AstraZeneca

EXANTA® (ximelagatran) Tablets
NDA 21-686
FDA Advisory Committee Briefing Document

Cardiovascular and Renal Drugs Advisory Committee
10 September 2004

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EXECUTIVE SUMMARY

New Drug Application (NDA) 21-686, submitted by AstraZeneca LP (AstraZeneca), requests approval for the use of EXANTA® (ximelagatran) Tablets as:

- An oral 24-mg twice daily (bid) fixed dose for the long-term secondary prevention of venous thromboembolism (VTE) after standard treatment for an episode of acute VTE
- An oral 36-mg bid fixed dose initiated post-operatively for the prevention of VTE in patients undergoing total knee replacement (TKR) surgery
- An oral 36-mg bid fixed dose for the prevention of stroke and systemic thromboembolic complications associated with atrial fibrillation (AF).

The Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) Division of Gastrointestinal and Coagulation Drug Products has requested that AstraZeneca participate in a Cardiovascular and Renal Drugs Advisory Committee review of this application. This briefing document has been prepared to support that review.

In this briefing document, AstraZeneca will provide the information necessary to make an assessment of the benefit-risk profile for ximelagatran as an oral anticoagulant and antithrombotic based on comparisons of ximelagatran to warfarin and to placebo. To facilitate the evaluation, this document and the presentation to the committee will briefly address the following key areas in the ximelagatran development program: development objectives, efficacy, safety, the proposed patient Risk Minimization Action Plan (RiskMAP), and the benefit-risk profile of ximelagatran.

Clinical pharmacology

The development program goal for ximelagatran was to develop and characterize the first of a new class of oral direct thrombin inhibitors as an alternative oral anticoagulant to warfarin for the claimed indications. Following oral administration, ximelagatran is rapidly absorbed and bioconverted to melagatran, a potent, competitive and reversible-binding direct thrombin inhibitor. Melagatran has a predictable response based on stable and reproducible pharmacokinetics and pharmacodynamics with a rapid onset and offset of action. Melagatran does not interact with food or alcohol and has a low potential for drug interactions. Systemic melagatran is primarily eliminated via glomerular filtration. For each indication studied, there was consistent efficacy and safety versus comparator across demographic sub-groups including gender, age, race, body weight, body mass index (BMI) and renal function (calculated creatinine clearance [CrCL]) following fixed-dose ximelagatran (24-mg bid or 36-mg bid). The stable and reproducible plasma concentrations of melagatran following oral ximelagatran administration in patients enable long-term fixed dosing without coagulation monitoring.

Development of ximelagatran

The efficacy and safety of ximelagatran has been studied in a broad range of thrombogenic states in large, worldwide, comparator-controlled, and primarily outcome-based clinical studies. The studies were designed to investigate whether fixed-dose ximelagatran, without coagulation monitoring or dosage adjustment, offers superiority to placebo in secondary prevention of VTE, superiority to well-controlled warfarin for prophylaxis for VTE following orthopedic surgery (OS), and non-inferiority to well-controlled warfarin in preventing stroke and thromboembolic complications in AF. The clinical development program to be reviewed by the Advisory Committee consists of 82 studies, including 5 Phase III pivotal trials. Over 30000 individuals (30698) participated in the clinical trial program, of whom 17365 were exposed to ximelagatran (the prodrug) and/or melagatran (the active compound).

Population studies have shown the annual incidence of VTE disease is 1 to 2 per 1000 people and is a major contributor to morbidity, mortality, and healthcare costs. More than 250000 cases of VTE are diagnosed annually in the United States (US) and at least 50000 of these cases are fatal. In the US, the prevalence of AF is approximately 3% in the adult population, with a corresponding incidence of 1 case per 1000 adults per year. AF is an important independent risk factor for stroke; approximately 15% to 25% of all strokes in the US (75000 per year) can be attributed to AF.

Warfarin is an effective anticoagulant, but its challenges and management issues are significant: (1) warfarin administration requires complex management that is a challenge for the patient, healthcare provider, and healthcare system; (2) as a result, a large number of patients who would benefit from treatment with an anticoagulant long-term are not treated; and (3) treated patients have international normalized ratios (INRs) within the recommended target range only 35% to 68% of the time (Samsa et al 2000, Ansell et al 2001). The limitations of warfarin have a significant impact on patient acceptance of lifestyle change and compliance with complex warfarin regimens.

