosis, pulmonary embolism, and/or all-cause mortality (blinded ICAC assessment)

The frequency of proximal DVT, PE, and/or all-cause mortality using blinded ICAC assessments among patients undergoing TKR was 3.9% for patients randomized to ximelagatran 36 mg and 4.1% for patients randomized to warfarin (Table B4).

Table B4 Frequency of proximal DVT, pulmonary embolism, and/or all-cause mortality (efficacy ITT population; blinded ICAC assessment)

				Ximelagatran vs Warfarin		
Treatment Group	%	(n/N)	Exact 95% CI	%	95% CI	CMH p-value[a]
Ximelagatran 36 mg	3.9	(38/976)	(2.8, 5.3)	-0.3	(-2.0, 1.5)	0.802
Warfarin	4.1	(40/964)	(3.0, 5.6)			

Data derived from Table 11.2.1.1, Section 11.2.
[a] Treatment differences were tested using the Cochran-Mantel-Haenszel (CMH) chi-square test, adjusted for the type of surgery performed (unilateral/bilateral).
CI confidence interval; ICAC Independent Central Adjudication Committee; ITT intention-to-treat.

There was no difference for reduction in the frequency of proximal DVT, PE, and/or all-cause mortality between the patients in ximelagatran 36 mg group and warfarin group (p=0.802).

Incidence of total VTE and/or all-cause mortality (local assessment)

The frequency of total VTE and/or all-cause mortality assessed locally at study centers was slightly higher in both treatment groups (<10% difference) than when assessed centrally by the ICAC. The locally assessed frequency of total VTE and/or all-cause mortality among patients undergoing TKR was 30.1% in the ximelagatran group and 35.8% in the warfarin group (Table B5).

Table B5 Frequency of total venous thromboembolism and/or all-cause mortality according to local assessments (safety population with evaluable local assessments)

				Ximelagatran vs Warfarin		
Treatment Group	%	(n/N)[a]	Exact 95% CI	%	95% CI	CMH p-value[b]
Ximelagatran 36 mg	30.1	(300/996)	(27.3, 33.1)	-5.7	(-9.8, -1.6)	0.007
Warfarin	35.8	(363/1014)	(32.8, 38.8)			

Data derived from Table 11.2.10, Section 11.2.
[a] Patient population based on patient evaluations using venographic assessments at the individual study sites.
[b] Treatment differences were tested using the Cochran-Mantel-Haenszel (CMH) chi-square test, adjusted for the type of surgery performed (unilateral/bilateral).
Note: Total venous thromboembolism includes distal DVT, proximal DVT, and pulmonary embolism.
CI confidence interval; DVT deep vein thrombosis.

Ximelagatran 36 mg was superior compared to warfarin in reducing total VTE and/or all-cause mortality among patients with TKR according to local assessments (p=0.007). Using local assessments, the absolute reduction in the frequency of total VTE and/or all-cause mortality in the ximelagatran group was 5.7% in relation to patients in the warfarin group, providing a relative risk reduction of 15.9 (95% CI: 4.6 to 2.58).

The rate of proximal VTE and/or all-cause mortality was numerically higher using local versus central assessments, 6.8% in the ximelagatran group compared with 5.7% in the warfarin group (p=0.298; 95% CI of -1.0 to 3.3 surrounding the between-group difference of 1.1%).

2.10.3 Subgroup analysis

The results of the subgroup analysis were generally consistent with the overall pattern of results seen the total efficacy ITT population, with the incidence of total VTE and/or all-cause mortality consistently lower in the ximelagatran group compared with the warfarin group. The frequency of total VTE and/or all-cause mortality is shown for selected subgroups in Table B6.

Table B6 Impact of selected subgroups on the frequency of total VTE and/or all-cause mortality (efficacy ITT population; blinded ICAC assessment)

Subgroup/ Factor	Ximelagatran 36 mg (n=982) %	(n/N)	Warfarin (n=967) %	(n/N)	p-value[a,b]
Gender					<0.001
Male	18.4	(72/391)	26.3	(94/358)	
Female	25.2	(149/591)	35.1	(214/609)	
Age					0.001
<65 years	19.2	(71/370)	26.5	(90/339)	
65 to 74 years	21.9	(87/398)	34.9	(148/424)	
≥75 years	29.4	(63/214)	34.3	(70/204)	
Country					<0.001
United States	15.8	(61/386)	25.0	(97/388)	
Canada	31.8	(87/274)	39.1	(99/253)	
Israel	19.4	(7/36)	34.3	(12/35)	
Mexico	26.6	(34/128)	34.6	(45/130)	
Brazil	20.3	(32/158)	34.2	(55/161)	
History of VTE					0.001
No	21.9	(205/938)	31.2	(292/936)	
Yes	36.4	(16/44)	51.6	(16/31)	
Time to venography					<0.001
Missing	100.0	(6/6)	100.0	(6/6)	
<7 days	16.7	(1/6)	75.0	(6/8)	
7 to 9 days	24.7	(179/726)	33.6	(234/697)	
10 to 12 days	14.4	(34/236)	25.2	(62/246)	
>12 days	12.5	(1/8)	0.0	(0/10)	

A higher frequency of total VTE and/or all-cause mortality was observed across both treatment groups for female patients (relative to males), older patients (relative to younger patients),

patients enrolled at sites in Canada (relative to those in the United States and the rest of the world), patients with bilateral surgery (relative to unilateral surgery), patients with a history of VTE (relative to no VTE history), and patients with earlier scheduled venograms (relative to later venograms) ($p<0.016$ across all factors).

2.10.4 Symptomatic and asymptomatic thromboembolic events

Over the entire study period (treatment and follow-up), there were 45 objectively confirmed, symptomatic thromboembolic events in the efficacy ITT population occurring in 20 (2.0%) patients in the ximelagatran 36 mg group and 24 (2.5%) patients in the warfarin group (Table B7).

Table B7 Objectively confirmed symptomatic and asymptomatic thromboembolic events over the entire study (efficacy ITT population)

	Ximelagatran 36 mg (n=982)		Warfarin (n=967)	
Event[a]	**%**	**(n/N)**	**%**	**(n/N)**
Asymptomatic Total DVT[b]	21.8	(214/982)	31.1	(301/967)
Proximal DVT	3.1	(30/982)	3.4	(33/967)
Distal DVT[c]	18.7	(184/982)	27.7	(268/967)
Symptomatic Total DVT	1.1	(11/982)	1.7	(16/967)
Proximal DVT	0.4	(4/982)	0.2	(2/967)
Distal DVT	0.7	(7/982)	1.4	(14/967)
Pulmonary embolism	0.3	(3/982)	0.5	(5/967)
Death	0.7	(7/982)	0.3	(3/967)

Data derived from Tables 11.2.5.2 and 11.2.6.2, Section 11.2.
[a] Each patient with a confirmed DVT (asymptomatic or symptomatic) is counted only once using the worst case principle.
[b] Asymptomatic DVT recorded at mandatory venography.
[c] Distal DVT = Total DVT minus proximal DVT.
DVT deep vein thrombosis; ITT intention-to-treat.

The proportions of patients with objectively confirmed, symptomatic total DVT and proximal DVT were low in both treatment groups (1.1% and 0.4% in the ximelagatran group, respectively; and 1.7% and 0.2% in the warfarin group, respectively). During the treatment period, the incidence of any confirmed thromboembolic event was lower in the ximelagatran group (n=14, 1.4%) compared with the warfarin group (n=22, 2.3%).

Among patients included in the efficacy ITT population, 21.8% of ximelagatran-treated and 31.1% of warfarin-treated patients had asymptomatic DVTs detected at mandatory venography. Corresponding proportions of patients with proximal DVTs at mandatory venography were 3.1% and 3.4%. Venograms were not evaluable for 15.2% of all patients. The most common reasons provided by the sites for not performing the venogram included failed venous access and withdrawal of patient consent. There was no appreciable difference in the number of patients

without central venogram assessments between the ximelagatran and warfarin groups (14.7% and 15.8%, respectively).

2.10.5 International normalized prothrombin time ratios (INR) in the warfarin treatment arm

At the End of Treatment Period Study Visit, 54.6% of patients in the warfarin treatment group had INR values within the therapeutic range of 1.8 to 3.0 (Table B8).

Table B8 Proportion of patients in the warfarin treatment group with INR within 1.8 and 3.0 (efficacy ITT population)

	International normalized ratios[a]					
	<1.8		1.8 to 3.0		>3.0	
Visit	%	(n/N)	%	(n/N)	%	(n/N)
Postoperative Day 1	99.3%	(950/957)	0.5%	(5/957)	0.2%	(2/957)
Postoperative Day 2	60.6%	(582/961)	35.3%	(339/961)	4.2%	(40/961)
Postoperative Day 3	33.1%	(316/956)	49.0%	(468/956)	18.0%	(172/956)
End of Treatment	26.9%	(254/944)	54.6%	(515/944)	18.5%	(175/944)

Data derived from Table 11.1.18.2, Section 11.1.
[a] The therapeutic range of the international normalized ratio is 1.8 to 3.0. There were 967 patients in the efficacy ITT population who were randomized to warfarin treatment.
ITT intention-to-treat.

On postoperative Day 3 and at the End of Treatment Period Study Visit, 66.9% and 73.1% of warfarin patients, respectively, had INR values of 1.8 or greater.

There was no appreciable difference in mean INR between patients in the warfarin group with confirmed VTE or no confirmed VTE at the postoperative Day 3 and End of Treatment Period Study visits. The mean INR for patients with confirmed vs no confirmed VTE was 2.319 and 2.393, respectively at postoperative Day 3 and 2.342 and 2.445, respectively, at the End of Treatment Period Study Visit.

There were no appreciable differences between the distribution of INR values in patients with and without confirmed VTE, with approximately one-third of patients with a confirmed event within the therapeutic range of 1.8 to 3.0 on both postoperative Day 3 and at the End of Treatment Period Study Visit.

There are several major problems in this study using warfarin as a comparator. Warfarin is not suitable for short-term therapy for prevention of VTE in patients with TKR surgery. Warfarin is not approved for this indication. The comparison is unfair, because warfarin will take about 3-5 days to reach therapeutic level, while Exanta reaches therapeutic levels within hours. The results show that 33.1% of patients receiving warfarin had an INR less than 1.8 by postoperative day 3, and 26.9% by end of treatment (day 7 – 12). Therefore, although the study demonstrated that the

36 mg dose of ximelagatran was superior to "warfarin group" ($p<0.001$) for primary endpoints, it is unacceptable to claim that ximelagatran is better than warfarin for this indication.

2.10.6 Conclusions on efficacy results

In this study (EXULT B), an oral treatment regimen of ximelagatran 36 mg bid begun at least 12 hours following TKR and continued for 7 to 12 days was associated with a low rate of VTE (22.5%) in comparison with warfarin (31.9%). According to blinded ICAC assessment, the absolute reduction in the frequency of total VTE and/or all-cause mortality was 9.3% with ximelagatran (31.9% warfarin vs 22.5% ximelagatran 36 mg, $p<0.001$), providing a relative risk reduction of 29.3% (95% CI: 18.1 to 39.1) and a number needed to treat to obtain benefit (1/ARR) of 11(95% CI: 8 to 19). The benefit was mainly due to a reduction in asymptomatic distal DVT diagnosed by venography which is not clinically meaningful. There were no clinically or statistically significant differences between ximelagatran and warfarin in reducing the frequency of proximal DVT, PE, and/or all-cause mortality in this population. The incidence of proximal DVT, PE, and/or all-cause mortality was low in both treatment groups, 3.9% for ximelagatran and 4.1% for warfarin ($p=0.802$).

The reduction in total VTE and/or all-cause mortality observed for the efficacy ITT population was confirmed by analyses of data from patients in the PP population ($p<0.001$) and using local assessments ($p=0.007$). The locally assessed frequency of total VTE and/or all-cause mortality among patients undergoing TKR was 30.1% for ximelagatran and 35.8% for warfarin (absolute reduction of 5.7%).

A higher frequency of total VTE and/or all-cause mortality was observed across both treatment groups for female patients (relative to males), older patients (relative to younger patients), patients enrolled at sites in Canada (relative to those in the United States and the rest of the world), patients with bilateral surgery (relative to unilateral surgery), patients with a history of VTE (relative to no VTE history), and patients with earlier scheduled venograms (relative to later venograms) ($p<0.016$ across all factors).

There are several major problems for comparison of ximelagatran with warfarin in this study. Warfarin is not suitable for short-term therapy for prevention of VTE in patients with TKR surgery. Warfarin is not approved for this indication and has not been used for this purpose in medical practice. The comparison is unfair, because warfarin will take about 3-5 days to reach therapeutic level, while Exanta reaches therapeutic levels within hours. The results show that 33.1% of patients receiving warfarin had an INR less than 1.8 by postoperative day 3, and 26.9% by end of treatment (day 7 – 12). More patients (44, 3.8%) in the warfarin group than the ximelagatran group (11, 1.0%) did not receive first dose of study drug on schedule. Therefore, although the study demonstrated that the 36 mg dose of ximelagatran was superior to warfarin group ($p<0.001$) for the primary endpoint efficacy analysis, it is unacceptable to claim that ximelagatran is better than warfarin.

2.11 Safety results

2.11.1 Extent of exposure

Of the 2303 patients randomized to study drug in this study, 4 patients (1 ximelagatran, 3 warfarin) never received study drug following surgery and were therefore excluded from the safety population.

The duration of exposure to study drug is summarized in Table B9 for the safety population.

Table B9 Overview of exposure in the safety population

Days on treatment	Ximelagatran (n=1151)	Warfarin (n=1148)
1 to 6, n (%)	56 (4.9)	218 (19.0)
7 to 9, n (%)	825 (71.7)	674 (58.7)
10 to 12, n (%)	257 (22.3)	245 (21.3)
>12, n (%)	9 (0.8)	11 (1.0)
Missing, n (%)	4 (0.3)	0 (0.0)
Mean (SD)	8.2 (1.8)	7.6 (2.4)

Data derived from Tables 11.3.1.1 and 11.3.1.2, Section 11.3.
SD standard deviation.

The mean number of days on treatment was 8.2 days in the ximelagatran group and 7.6 days in the warfarin group. There was a disparity between the 2 treatment groups, with a higher percentage of patients in the warfarin group treated for only 1 to 6 days (19.0%) compared with patients in the ximelagatran group (4.9%). Of the 218 patients recorded as receiving 1 to 6 days of warfarin treatment, most (n=171) were reported to have completed therapy. The remaining 47 patients discontinued study drug prematurely, most commonly due to AEs (n=30) and a confirmed VTE event (n=6). The above discrepancy resulted in a higher proportion of patients in the ximelagatran group (71.7%) compared with the warfarin group (58.7%) who were treated for 7 to 9 days; there were no appreciable differences in exposure to study drug between the treatment groups from postoperative Day 10 onwards.

2.11.2 Adverse events

A summary of treatment-emergent AEs in each category of seriousness is presented for the safety population in Table B10.

Table B10 Number (%) of patients with treatment-emergent adverse events (safety population, follow-up included)

	Ximelagatran (n=1151)		Warfarin (n=1148)	
Category	**n**	**(%)**	**n**	**(%)**
At least 1 adverse event	699	(60.7)	707	(61.6)
Bleeding-related adverse event	102	(8.9)	94	(8.2)
Non-bleeding-related adverse event	670	(58.2)	673	(58.6)
Drug-related adverse event	156	(13.6)	169	(14.7)
Serious adverse event[a]	79	(6.9)	79	(6.9)
Discontinued due to adverse event[b]	28	(2.4)	34	(3.0)
Death	7	(0.6)	3	(0.3)

Data derived from Table 11.3.3.1, Section 11.3.

[a] One additional patient in the ximelagatran group (237/12706) and 2 additional patients in the warfarin group (201/12340, 201/12350) had SAEs that resolved prior to the first dose of study medication (ie, not treatment-emergent) and are discussed in Section 8.4.2. In addition, 1 warfarin patient (201/12136) who did not receive treatment experienced an SAE.

[b] One additional patient in the ximelagatran group discontinued study drug prematurely. Patient 6/10829 was coded by the investigator on the End of Study Status page as having discontinued the study due to an AE, but the action taken with study drug on the AE page was coded as "None" rather than "Stopped." As a result, this patient does not appear on the tables and listings of patients who discontinued due to an AE (Section 11.3, Tables 11.3.6.1 and 11.3.6.2.). Thus, the total number of patients in the ximelagatran group who discontinued study drug prematurely due to AE is 29.

AE adverse event; SAE serious adverse event

The overall tolerability profiles for ximelagatran and warfarin were similar, with approximately 61% of patients in each treatment group reporting at least 1 treatment-emergent AE and approximately 14% of patients reporting drug-related AEs. There were no appreciable differences between treatment groups in the proportions of patients with bleeding-related and non-bleeding-related AEs. In addition, the proportions of patients who experienced an SAE or who discontinued treatment prematurely for an AE were similarin the ximelagatran and warfarin groups. Ten patients, 7 in the ximelagatran group and 3 in the warfarin group, died during treatment or within the study-defined 4- to 6-week follow-up visit.

2.11.2.1 Most common treatment-emergent adverse events (safety population)

The most frequently reported AE in both treatment groups was postoperative complications (preferred term coding for events such as anemia, pain, wound infection, and bleeding) which was reported by 18.6% of patients in the ximelagatran group and 17.0% of patients in the warfarin group. The remaining common AEs experienced by at least 5% of the patients in either treatment group were fever, nausea, and increased levels of GGT. The types and incidence rates of common AEs in the study were generally comparable in the ximelagatran and warfarin groups.

Among the less commonly reported AEs, there was at least a 2-fold higher incidence of chest pain in the ximelagatran group (1.9%) compared with the warfarin group (0.8%). None of the episodes of chest pain were considered related to study drug. No additional AEs occurred with at least a 2-fold higher incidence in the ximelagatran group compared with the warfarin group.

Drug-related treatment-emergent AEs were reported for comparable percentages of patients in the ximelagatran (13.6%) and warfarin (14.7%) groups. The types and incidence rates of treatment-emergent drug-related AEs were generally comparable between treatment groups. The most frequently reported treatment-emergent, drug-related AEs in the ximelagatran and warfarin groups were increased serum levels of GGT (4.8% and 3.6% for ximelagatran and warfarin, respectively), postoperative complications (3.7% and 2.9%, respectively), increased SGPT (2.6% and 2.3%, respectively), and increased alkaline phosphatase (2.6% and 2.5%, respectively).