The development of the direct thrombin inhibitor ximelagatran was undertaken with the aim of creating a new, oral, anticoagulant for the treatment of life-threatening thrombosis and to, thereby, provide an alternative to warfarin.

Efficacy: secondary prevention of VTE

The THRIVE III study (SH-TPV-0003) was a double-blind, randomized trial that evaluated prolonged prophylaxis of VTE with ximelagatran 24 mg bid compared to placebo in patients having completed a standard 6-month anticoagulation treatment (vitamin K antagonists [VKAs]) for acute VTE. The primary endpoint was the time to symptomatic, objectively confirmed VTE event during treatment (up to 18 months or until premature discontinuation from the study). A total of 1233 patients were randomized into this study.

Ximelagatran significantly reduced the recurrence rate of VTE, the primary study endpoint, compared with placebo. The estimated cumulative risk of an event during up to 18 months of prophylactic treatment was 2.8% and 12.6% for patients on ximelagatran and placebo, respectively (hazard ratio 0.16; 95% confidence interval [CI] 0.09 to 0.30; $p<0.0001$). The

9.8% absolute reduction of VTE events corresponds to a number needed to treat (NNT) of 10, ie, only 10 patients would need to be treated with ximelagatran for up to 18 months to prevent one recurrence of deep vein thrombosis (DVT) or pulmonary embolism (PE).

The prophylactic regimen of 24 mg oral ximelagatran bid for up to 18 months demonstrated a clinically meaningful reduction in the recurrence rate of VTE events, compared to placebo during long-term therapy. AstraZeneca believes that this study adequately supports the use of oral ximelagatran 24 mg bid for the long-term secondary prevention of VTE after standard treatment for an episode of acute VTE.

Efficacy: prevention of VTE after knee replacement surgery

Three double-blind, randomized trials, the initial Phase III study (PLATINUM KNEE, SH-TPO-0006) and the 2 pivotal studies, EXULT A (SH-TPO-0010) and EXULT B (SH-TPO-0012), evaluated short-term prophylaxis (7 to 12 days) with ximelagatran 24 mg bid and/or 36 mg bid compared to warfarin for the prevention of VTE in patients undergoing knee replacement surgery. The primary endpoint for the EXULT trials (SH-TPO-0010 and SH-TPO-0012) was the incidence of total VTE (ie, distal and/or proximal DVT and/or symptomatic PE, with objective adjudication committee confirmation) and/or all-cause mortality during the treatment period. A total of 5284 patients were randomized into these 3 studies.

Each of the 2 pivotal studies (EXULT A, SH-TPO-0010 and EXULT B, SH-TPO-0012) met the primary objective: statistically significant reduction with oral ximelagatran 36 mg bid compared with well-controlled warfarin (INR 2.0 to 3.0) in prevention of the composite of total VTE and all-cause mortality in patients undergoing primary elective TKR surgery. The frequency of total VTE and/or all-cause mortality in EXULT A (SH-TPO-0010) was 24.9% (ximelagatran 24 mg), 20.3% (ximelagatran 36 mg) and 27.6% (warfarin). In EXULT B (SH-TPO-0012), the endpoint frequency rates were 22.5% for the ximelagatran group and 31.9% for the warfarin group. Absolute risk reductions (ARRs) of 7.3% ($p=0.003$) and 9.3% ($p<0.001$) were demonstrated with oral ximelagatran 36 mg bid compared to well-controlled warfarin in EXULT A (SH-TPO-0010) and EXULT B (SH-TPO-0012), respectively. Relative risk reductions (RRR) of 27% and 29%, and numbers needed to benefit of 14 and 11 were obtained in the studies, respectively. The 24-mg dose of ximelagatran, evaluated in studies PLATINUM KNEE (SH-TPO-0006) and EXULT A (SH-TPO-0010), showed a numerically lower incidence of VTE with 24 mg ximelagatran compared to warfarin, although the differences were not statistically significant.

The prophylactic treatment regimen of 36 mg oral ximelagatran bid for 7 to 12 days after surgery offers a clinically meaningful reduction in the rate of VTE events. AstraZeneca believes that these studies adequately support the use of oral ximelagatran 36 mg bid for the prevention of VTE in patients undergoing TKR surgery.

Efficacy: prevention of stroke and systemic embolic events (SEEs) in AF

Two randomized, controlled studies SPORTIF III (SH-TPA-0003) and SPORTIF V (SH-TPA-0005) evaluated the long-term prevention of stroke and SEE in patients with

nonvalvular AF. SPORTIF III (SH-TPA-0003) was open-label and SPORTIF V (SH-TPA-0005) was double-blind; both had a single independent Adjudication Committee that completed blinded adjudication of all endpoint events. The primary endpoint of the SPORTIF trials was the time to first occurrence of the composite of stroke and SEE. A total of 7329 patients were randomized into these 2 studies.

Each pivotal study met its primary objective by demonstrating that fixed-dose oral ximelagatran 36 mg bid was non-inferior to well-controlled warfarin in preventing all strokes and/or SEEs, using a non-inferiority margin of 2.0% per year. The rate of all strokes and SEEs in SPORTIF III (SH-TPA-0003) and SPORTIF V (SH-TPA-0005) did not differ between treatment groups (2.3% versus 1.6% in SPORTIF III [SH-TPA-0003], and 1.2% versus 1.6% for SPORTIF V [SH-TPA-0005] for warfarin and ximelagatran, respectively), with the upper bound of the 2-sided 97.5% CI of the difference in event rates (0.13% per year for SPORTIF III [SH-TPA-0003], and 1.03% per year for SPORTIF V [SH-TPA-0005]) well below the pre-specified 2.0% margin. Results of sensitivity analyses, and of secondary and tertiary endpoint analyses, confirmed that of the primary analysis and demonstrated robustness of these results. Putative placebo analyses, using original data from the 6 prior stroke prevention studies (BAATAF 1990, Connolly et al 1991, EAFT 1993, Ezekowitz et al 1992, Petersen et al 1989, SPAF 1991), and an identical primary outcome, demonstrated superiority of ximelagatran to placebo both in SPORTIF III (SH-TPA-0003) (RRR=75%; 95% CI: 58% to 85%) and in SPORTIF V (SH-TPA-0005) (RRR=50%; 95% CI: 17% to 70%).

The study for the prophylactic treatment regimen of 36 mg oral ximelagatran bid for up to 2.5 years demonstrated that ximelagatran was non-inferior to well-controlled warfarin in the prevention of stroke and SEE during AF. AstraZeneca believes that these studies adequately support the use of oral ximelagatran 36 mg bid for the long-term prevention of stroke and other thromboembolic complications associated with AF.

Safety of ximelagatran

Of 17365 patients treated with ximelagatran or melagatran, 6931 patients received ximelagatran for long-term treatment; 5024 patients received ximelagatran for more than 6 months, and 3509 patients received ximelagatran for at least 12 months. Five thousand two hundred and thirty-six (5236) patients took part in the 3 North American Phase III TKR studies and received post-operative ximelagatran for up to 12 days.

In the surgical population (patients undergoing TKR surgery and receiving short-term treatment for <35 days, typically up to 12 days), analysis of the adverse events (AEs) in the 5236 patients showed that both the ximelagatran and warfarin comparator groups demonstrated similar frequencies and types of AEs. Comparability was also noted for serious adverse events (SAEs). There were 4 fatal SAEs during treatment in the ximelagatran group compared to 3 in the warfarin group. A low and similar incidence of discontinuations was observed in the ximelagatran and warfarin groups. There appeared to be no dose effect between the 24-mg and 36-mg doses.

On-treatment (OT) adjudicated major bleeding events were uncommon and the rates of any major or minor bleeding events were not statistically different between the treatment groups. Bleeding AEs with post-operative administration of ximelagatran 24 mg or 36 mg bid after TKR were numerically greater than with warfarin. Bleeding AEs occurred in 6.7% of patients with 36 mg ximelagatran and 5% with warfarin and 7.2% with 24 mg ximelagatran and 5.6% with warfarin. The bleeding with 36-mg and 24-mg doses of ximelagatran did not demonstrate a dose effect. The incidence of serious bleeding AEs was similar between the ximelagatran and warfarin groups. Evaluation of bleeding by the demographic subgroups for age, gender, BMI, race and CrCL did not demonstrate a consistent difference in risk of a bleeding AE with 36 ximelagatran compared to warfarin. There was no increase in transfusion volume or bleeding-related wound complications. Wound appearance was to be assessed by the investigator and was rated as "as expected", "better than expected", or "worse than expected." The wound appearance was reported as "as expected" or "better than expected" in most patients and was similar between the groups. Other bleeding indicators, blood loss and transfusions, were similar between the ximelagatran 36-mg and warfarin groups. Exposure-response analysis suggests that exposure to melagatran does not predict the likelihood of a bleeding event on an individual basis.