2.11.2.2 Treatment-emergent adverse events (modified safety population)

The modified safety population included patients who had TKR performed and received at least 1 dose of active study medication at any point on or after postoperative Day 1.

Seven patients (4 ximelagatran, 3 warfarin) were excluded from the modified safety population. Each of the 4 ximelagatran-treated patients received warfarin placebo on the day of surgery but were discontinued from the study prior to receiving the morning dose of ximelagatran on Day 1. Similarly, the 3 warfarin-treated patients received a single dose of warfarin on the day of surgery but were discontinued prior to receipt of study medication on Day 1 (ximelagatran placebo or warfarin).

The percentage of patients included in this population who reported at least 1 treatment-emergent AE (60.8% and 61.5% for the ximelagatran and warfarin groups, respectively) was almost identical to that of the overall safety population (60.7% and 61.6%, respectively).

Of the 4 patients in the ximelagatran group who were excluded from the modified safety population, 1(6/10829) died as the result of ventricular fibrillation and cardiomyopathy on postoperative Day 1. One additional patient in the ximelagatran group (29/10944) and the 3 patients in the warfarin group (105/10382, 207/12335, and 210/12327) discontinued treatment prematurely as the result of AEs that began on postoperative Day 1.

2.11.2.3 Bleeding events

As seen in Table B11, the majority of bleeding-related AEs in the ximelagatran and warfarin groups were assessed by the ICAC as a minor bleeding event or no bleeding event. A higher incidence of major bleeding events was found in the ximelagatran group than warfarin group, 1.1% and 0.5% of patients, respectively.

Table B11 Number (%) of patients with treatment-emergent bleeding-related AEs by ICAC adjudication (safety population)

Type of event	Ximelagatran (n=1151)	Warfarin (n=1149)
Total bleeding-related AEs	102 (8.9)	94 (8.2)
No bleed	47 (4.1)	53 (4.6)
Minor bleed	50 (4.3)	41 (3.6)
Major bleed	13 (1.1)	6 (0.5)

Data derived from Table 11.3.3.7, Section 11.3.
AE adverse event; ICAC Independent Central Adjudication Committee.

Five patients (0.4%) in each treatment group had GI hemorrhage reported as a bleeding-related AE. For 3 of these patients (2 ximelagatran, 1 warfarin), the ICAC assessed the GI hemorrhage as a major bleeding event. One patient in the ximelagatran group (227/12588) died as a result of the GI hemorrhage following attempted cardiopulmonary resuscitation due to loss of melenic stool, sudden volume depletion, and peripheral shut down.

Incidence of adjudicated bleeding events

The frequencies of adjudicated bleeding events on treatment are summarized by event type in Table B12.

Table B12 Frequency of ICAC adjudicated on-treatment bleeding events by event type (safety population)

				Ximelagatran vs Warfarin		
Event type Treatment group	%	(n/N)	Exact 95% CI	%	95% CI	CMH p-value[a]
Major bleeding events						
Ximelagatran 36 mg	1.0	(12/1151)	(0.5, 1.8)	0.6	(-0.1, 1.3)	0.087
Warfarin	0.4	(5/1148)	(0.1, 1.0)			
Minor bleeding events						
Ximelagatran 36 mg	4.2	(48/1151)	(3.1, 5.5)	0.8	(-0.8, 2.3)	0.327
Warfarin	3.4	(39/1148)	(2.4, 4.6)			
Major/minor bleeding events						
Ximelagatran 36 mg	5.0	(58/1151)	(3.8, 6.5)	1.2	(-0.5, 2.9)	0.158
Warfarin	3.8	(44/1148)	(2.8, 5.1)			

Data derived from Table 11.3.2.10, Section 11.3.
[a] Treatment differences were tested using the Cochran-Mantel-Haenszel (CMH) chi-square test, adjusted for the type of surgery performed (unilateral/bilateral).
CI confidence interval; ICAC Independent Central Adjudication Committee.

Major bleeding events were uncommon during the treatment period and were reported for only 12 of the 1151 (1.0%) patients treated with ximelagatran 36 mg and 5 of the 1148 (0.4%) of the

patients treated with warfarin. Minor bleeding events were reported during treatment for 4.2% and 3.4% of patients in the ximelagatran and warfarin groups, respectively, while 5.0% and 3.8% of patients, respectively, were reported to have any bleeding event (major or minor). Only 7 additional patients (3 ximelagatran, 4 warfarin) experienced adjudicated major or minor bleeding events between administration of the last dose of study medication and the follow-up visit. Although there were no statistically significant differences between the 2 treatment groups in the frequency of major, minor, or combined major or minor bleeding events while receiving study medication ($p \geq 0.087$) or during the entire study ($p \geq 0.105$), a numerically higher incidence of major bleeding events in the ximelagatran group was found.

The frequency of on-treatment bleeding events for patients treated with warfarin by INR range is summarized in Table B13.

Table B13 Frequency of on-treatment bleeding events for patients treated with warfarin by international normalized ratios (safety population)

Visit / Event type	International normalized ratios <1.8 %	<1.8 (n/N)	1.8 to 3.0 %	1.8 to 3.0 (n/N)	>3.0 %	>3.0 (n/N)
Postoperative Day 3						
No confirmed bleeding	95.8	(366/382)	96.1	(521/542)	97.5	(198/203)
Major/minor bleeding	4.2	(16/382)	3.9	(21/542)	2.5	(5/203)
End of Treatment Period						
No confirmed bleeding	96.2	(279/290)	96.8	(578/597)	96.1	(199/207)
Major/minor bleeding	3.8	(11/290)	3.2	(19/597)	3.9	(8/207)

Data derived from Table 11.3.2.18, Section 11.3.

There were no appreciable differences between the distribution of INR values in patients without a confirmed bleeding event at postoperative Day 3 or the End of Treatment Period Study Visit or with a confirmed bleeding event at the End of Treatment Period Study Visit. On postoperative Day 3, however, most patients with a confirmed bleeding event had an INR value of <3.0.

Subgroup analyses of adjudicated bleeding events

The frequency of adjudicated on-treatment major/minor bleeding events was examined by subgroup factors relating to pre-specified demographic and other patient characteristics (Table B14). For the majority of subgroups examined, the pattern of results was consistent with that of the overall population, with the incidence of bleeding events in the ximelagatran group comparable to or slightly higher than that in the warfarin group. A logistic regression analysis examining on-treatment bleeding events found that across both treatment groups there was a statistically significant effect of age and gender on the incidence of major/minor bleeding events, with male patients and older patients associated with an increased risk of bleeding ($p < 0.02$ for both factors). The interaction of each subgroup factor with treatment was also analyzed and indicated a statistically significant interaction between treatment and age and treatment and body

mass index (p‹0.048). In the warfarin group, the rate of on-treatment bleeding events was highest in patients aged >75 years and those with a body mass index of <30 kg/m^2. By comparison, rates of on-treatment adjudicated major/minor bleeding events in the ximelagatran group were similar across all 3 age and body mass index subcategories.

Table B14 Impact of selected subgroups on the frequency of on-treatment bleeding events (combined major and minor) (safety population)

Subgroup Factor	Ximelagatran 36 mg (n=1151) %	(n/N)	Warfarin (n=1148) %	(n/N)	p-value[a,b]
Gender					<0.001
Male	8.3	(37/446)	5.8	(24/415)	
Female	3.0	(21/705)	2.7	(20/733)	
Age					0.02
<65 years	5.9	(25/427)	2.3	(9/395)	
65 to 74 years	4.1	(19/469)	3.2	(16/500)	
≥75 years	5.5	(14/255)	7.5	(19/253)	
Body mass index					0.091
Missing	0.0	(0/5)	14.3	(1/7)	
<25kg/m^2	6.9	(10/144)	6.2	(8/130)	
25 to 30 kg/m^2	5.1	(22/433)	4.3	(18/417)	
>30 kg/m^2	4.6	(26/569)	2.9	(17/594)	
Estimated Cr/CL					0.343
Missing	0.0	(0/22)	3.1	(1/32)	
Severe (CrCL <30 mL/min)	0.0	(0/4)	0.0	(0/1)	
Moderate (CrCL 30 to <50 mL/min)	8.3	(4/48)	9.5	(7/74)	
Mild (CrCL >50 to <80 mL/min)	3.4	(11/324)	3.4	(11/320)	
Normal (CrCL ≥80 mL/min)	5.7	(43/753)	3.5	(25/721)	

Data derived from Tables 11.3.2.14 and 11.3.2.15, Section 11.3.

[a] Influence of subgroup factors on the incidence of bleeding events were tested using logistic regression techniques.

[b] Data from 32 ximelagatran patients and 41 warfarin patients were excluded from the logistic regression analysis due to missing data.

CrCL creatinine clearance.

2.11.2.4 Deaths, serious adverse events, discontinuation due to adverse events, and other significant adverse events

Deaths

Among all randomized patients, 10 died, including 7 in the ximelagatran group and 3 in the warfarin group. One death was considered by the investigator to be related to study drug: Patient 227/12588 in the ximelagatran group died as the result of a GI hemorrhage on postoperative Day

8 while receiving study medication. Six of the 10 deaths occurred while patients were receiving treatment, including 4 in the ximelagatran group and 2 in the warfarin group. Deaths while on treatment with ximelagatran included ventricular fibrillation with cardiomyopathy, MI, sudden death, and GI hemorrhage, while those occurring on treatment with warfarin included cardiac arrest with AV block and MI. The remaining 4 deaths occurred during the 4- to 6-week follow-up period.

Of the 7 patients in the ximelagatran group who died, the ICAC could not rule out that the death was associated with a PE for 3 patients; 2 had experienced a MI (401/15134 and 507/14091) and 1 died suddenly and the exact cause of death was unknown (510/14366). One of these deaths occurred on treatment (507/14091), while the other 2 deaths occurred during follow-up. None of these 3 patients had an objectively confirmed clinical PE. The ICAC assessed 1 death to be the result of a major bleeding event; Patient 227/12588 in the ximelagatran group died as the result of a GI hemorrhage on postoperative Day 8 following his morning dose of study drug. The remaining 3 deaths in the ximelagatran group were not associated with a VTE or bleeding event as assessed by the ICAC. Of the 3 deaths occurring in the warfarin group, none were associated with a VTE or bleeding event as assessed by the ICAC. All patients who died are listed in Table B15.

Table B15 Listing of all patients who died

Treatment group	Center/ patient number	Sex	Age (year)	Adverse event (preferred term)	Adverse event (investigator text)	Time from start of treatment to onset of AE (days)	Time from last dose (days)[a]	Time from start of treatment to death (days)	Causality (as assessed by the investigator)	Adjudication
Ximelagatran 36 mg	6/10829	M	43	Fibrillation ventricular	Cardiac arrhythmia (Ventricular fibrillation)	1	0	1[b]	Not related	Other
				Cardiomyopathy	Hypertrophic cardiomyopathy	1	0	1	Not related	Other
Ximelagatran 36 mg	227/12588	M	80	GI hemorrhage	Upper gastrointestinal bleed	8	0	8	Related	Bleed
Ximelagatran 36 mg	235/12122	M	81	Sudden death	Sudden death	4	1	4	Not related	Other
Ximelagatran 36 mg	401/15134	F	80	Myocardial infarction	Myocardial infarction	12	4	12	Not related	PE[c]
Ximelagatran 36 mg	505/14031	F	60	Pneumonia	Pneumococcal pneumonia	48	40	48	Not related	Other
Ximelagatran 36 mg	507/14091	F	57	Myocardial infarction	Myocardial infarction	6	0	6	Not related	PE[c]
Ximelagatran 36 mg	510/14366	F	80	Death	Death: unknown reason	15	8	15	Not related	PE[c]
Warfarin	82/10854	F	67	Cardiac arrest	Cardio-pulmonary arrest	1	0	1	Not related	Other
				AV block	Cardiac arrhythmia (3rd degree heart block)	1	0	1	Not related	Other

Treatment group	Center/ patient number	Sex	Age (year)	Adverse event (preferred term)	Adverse event (investigator text)	Time from start of treatment to onset of AE (days)	Time from last dose (days)[a]	Time from start of treatment to death (days)	Causality (as assessed by the investigator)	Adjudication
Warfarin	97/10823	F	78	Myocardial infarction	Myocardial infarction	2	0	6	Not related	Other
Warfarin	404/15016	M	77	Myocardial infarction	Fatal myocardial infarction	21	15	21	Not related	Other

Data derived from Table 11.3.5.2, Section 11.3, and Appendix 12.2.6.10.
[a] Time from last dose = AE start day minus last day of study drug.
[b] This patient received only 1 dose of warfarin placebo and no active ximelagatran prior to death.
[c] PE could not be ruled out as the cause of death.
F female; M male; PE pulmonary embolism.

Narratives for patients 6/10829, 227/12588, 235/12122 and 510/14366 are presented below:

- Patient 6/10829 was a 43 year old male Caucasian. The subject had a history of hyperlipidemia, coronary angiogram, type II diabetes mellitus, ischemic colitis, obstructive sleep apnea, ear infection, H. pylori, right knee arthroscopy, laminectomy and fusion, adenoidectomy and septoplasty. He underwent right total knee replacement for osteoarthritis. Operative blood loss was 400 mL, and no postoperative drainage volume was reported. The subject received the first dose of warfarin placebo approximately 8 hours after surgery but did not receive any doses of ximelagatran. On postoperative day 1, the subject died suddenly. Based on an autopsy performed the next day, cardiac arrhythmia (ventricular fibrillation) due to hypertrophic cardiomyopathy was the primary cause of death, and hepatomegaly and obesity were secondary causes of death. No embolism, infarction, or hemorrhage was reported as contributing to death. The mandatory venography was not performed for this subject because he died before venography was performed. The study investigator assessed these events of cardiac arrhythmia (ventricular fibrillation) and hypertrophic cardiomyopathy as not related to the study drug.

- Patient 227/12588 was an 80 year old male Caucasian. The subject had a history of cardiomegaly, abnormal electrocardiogram (EKG), bifascicular block, right bundle branch block with left axis deviation, benign microhematuria, rotator cuff tear, hiatal hernia, right hand tremors, bilateral glaucoma, and umbilical hernia repair. He underwent right total knee replacement for osteoarthritis. Operative blood loss was 50 mL, and postoperative drainage was 400 mL. The subject received the first dose of warfarin placebo approximately 10 hours after surgery. He received 8 days of treatment with ximelagatran 36 mg for a total of 13 doses. Postoperatively, the subject had agitation and intermittent confusion. On postoperative day 2, the subject developed a decreased level of consciousness. Study drug was withheld until the neurologist assessed the subject. A computed tomography (CT) scan was negative for bleed, lesion, or cerebrovascular accident. Study drug continued to be withheld due to drowsiness. Hemoglobin and hematocrit were 85 g/ L and 24.1%, respectively. Lasix (furosemide) was given intravenously per blood transfusion protocol. On postoperative day 7, some non- progressive bruising on the subject's thigh was noted. Hemoglobin and hematocrit were 98 g/ L and 28.6%, respectively. PT and PTT were elevated above normal reference ranges. Cardiac enzymes were within normal range. Red blood cell count was below normal limits at 3.24×10^9/ L. That same day, the subject became diaphoretic, pale, and

weak, and a large amount of melenic stool was found in the bed. He became unresponsive, and his blood pressure dropped significantly. Thirty minutes later, hemoglobin was decreased to 84 g/ L; red blood cells and hematocrit decreased to $2.74x10^9$/ L and 24.9%, respectively. PT, PTT, and BUN were above normal limits at 1.4, 40 seconds, and 10.2 mmol/ L, respectively. Cardiac enzymes were within normal range. The subject's condition continued to deteriorate. Cardiopulmonary resuscitation was performed, but the subject expired one hour after onset of symptoms. The study investigator and hospital physician thought that a massive gastrointestinal bleed had occurred due to symptoms of the large melena stool immediately before the event, the sudden volume depletion, and peripheral shut down. The autopsy assessment note and a review with the coroner concluded the cause of death to be a massive upper gastrointestinal bleed due to a chronic duodenal ulcer perforation due to anticoagulation. The mortality classification status was fatal bleed. The upper gastrointestinal bleed was centrally adjudicated as a major bleeding event. The study investigator assessed the upper gastrointestinal bleed as related to the study drug.

- Patient 235/12122 was an 81 years old male Caucasian. The subject had a history of coronary artery disease, hyperlipidemia, prostate cancer, non- insulin dependent diabetes, hiatal hernia, alcoholism (21 drinks/ week), and right total knee replacement. He underwent left total knee replacement for osteoarthritis. Operative blood loss was 75 mL, and no postoperative drain was used. The subject received the first dose of warfarin placebo approximately 4 hours after surgery. He received 3 days of treatment with ximelagatran 36 mg for a total of 5 doses. On postoperative day 1, the subject received a blood transfusion for decreased hemoglobin of 83 g/ L. The subject developed confusion after the transfusion (approximately 24 hours postoperatively), which the study investigator attributed to alcohol withdrawal. The subject was treated with a benzodiazepine medication. On postoperative day 2, the subject became aggressive and violent, assaulted one of the nurses, and had to be restrained. On postoperative day 3, his confusion was still fairly significant. The study investigator noted the subject to be improved, fairly lucid, and denying any problems in regard to the knee replacement. On postoperative day 4, the subject was discovered unresponsive with absent vital signs. Resuscitation was attempted but was unsuccessful, and the subject expired. An autopsy was performed. The coroner stated the subject's death was due to cardiac arrhythmia, on the basis of extensive coronary artery disease with no evidence of any thromboembolic events. Cardiac arrhythmia was therefore the cause of death recorded on the death certificate. The study investigator assessed the sudden death as not related to the study drug. The mandatory venography was not performed for this subject due to his death.