In the long-term population (patients who were to be dosed for ≥35 days and up to 5 years [4 years at cut-off for the NDA]), oral administration of ximelagatran (24 mg and 36 mg bid) was generally well tolerated. Similar frequencies and types of AEs were reported for ximelagatran and the comparator groups (placebo or warfarin). Most AEs were mild or moderate in intensity. A similar frequency was also reported for SAEs, the majority of which were nonfatal. Fatal SAEs were low in both groups, 1.6% for ximelagatran compared with 1.8% for comparators. The higher incidence of discontinuations in the ximelagatran group was primarily due to a protocol-mandated requirement to discontinue for increases in alanine aminotransferase (ALT).

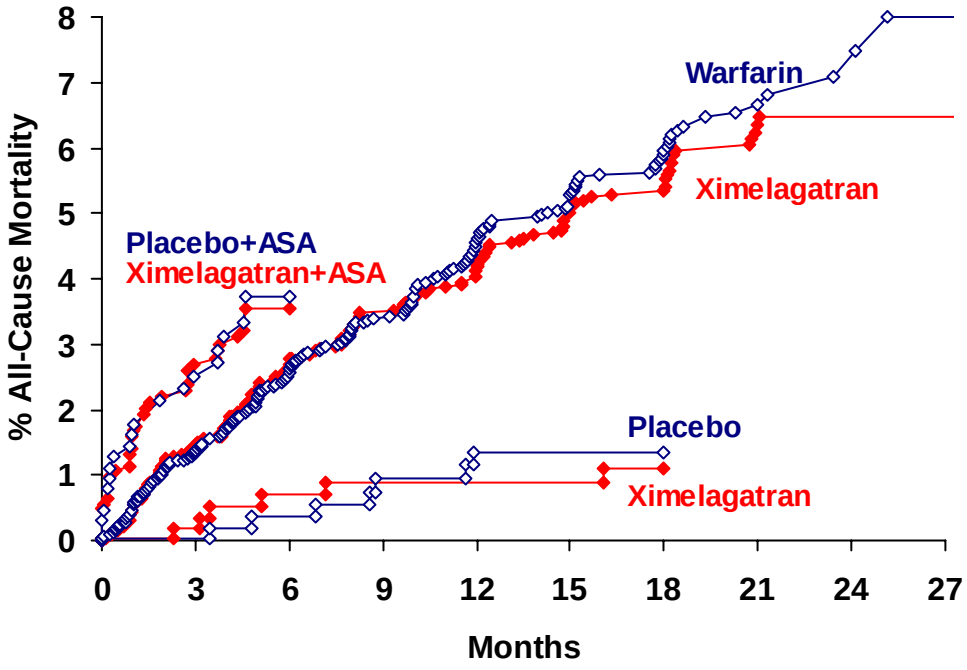
The incidence of adjudicated major bleeding events during the long-term studies was low and similar between the treatment groups. In the Long-term exposure (LTE) population, fewer bleeding AEs were observed with chronic administration of ximelagatran than with the comparator groups (placebo or warfarin). The incidence of bleeding AEs was lower in the ximelagatran group than in the comparators, with an incidence of 27% in the ximelagatran group versus 32% in comparator groups, which includes placebo-treated patients. The ximelagatran group also demonstrated fewer serious bleeding AEs (2.9% compared to 3.6% with comparators). The majority of the serious bleeding events were non-fatal bleeding events. There were 5 fatal bleeding events in the ximelagatran group and 8 fatal events in the comparators group. Across all the long-term studies, most of the bleeding events were minor and did not lead to discontinuation of treatment. Exposure-response analysis suggests that exposure to melagatran does not predict the likelihood of a bleeding event on an individual basis.