- Patient 510/14366 was an 80 years old female Caucasian. The subject had a history of hypertension, gastritis, varicose veins, perineoplasty, and removal of dorsal sebaceous cyst. She underwent right total knee replacement for osteoarthritis. Operative blood loss was 300 mL, and postoperative drainage was 1340 mL. The subject received the first dose of warfarin placebo approximately 5 hours after surgery. She received 7 days of treatment with ximelagatran 36 mg for a total of 13 doses. The subject was discharged to home on postoperative day 4. On postoperative day 7, the subject had a mandatory bilateral venogram assessed as positive for intraluminal- filling defects in the left muscular and right fibular veins. Both legs were classified as having any deep vein thrombosis (DVT) distally. The

subject received Clexane (heparin- fraction, sodium salt) and open- label warfarin sodium for treatment of the DVT. On postoperative day 19, the subject's family reported to the study investigator that the subject had died at home on postoperative day 15. The cause of death was unknown. No autopsy was performed. Based on central adjudication, the mortality classification status was fatal pulmonary embolism (PE), as PE could not be excluded as the cause of the unexplained, undescribed death at home two weeks after surgery. The study investigator assessed the death (unknown reason) as not related to the study drug.

Serious adverse events other than deaths

Of the 2299 patients included in the safety population, 158 patients had a treatment-emergent SAE, and the proportion of patients with an SAE was identical in the ximelagatran and warfarin groups (n=79, 6.9% for each). A summary of the SAEs (including death) experienced by at least 2 patients in either treatment group is provided in Table B16 by preferred term.

Table B16 Number (%) of patients with SAEs occurring in at least 2 patients

Serious adverse event Preferred term	Ximelagatran 36 mg (n=1151) n (%)	Warfarin (n=1148) n (%)
At least 1 serious adverse event	79 (6.9)	79 (6.9)
Postoperative complications	24 (2.1)	16 (1.4)
Myocardial infarction	6 (0.5)	3 (0.3)
Pneumonia	6 (0.5)	1 (0.1)
GI hemorrhage	4 (0.3)	3 (0.3)
Urinary tract infection	3 (0.3)	1 (0.1)
Ileus	3 (0.3)	3 (0.3)
Accident and/or injury	2 (0.2)	0 (0.0)
Cerebrovascular disorder	2 (0.2)	1 (0.1)
Chest pain	2 (0.2)	1 (0.1)
Confusion	2 (0.2)	0 (0.0)
Coronary artery disorder	2 (0.2)	1 (0.1)
Fibrillation atrial	2 (0.2)	6 (0.5)
Hemarthrosis	2 (0.2)	1 (0.1)
INR increased	2 (0.2)	5 (0.4)
Joint disorder NOS	2 (0.2)	0 (0.0)

In both treatment groups, the most common SAE was postoperative complications, occurring in 2.1% of ximelagatran patients and 1.4% of warfarin patients. Pneumonia and MI were considered serious for more patients in the ximelagatran group (n=6, 0.5% for both) compared with the warfarin group (n=1, 0.1% and n=3, 0.3%, respectively). Serious postoperative

complications were experienced by 18 patients, 13 (0.9%) randomized to ximelagatran and 5 (0.7%) to warfarin. In contrast, atrial fibrillation and increased INR were considered serious for more patients in the warfarin group (n=6, 0.5% and n=5, 0.4%, respectively) compared with the ximelagatran group (n=2, 0.2% for each).

The proportion of patients with SAEs considered related to study medication by the investigator was similar in the ximelagatran (n=13, 1.1%) and warfarin (n=19, 1.7%) groups. Few patients had serious postoperative complications that were assessed by the investigator as related to study drug (5 in the ximelagatran group; 4 in the warfarin group). Seventeen patients in the ximelagatran group (including 3 who died) and 19 in the warfarin group (including 2 who died) had treatment discontinued prematurely as the result of a SAE(s).

Treatment-emergent SAEs were assessed by the ICAC as a major bleeding event for 8 patients in the ximelagatran group and included GI hemorrhage (2), postoperative complications (2), hemorrhoids (1), hemarthrosis (1), purpura (1), and intracranial hemorrhage (1). In the warfarin group, treatment-emergent SAEs were assessed by the ICAC as major bleeding events for 4 patients, including hemarthrosis (1), purpura (1), GI hemorrhage (1), and postoperative complications (1).

Discontinuations due to adverse events

A summary of the treatment-emergent AEs leading to discontinuation of study drug by at least 2 patients in either treatment group is provided in Table B17 by preferred term in decreasing order of frequency in the ximelagatran group.

The proportion of patients for whom the investigator coded the AE as having caused premature discontinuation of study drug was comparable in the ximelagatran group (n=28, 2.4%) and the warfarin group (n=34, 3.0%).

Table B17 Number (%) of patients who discontinued from treatment due to a treatment-emergent adverse event (safety population)

AE leading to discontinuation of study drug Preferred term	Ximelagatran 36 mg (n=1151) n (%)	Warfarin (n=1148) n (%)
At least 1 AE leading to discontinuation[a]	28 (2.4)	34 (3.0)
Postoperative complications	5 (0.4)	8 (0.7)
GI hemorrhage	3 (0.3)	2 (0.2)
Hemarthrosis	3 (0.3)	2 (0.2)
Myocardial infarction	3 (0.3)	1 (0.1)
Anxiety	2 (0.2)	2 (0.2)
Confusion	2 (0.2)	0 (0.0)
Dyspnea	2 (0.2)	0 (0.0)
Ileus	2 (0.2)	3 (0.3)
Melena	2 (0.2)	0 (0.0)
Fibrillation atrial	1 (0.1)	2 (0.2)
Allergic reaction	0 (0.0)	2 (0.2)
Hematemesis	0 (0.0)	2 (0.2)
INR increased	0 (0.0)	4 (0.3)
Nausea	0 (0.0)	2 (0.2)
Nonprotein nitrogen increased	0 (0.0)	2 (0.2)
Rash	0 (0.0)	2 (0.2)

2.11.3 Clinical laboratory evaluation

At baseline, mean hemoglobin levels and platelet counts were comparable in the ximelagatran and warfarin groups. There was a steady decline in hemoglobin levels and platelet counts during the first 3 days postoperatively in both treatment groups, with the largest mean decrease in both parameters observed on postoperative Day 3 (mean percent reduction of 25% to 26% in both groups). By the End of Treatment Period Study Visit, hemoglobin levels had increased slightly and had returned to near baseline levels by the end of the follow-up period in both the ximelagatran and warfarin groups. Mean platelet counts at the End of Treatment Period Study Visit were elevated above baseline values, likely due to the receipt of transfusions. Mean platelet count had returned to near baseline levels during follow-up.

Each of the liver function parameters and total bilirubin were increased relative to baseline in both treatment groups at the End of Treatment Period Study Visit and there was no difference between treatment groups in the magnitude of the increase. In both treatment groups, the largest mean increase from baseline was observed for ALAT (mean percent increase of approximately 55%). At follow-up, ALAT, ASAT, and total bilirubin values were at or near baseline values while alkaline phosphatase values remained elevated.

The frequencies in measures of liver function outside the extended reference ranges for liver enzymes (ASAT, ALAT, and alkaline phosphatase) and total bilirubin are summarized in Table B18.

Table B18 Frequency of selected liver function test values elevated above upper limits of normal (safety population)

Laboratory parameter Visit	Level (x ULN)	Ximelagatran 36 mg (n=1151) % (n/N)	Warfarin (n=1148) % (n/N)
ALAT			
Baseline	>3	0.0 (0/1130)	0.0 (0/1120)
End of Treatment	>3	0.5 (5/1078)	0.6 (6/1071)
Follow-up[a]	>3	0.6 (7/1091)	0.2 (2/1083)
ASAT			
Baseline	>3	0.0 (0/1127)	0.0 (0/1118)
End of Treatment	>3	0.0 (0/1077)	0.4 (4/1071)
Follow-up[a]	>3	0.2 (2/1090)	0.0 (0/1083)
Alkaline phosphatase			
Baseline	>3	0.0 (0/1129)	0.0 (0/1120)
End of Treatment	>3	0.6 (7/1078)	0.4 (4/1072)
Follow-up[a]	>3	0.2 (2/1091)	0.1 (1/1083)
Total bilirubin			
Baseline	>3	0.0 (0/1130)	0.0 (0/1120)
End of Treatment	>3	0.0 (0/1078)	0.0 (0/1073)
Follow-up[a]	>3	0.1 (1/1091)	0.0 (0/1084)

Data derived from Table 11.3.8.7, Section 11.3.
[a] Follow-up is defined as >2 days after the last dose of study medication.
ALAT alanine aminotransferase; ASAT aspartate aminotransferase; ULN upper limit of normal.

Few patients (<3%) in the ximelagatran or warfarin groups had abnormalities outside the extended range at any time point for any of the liver function parameters. Less than 1% of patients in either treatment group had increases of >3x ULN for any liver function parameter during the study. All patients in both treatment groups with an elevation in ALAT of >3x ULN at the end of treatment or at follow-up (ie, more than 2 days after the last dose of study medication), had normalized values within 4 weeks of onset. It should be noted that there were more patients with ALT elevation ($\geq$ 3ULN) in ximelagatran group (n=7) than in the warfarin group (n=2) during the following up period. This may indicate that ximelagatran may cause late occurrence of liver toxicity and 4-6 weeks of follow-up may not be adequate to assess the safety for short-term use of ximelagatran.

2.11.4 Conclusions on safety results

There were no statistically significant differences between ximelagatran and warfarin in the frequency of major bleeding events, the frequency of minor bleeding events, or the frequency of any (major and minor) bleeding events on-treatment or over the entire study ($p \geq 0.087$). With the exception of a significantly higher incidence of unusual bruising or hematoma on postoperative Day 3 in the ximelagatran group compared with the warfarin group ($p=0.015$), there were no significant differences between treatment groups at any other time point in the incidence of any other wound assessments ($p \geq 0.245$).

No appreciable differences were detected between treatment groups in the incidence of treatment-emergent AEs, SAEs, or discontinuations due to study drug. However, a larger number of patients in the ximelagatran group died (n=7) compared with the warfarin group (n=3). MI was considered serious for more patients in the ximelagatran group (n=6, 0.5%) compared with the warfarin group (n=3, 0.3%, respectively). It should be noted that there were more patients with ALT elevation ($\geq$ 3ULN) in ximelagatran group (n=7) than in the warfarin group (n=2) during the following up period. This may indicate that ximelagatran may cause late occurrence of liver toxicity and 4-6 weeks of follow-up may not be adequate to assess the safety for short-term use of ximelagatran.

3 Study SH-TPV-0003 (THRIVE III) for the Indication of Prolonged prophylaxis VTE after a six-month anticoagulation treatment for VTE

The sponsor provided only one study, SH-TPV-0003 (THRIVE III) to support this indication. This was a multicentre, double-blind, parallel-group, placebo control study.

Title: Oral Thrombin Inhibitor Ximelagatran given to Patients as Prolonged Prophylaxis after a Six-month Anticoagulation Treatment for Venous Thromboembolism. An International Multicentre Double-blind Placebo Controlled Study (THRIVE III)

3.1 Study objectives

Primary objectives

To assess whether the oral thrombin inhibitor ximelagatran given as prolonged prophylaxis after a six-month anticoagulation treatment for VTE reduces the recurrence rate of symptomatic objectively confirmed VTE event compared to placebo (time to event).

Secondary objectives

To estimate all-cause mortality, the safety of treatment with ximelagatran with special regard to bleeding and the pharmacokinetics of melagatran during long term treatment with ximelagatran.

3.2 Overall study design

This was a double-blind, randomized, placebo-controlled, parallel-group multi-center study comparing the efficacy and safety of ximelagatran 24 mg twice daily with placebo when given orally as long term secondary prevention for 18 months to patients after a six-month anticoagulation treatment for VTE.

The clinical endpoints were symptomatic objectively confirmed VTE, non-fatal or fatal, and all-cause mortality and major bleeding. The primary variable was time to symptomatic objectively confirmed VTE event during 18 months of treatment.

A total of 1,200 patients at approximately 150 centers in 18 countries, with roughly 10 (6-20) patients per center, were planned to be randomized into the study.

The study comprised the following 4 periods:

Anticoagulant and wash-out periods

Patients who had received anticoagulation treatment for six (five to seven) months after an objectively verified, symptomatic VTE were to be included. Dates for the bilateral ultrasonography of the legs and the perfusion scan of the lungs (baseline) were to be scheduled shortly before randomization. The patients were instructed to stop treatment with vitamin K antagonist (VKA) two to seven days before the scheduled randomization visit.

Randomization

The randomization was stratified on the basis of the presence or absence of known active malignancy during the past five years. The patients were randomized in equal proportions to receive either ximelagatran tablets 24 mg or placebo tablets orally twice daily for 18 months.

18-month randomized treatment period

Study visits were scheduled at two weeks and four weeks and then every month (three to five weeks) during the first six months after the randomization and thereafter every three months (10-14 weeks).

Follow-up period

A follow-up visit was to be planned two weeks after completing the randomized treatment period.

3.3 Selection of study population

The first exclusion criterion (patients with a need of continuous treatment with anticoagulants) implies that patients considered to be at high risk of recurrence were not to be included in the study. This criterion was set for ethical reasons, since it would not have been appropriate to randomize this type of patient to treatment with placebo.

Inclusion criteria

For inclusion in the study, patients had to fulfill all of the following criteria:
1. Patients with symptomatic objectively confirmed VTE treated with anticoagulants for six months (no recurrent VTE was allowed during this period)
2. Age ≥18 years
3. Signed informed consent

Exclusion criteria

Any of the following was regarded as a criterion for exclusion from the study:
1. Patients with a need of continuous treatment with anticoagulants
2. Conditions associated with an increased risk of bleeding
3. Anemia (Hb < 90 g/L)
4. Platelet count < $90x10^{9}$ /L
5. Renal impairment (calculated creatinine clearance < 30 mL/min)
6. Known clinically significant liver disease (as judged by the investigator) or persistent ASAT and/or ALAT ≥ 3 x ULN (defined by central laboratory)
7. Pregnancy and/or lactation
8. Childbearing potential without reliable contraception
9. Concomitant treatment with other anticoagulant, antiplatelet or fibrinolytic agents; continuous treatment with acetylsalicylic acid (ASA) >500 mg per day or continuous treatment with NSAID.
10. Participation in an interventional clinical study during the last three months
11. Planned surgery
12. Involvement in the planning and conducting of the study
13. Previous randomization in the present study
14. Known drug addiction and/or alcohol abuse
15. Mental condition preventing understanding of the study
16. Poor compliance, as evidenced during the six months of anticoagulation treatment before randomization, as judged by the investigator
17. Serious illness, with survival for 18 months being unlikely ie, terminally ill patients

3.4 Criteria for discontinuation

1. Patients for whom the treatment code was prematurely broken were withdrawn from further study treatment and assessments.
2. Major bleeding.
3. Objectively confirmed venous thromboembolic event.
4. Other AEs severe enough to necessitate discontinuation of study drug administration.

5. If a pregnant woman was included by mistake or a woman became pregnant.

Discontinuation of the study drug should also have been considered if:

- S-ALAT was >7 times the ULN
- Repeated measurements showed that S-ALAT was 3-7 times the ULN during a 2- month period without showing any tendency to decrease.

3.5 Doses and treatment regimens

The patients were randomized to treatment with either one 24-mg ximelagatran tablet twice daily or one tablet of placebo twice daily, taken orally in the morning and in the evening for 18 months.

3.6 Efficacy variable

Primary variable
The primary variable was time to symptomatic objectively confirmed VTE event during the 18 months of treatment or until premature discontinuation of the study.

Secondary variable
Time to death from any cause and time to major bleeding event, during 18 months of treatment or until premature discontinuation of the study (ITT population).

3.7 Statistical analysis methods

In the primary analysis, only centrally adjudicated events are considered as events. Because of the long treatment period, the number of drop-outs in the study was expected to be substantial. Therefore, the equality of time until event between ximelagatran and placebo is tested with a log rank test. Due to the independent Safety Committee monitoring for a positive trend of the pre-planned interim analyses, the significance level for the primary analysis is 4.76%. For all other analyses a significance level of 5% is used. Survival curves for the time to event, based on Kaplan-Meier estimates, are presented, as is the estimated risk for an event by 3, 6, 9, 12, 15 and 18 months. The hazard ratio between treatments is estimated together with 95% confidence intervals using a Cox-regression model assuming a proportional hazard.

Data from the 18-month follow-up of prematurely discontinued patients will be presented together with the original study data. The combined data will be analyzed as a complementary ITT analysis using the same methods as described above. The events collected at the 18-month follow-up will not be centrally adjudicated, however.

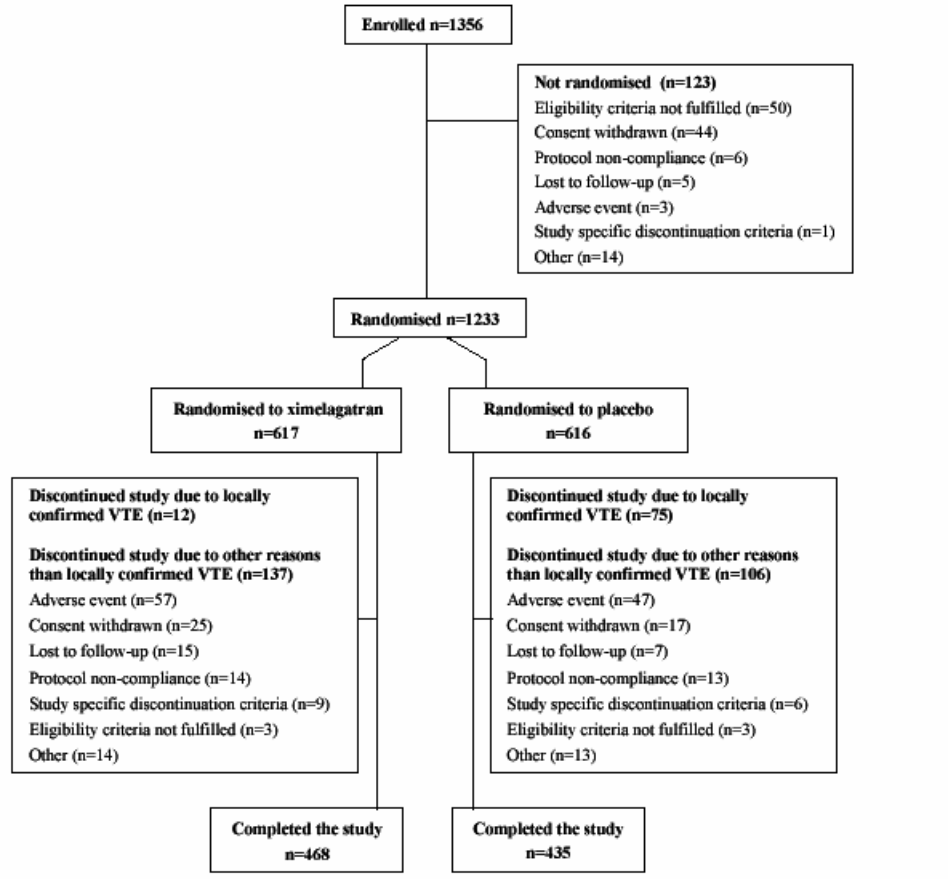
Time until death by any cause, locally confirmed VTE events, the composite of VTE event and death of any cause, major and major and/or minor bleedings are analyzed and presented using the same methods as for the primary variable.