No hepatic safety issue was detected in the non-clinical studies, in the Phase I clinical trials, nor in the surgical population during, or following, short-term (<35 days) exposure to subcutaneous (sc) melagatran or oral ximelagatran bid. In all long-term studies (>35 days),

use of ximelagatran was associated with an increased incidence of ALT >3x upper limit of normal (ULN) (7.9%). In addition, there was an increase in discontinuations related to ALT increases (ALT >3x ULN 3.2%, ALT <3x ULN 0.7%), the majority of which were mandated by a protocol-defined liver function testing algorithm and were not associated with symptoms. These ALT elevations occurred consistently between 1 and 6 months after the start of therapy, reversed with or without discontinuation of treatment as based on protocol recommendations, and were for the majority, asymptomatic. There was one case of biopsy documented hepatic necrosis in the entire program. ALT testing will be recommended for all patients receiving ximelagatran for more than 1 month.

The overall mortality in the ITT population was 3.9% in the ximelagatran group and 4.4% in the comparators group. In comparisons of ximelagatran with placebo, the risk of death from any cause was numerically lower in the ximelagatran group (Figure 1). Analysis of data from the long-term Phase III studies, comparing ximelagatran with warfarin, indicated that mortality in the ximelagatran group was numerically lower than with comparator (Figure 1).

Figure 1 **All-cause mortality in the placebo-controlled, long-term studies (THRIVE III, SH-TPV-0003 and ESTEEM, SH-TPC-0001 [+ASA]) and the warfarin-controlled, long-term studies (SPORTIF III, SH-TPA-0003; SPORTIF V, SH-TPA-0005; SPORTIF II/IV, SH-TPA-0002/0004; and THRIVE Treatment, SH-TPV-0002/0005), Intention-to-treat (ITT) population**



Refer to Table 10 for details of the individual studies and indications; excluding SPORTIF II/IV (SH-TPV-0002/0004), which is the ongoing long-term study for the prevention of stroke and SEE in patients with AF.

In summary, short-term and long-term safety of ximelagatran has been evaluated in several large populations at risk for thrombosis. The majority of these patients were elderly and had a large number of co-morbidities. Bleeding was similar to placebo and similar to or less than well-controlled warfarin. The increase in ALT was typically asymptomatic and reversible. Severe hepatic injury was rare and, in the one reported case, was preceded by an ALT rise. ALT testing will be recommended and the RiskMAP will support compliance with ALT testing. Mortality was similar to comparators, including placebo.

Risk Minimization Action Plan (RiskMAP)

AstraZeneca believes that a RiskMAP based on an ALT-testing and management algorithm will minimize the potential risk of severe hepatic injury associated with ximelagatran use and, thereby, maximize its benefit-risk profile. The proposed RiskMAP is an education-based system reinforced by a complementary, interconnected set of materials and programs that emphasize and support compliance with the ALT-testing and management algorithm. The RiskMAP was developed using a systematic approach to identify potential failures in the medication and use process, and create redundant interventions that were then field-tested with 3 key groups (physicians and their hospital or office staff, pharmacists, and patients and their caregivers), and integrated into the marketing program as "Exanta ps" for Exanta patient support.

At launch and beyond, AstraZeneca will actively measure compliance with the ALT-testing algorithm and the occurrence of hepatic events. Tested epidemiologic measures of compliance (using large automated healthcare databases) will be evaluated against target compliance levels to be agreed with the FDA in the context of measures of hepatic outcomes. Rapid and complete assessment of post-marketing hepatic events, including standardized data collection, enhanced follow-up, and epidemiology studies of large automated healthcare databases will be evaluated against known background rates. Both compliance and outcomes will be reviewed with the FDA on a periodic basis.

Benefit-risk profile of ximelagatran

Ximelagatran provides effective anticoagulation as an oral direct thrombin inhibitor for the extended secondary prevention of VTE, the prevention of VTE following TKR surgery, as well as prevention of stroke and systemic embolism in patients with chronic AF. It is important to note that the warfarin INR control in these studies was high and likely exceeded levels in usual practice. There was no difference in bleeding events or the overall mortality between ximelagatran and all other comparators. The safety and efficacy profile for ximelagatran was achieved in these 3 indications without dose adjustment or coagulation monitoring. The use of a fixed dose of oral ximelagatran for the proposed indications is supported by the consistent safety and efficacy demonstrated across the various demographic sub-groups.

Long-term dosing with ximelagatran has been associated with ALT elevations in approximately 8% of patients. The incidence of ALT elevations was not matched by a high

frequency of severe hepatic injury cases, even when ximelagatran was continued. To support the appropriate use of ximelagatran and minimize the possible risk of severe hepatic injury, a comprehensive RiskMAP is being proposed.