Descriptive statistics and frequency tables on pertinent variables are calculated for baseline demographics, days on study medication, compliance, laboratory variables, ECG, physical examinations and vital signs. In addition, time to elevated ALAT is presented using Kaplan-Meier estimates. The influence of the potential prognostic factors mentioned above on the risk for ALAT >3 x ULN is investigated using logistic regression. Logistic regression is used in these analyses since an assumption of proportional hazard is unrealistic. Adverse events are presented using frequency tables.

3.8 Disposition

Of the 1356 patients enrolled, 1233 were randomized at 142 centers and 903 completed the study. The most common reason for premature termination the study was adverse event. Patient disposition and reason for premature study discontinuation are summarized in Figure 1. In the placebo group locally confirmed VTE recurrence was the most common reason for premature discontinuation of the study. In general, discontinuations for other reasons than VTE were slightly more common in the ximelagatran group.

Figure 1 **Patient disposition and reasons for premature discontinuation of the study**



There were no major differences between treatment groups in the number of patients who had protocol deviations that were considered serious enough to warrant exclusion of data from the PP analyses. Overall, the treatment groups were comparable for demographic characteristics, baseline parameters, treatment compliance and use of concomitant medication. The major part of the patients (93%) were Caucasians.

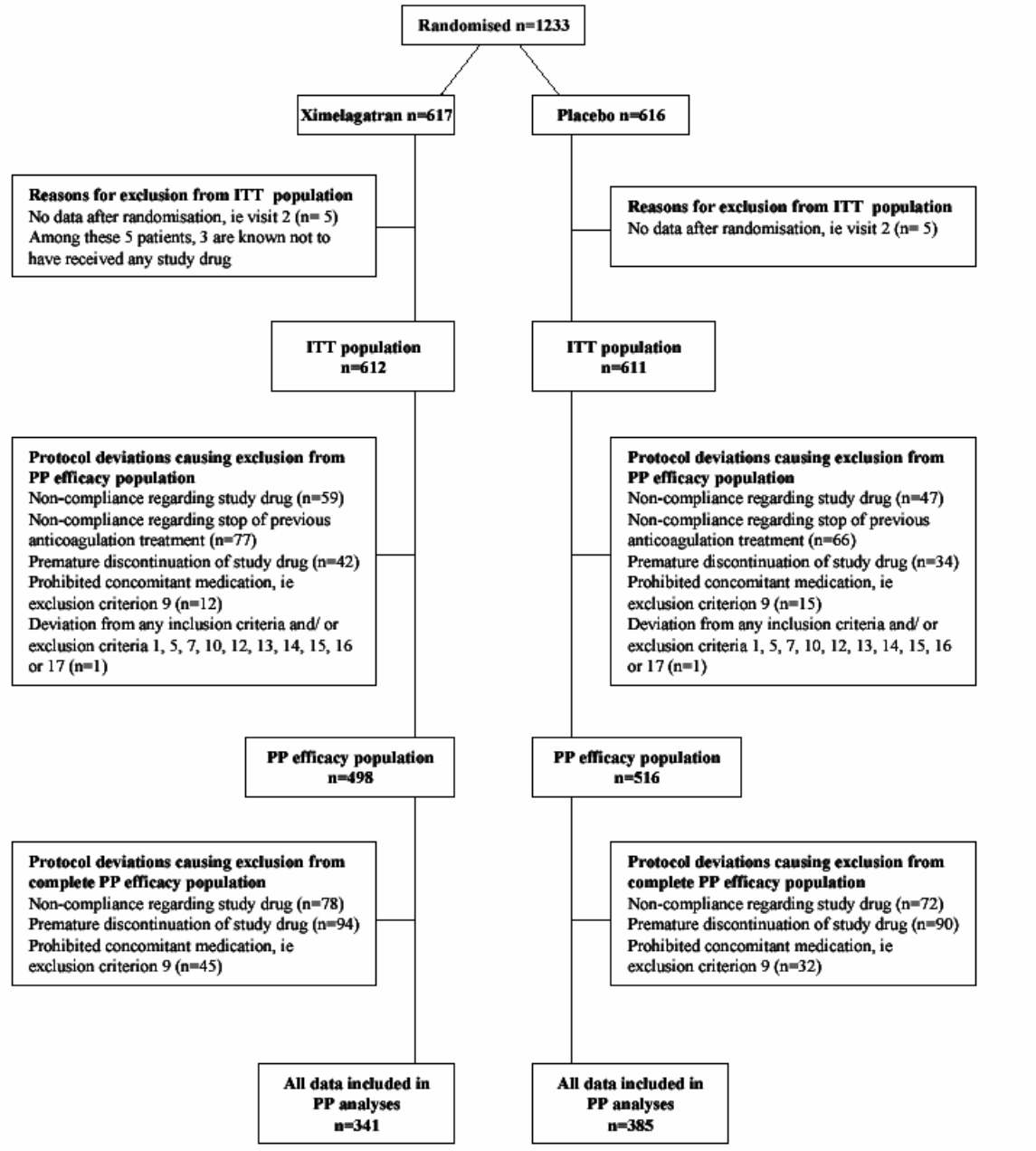
Patient populations analyzed

Three patient populations were analyzed:

- An ITT efficacy population, which included all randomized patients who had taken at least one dose of the study treatment and had at least one data point after randomization. This population was the primary population for analysis.
- A PP efficacy population, which included all patients in the ITT population who had no deviations from the protocol judged to affect the treatment effect. However, some patients who had a major deviation are included in the analyses up to the time of that deviation.
- A safety population, which included the same patients as in the ITT population.

The patient populations analyzed and the number of patients in each population are summarized in Figure 2.

Figure 2 **Study population and reasons for exclusion (more than one reason can be given for each patient)**



Of the 1233 randomized patients, 10 patients had no data after randomization, 5 of them randomized to ximelagatran and 5 to placebo. Of the 5 patients on ximelagatran, 3 patients were also confirmed not to have received any study medication, as can be seen in Figure 2.

Consequently, 1223 patients were analyzed for safety and efficacy in an ITT population. Among 1015 of the patients, all or a portion of the data was included in the PP analysis. Among 725 of the patients, all available data were included in a complete PP analysis. The most common reason for the exclusion of data was non-compliance as regarded the study drug.

3.9 Demographic and other patient characteristics

Overall, the demographic and other patient characteristics were comparable between the treatment groups. The demographic and baseline characteristics for the ITT population are summarised in Table C1.

Table C1 Demographics and baseline characteristics, ITT population

		Ximelagatran	Placebo	Total
Age (years)	N	612 (100%)	611 (100%)	1223 (100%)
	Missing	0 (0%)	0 (0%)	0 (0%)
	Mean	56	58	57
	SD	15	15	15
	Min	18	19	18
	Median	57	60	59
	Max	87	90	90
	60+	274 (45%)	319 (52%)	593 (48%)

		Ximelagatran	Placebo	Total
	70+	125 (20%)	146 (24%)	271 (22%)
	80+	15 (2%)	24 (4%)	39 (3%)
Sex	Male	331 (54%)	313 (51%)	644 (53%)
	Female	281 (46%)	298 (49%)	579 (47%)
Race	Caucasian	571 (93%)	569 (93%)	1140 (93%)
	Black	1 (0%)	4 (1%)	5 (0%)
	Oriental	1 (0%)	0	1 (0%)
	Other	34 (6%)	34 (6%)	68 (6%)
	Hispanic	5 (1%)	4 (1%)	9 (1%)
Smoking	None	343 (56%)	325 (53%)	668 (55%)
	Previous	143 (23%)	163 (27%)	306 (25%)
	Occasional	24 (4%)	28 (5%)	52 (4%)
	Habitual	102 (17%)	95 (16%)	197 (16%)
Malignancy (a)	No	578 (94%)	579 (95%)	1157 (95%)
	Yes	34 (6%)	32 (5%)	66 (5%)
Weight (kg)	N	612 (100%)	610 (100%)	1222 (100%)
	Missing	0 (0%)	1 (0%)	1 (0%)
	Mean	82	82	82
	SD	16	16	16
	Min	45	47	45
	Median	82	80	81
	Max	145	150	150
	80+	346 (57%)	332 (54%)	678 (55%)
	100+	86 (14%)	85 (14%)	171 (14%)
	120+	8 (1%)	10 (2%)	18 (1%)
Height (cm)	N	610 (100%)	607 (99%)	1217 (100%)
	Missing	2 (0%)	4 (1%)	6 (0%)
	Mean	170	170	170
	SD	10	10	10
	Min	144	142	142
	Median	170	170	170
	Max	200	200	200
BMI (kg/m^2)	N	610 (100%)	607 (99%)	1217 (100%)
	Missing	2 (0%)	4 (1%)	6 (0%)
	Mean	28	28	28
	SD	5	5	5
	Min	18	18	18
	Median	28	28	28
	Max	53	53	53
	25+	475 (78%)	486 (80%)	961 (79%)
	30+	213 (35%)	201 (33%)	414 (34%)
CrCl (ml/min)	N	597 (98%)	593 (97%)	1190 (97%)
	Missing	15 (2%)	18 (3%)	33 (3%)
	Mean	114	110	112

Information on the initial VTE event in the ITT population is summarized in Table C2.

Table C2: Information on initial VTE, ITT population

		Ximelagatran	Placebo	Total
Number of VTE events before initial VTE	0	534 (87%)	514 (84%)	1048 (86%)
	1	57 (9%)	80 (13%)	137 (11%)
	2	16 (3%)	11 (2%)	27 (2%)
	3	5 (1%)	5 (1%)	10 (1%)
	4		1 (0%)	1 (0%)
Type of event	Missing		1	1
	DVT only	406 (66%)	389 (64%)	795 (65%)
	- Proximal	272 (67%)	261 (67%)	533 (67%)
	- Distal only	134 (33%)	128 (33%)	262 (33%)
	PE only	106 (17%)	93 (15%)	199 (16%)
	DVT and PE	100 (16%)	128 (21%)	228 (19%)
Diagnosis of DVT	Missing	1	1	2
	Phlebography	114 (23%)	113 (22%)	227 (22%)
	Phlebography + Ultrasonography	39 (8%)	34 (7%)	73 (7%)
	Phlebography + Other	2 (0%)		2 (0%)
	Phlebography + Ultrasonography + Other	5 (1%)		5 (0%)
	Ultrasonography	322 (64%)	344 (67%)	666 (65%)
	Ultrasonography + Other	6 (1%)	4 (1%)	10 (1%)
	Other	17 (3%)	21 (4%)	38 (4%)
Diagnosis of PE	Missing	1	1	2
	Perfusion scan	43 (21%)	41 (19%)	84 (20%)
	Perfusion scan + Perfusion-ventilation scan	4 (2%)	5 (2%)	9 (2%)
	Perfusion scan + Spiral CT	2 (1%)	2 (1%)	4 (1%)
	Perfusion scan + Other	3 (1%)	2 (1%)	5 (1%)
	Perfusion scan + Perfusion-ventilation scan + Spiral CT		1 (0%)	1 (0%)
	Perfusion scan + Perfusion-ventilation scan + Other	1 (0%)		1 (0%)
	Perfusion-ventilation scan	88 (43%)	108 (49%)	196 (46%)
	Perfusion-ventilation scan + Pulmonary angiography	1 (0%)	2 (1%)	3 (1%)
	Perfusion-ventilation scan + Spiral CT	9 (4%)	7 (3%)	16 (4%)
	Perfusion-ventilation scan + Other	1 (0%)		1 (0%)

		Ximelagatran	Placebo	Total
	Perfusion-ventilation scan + Pulmonary angiography + Spiral CT	1 (0%)		1 (0%)
	Pulmonary angiography	8 (4%)	15 (7%)	23 (5%)
	Spiral CT	35 (17%)	28 (13%)	63 (15%)
	Spiral CT + Other	1 (0%)		1 (0%)
	Other	8 (4%)	9 (4%)	17 (4%)

The majority of the patients (97%) in both groups started the study medication within 3 days after randomization, and the number of days between randomization and the first dose of medication was comparable between the treatment groups.

The median time on study medication was slightly above 500 days, which is shorter than the anticipated 18 months (approximately 540 days). This might be explained by the flexibility in the time interval between visits allowed according to the protocol.

The use of concomitant medication at study entry was similar in the two treatment groups.

Conclusions on study patients

The study population, as demonstrated by baseline characteristics, includes important subgroups of a general population of patients with previous VTE. Different age groups were adequately represented and the balance between the sexes was appropriate. Patient weights were widely distributed and obese patients were well-represented. Fourteen percent of the patients had a history of more than one previous VTE event.

A total of 5% of patients with known malignancy at entry was enrolled in this study.

A limitation of the study population is the exclusion of patients with known liver disease and/or elevations in liver enzymes (ASAT and/or ALAT) at entry, and of patients with severely impaired renal function, as specified in the exclusion criteria. Consequently, the results of this study cannot safely be extended to these subgroups of the VTE population.

3.10 Efficacy results

3.10.1 Primary variable: symptomatic objectively-confirmed VTE, ITT population

The estimated cumulative risk of symptomatic objectively-confirmed VTE during 18 months of treatment was 2.8% and 12.6% for patients on ximelagatran and placebo, respectively, see Table C3.

Table C3 Estimated cumulative risk (%) of a VTE event, ITT population

Treatment	Days	Effective sample size	Estimate	95% Confidence Interval	
				Lower limit	Upper limit
Ximelagatran	90	590.0	0.7	0.0	1.3
	180	546.5	1.0	0.2	1.8
	270	522.0	1.2	0.3	2.1
	360	506.0	1.6	0.6	2.6
	450	474.5	1.8	0.7	2.9
	540	107.0	2.8	0.9	4.7
Placebo	90	557.0	4.8	3.1	6.5
	180	532.0	6.4	4.4	8.3
	270	502.0	8.4	6.1	10.6
	360	474.0	10.8	8.2	13.3
	450	438.5	11.9	9.3	14.6
	540	86.0	12.6	9.9	15.4

The estimated hazard ratio between treatments is 0.16 (95% CI 0.09; 0.30 and $p< 0.0001$). According to the outcome of the primary analysis, ximelagatran significantly reduced the recurrence rate of symptomatic, objectively confirmed VTE events as compared to placebo ($p<0.0001$).

The number of patients with a VTE event was 12 in the ximelagatran group and 71 in the placebo group. The number of patients with a PE event was lower in the ximelagatran group compared to the placebo group, 2 and 23, respectively. Number of patients with a VTE event is summarized in Table C4.

Table C4 Number of patients with a VTE event, ITT population

Event	Ximelagatran	Placebo
Total VTE	12	71
DVT only	10	48
PE only	2	15
DVT and PE	0	8

Of the VTE events described in Table C4, 3 occurred during the follow-up period i.e., after cessation of study medication (2 patients in the ximelagatran group and 1 in the placebo group).

The location of DVT is summarized in Table C5, the total numbers of proximal DVT were fewer in the ximelagatran group than in the placebo group, 6 and 41 respectively.

Table C5 Location of DVT events, ITT population

Part of the body	Location	Ximelagatran	Placebo
Leg	Proximal	6	41
	Distal	4	13
Other	Left popliteal vein	0	1
	Right arm	0	1

3.10.2 Secondary variables

All cause mortality, ITT population

There were few deaths and they were evenly distributed, 6 in the ximelagatran group and 7 in the placebo group. The estimated cumulative risk of a death (all-cause mortality) during 18 months of treatment was 1.1% and 1.4% for patients on ximelagatran and placebo, respectively. The estimated hazard ratio between treatments is 0.83 (95% CI 0.28; 2.46, p=0.7289). According to the outcome of the secondary analysis, there was no significant difference in all-cause mortality between the treatment groups during the 18 months.

All-cause mortality and/or VTE events, ITT population

The total number of patients who died and/or experienced a VTE event was 18 in the ximelagatran group and 75 in the placebo group. The estimated hazard ratio between treatments

is 0.23, p< 0.0001. Ximelagatran significantly reduced the recurrence rate of the combined endpoint, all-cause mortality and/or VTE events, compared to placebo (p<0.0001). The magnitude is similar to the difference seen with VTE event only.

Locally confirmed VTE events, ITT population

The agreement between the local investigator's judgement and the central adjudication by the independent Endpoint Committee was generally good, with few discrepancies. Consequently, the analysis of locally judged VTE events gave results similar to those for the centrally adjudicated events. Patients with suspected VTE events with local assessment versus central adjudication are summarized in Table C6.

Table C6 Patients with suspected VTE events. Local assessment versus central adjudication, ITT population

Treatment	Local Assessment	Central Adjudication	
		Confirmed	Rejected
Ximelagatran	Confirmed	10	3
	Rejected	2	63
Placebo	Confirmed	68	7
	Rejected	3	68
Total	Confirmed	78	10
	Rejected	5	131

By local assessment, the total number of patients who experienced a VTE event was 13 in the ximelagatran group and 75 in the placebo group. The estimated hazard ratio between treatments is 0.17, p< 0.0001. The difference between the treatments was statistically significant and of the same magnitude as in the case of the centrally confirmed events used in the primary efficacy analysis.

3.10.3 Summary of efficacy results

Ximelagatran significantly reduced the recurrence rate of symptomatic, objectively confirmed VTE (the primary variable of the study) as compared to placebo over 18 months of treatment (cumulative risk of 2.8% versus 12.6%; hazard ratio 0.16; p<0.0001). The results for the secondary variable, all-cause mortality, showed no significant difference between the treatment groups during the 18 months. Ximelagatran also reduced the recurrence rate of the composite endpoint, VTE and all-cause mortality, thereby supporting the results obtained for the primary objective. Complementary intention-to-treat analyses in randomized patients followed for the full intended 18 months period, regardless of any premature study medication discontinuation, did not change the aforementioned conclusions.

3.11 Safety results

See integrated review of safety for details.