In conclusion, half a century of medicine has relied on oral VKAs for anticoagulation. The most widely used VKA, warfarin, has dramatically improved the outcome for patients with thromboembolism, but is also associated with difficulties in use for both patients and physicians. Ximelagatran, an oral direct thrombin inhibitor, has been extensively investigated in a broad range of clinical indications, has consistently shown effectiveness as an anticoagulant and, on balance, has a favorable benefit-risk profile. Ximelagatran is the first new oral anticoagulant in 50 years to provide an alternative to warfarin and offers similar or superior efficacy compared to well-controlled warfarin with a greatly simplified oral treatment regimen.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ACS	Acute coronary syndrome
ACT	Activated clotting time
AE	Adverse event
AF	Nonvalvular atrial fibrillation
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
APTT	Activated partial thromboplastin time
ARR	Absolute risk reduction
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
AUC	Area under the curve
bid	Twice daily
BMI	Body mass index
CBT	Capillary bleeding time
CCK	Cholecystokinin
CDER	Center for Drug Evaluation and Research
CI	Confidence interval
C_{max}	Maximum plasma concentration
CrCL	Creatinine clearance. Calculated as: $\text{CrCL (mL/min)} = \frac{(140\text{-age [years]}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/100 mL)}}$ for males $\text{CrCL (mL/min)} = \frac{0.85 \times (140\text{-age [years]}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/100 mL)}}$ for females
CV	Coefficient of variation
DAE	Discontinuation due to an adverse event
DSMB	Data Safety Monitoring Board
DVT	Deep vein thrombosis
EC	Executive Committee
ESC	Executive Steering Committee
ESTEEM	SH-TPC-0001
EU	European Union

Abbreviation	Definition
EXULT	**EX**anta **U**sed to **L**essen **T**hrombosis
EXULT A	SH-TPO-0010 (290A) The first pivotal trial for the prevention of VTE after TKR surgery
EXULT B	SH-TPO-0012 (290B) The second pivotal trial for the prevention of VTE after TKR surgery
FDA	Food and Drug Administration
FMEA	Failure mode effects analysis
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
HMO	Health Maintenance Organization
INR	International normalized ratio
ITT	Intention-to-treat
iv	Intravenous
IVRS	Interactive voice response system
LFT	Liver function test
LMWH	Low molecular weight heparin
LTE	Long-term exposure
MAA	Marketing Authorization Application
MI	Myocardial infarction
NA	Not applicable
NDA	New Drug Application
NNT	Number needed to treat (calculated as 1/absolute risk ratio x 100)
NOS	Not otherwise specified
NSAID	Non-steroidal anti-inflammatory drug
od	Once daily
OS	Orthopedic surgery
OT	On-treatment
PD	Pharmacodynamic
PE	Pulmonary embolism
PK	Pharmacokinetic
PLATINUM KNEE	SH-TPO-0006 The initial Phase III trial for the prevention of VTE after TKR surgery
PP	Per protocol
PT	Prothrombin time
RiskMAP	Risk Minimization Action Plan

Abbreviation	Definition
RRR	Relative risk reduction
SAE	Serious adverse event
sc	Subcutaneous
SEE	Systemic embolic events, defined as abrupt vascular insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms, eg, atherosclerosis instrumentation. In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities requires arteriographic demonstration of abrupt arterial occlusion.
SPORTIF	**S**troke **P**revention using an **OR**al **T**hrombin **I**nhibitor in atrial **F**ibrillation
SPORTIF II	SH-TPA-0002
SPORTIF III	SH-TPA-0003 The first pivotal trial for the prevention of stroke and SEEs in AF
SPORTIF IV	SH-TPA-0004
SPORTIF V	SH-TPA-0005 The second pivotal trial for the prevention of stroke and SEEs in AF
THR	Total hip replacement
THRIVE	**THR**ombin **I**nhibitor in **V**enous **E**mbolism
THRIVE II&V	SH-TPV-0002 and SH-TPV-0005 (also known as THRIVE Treatment study)
THRIVE III	SH-TPV-0003 The pivotal trial for the secondary prevention of VTE
TIA	Transient ischemic attack
TKR	Total knee replacement
TT	Thrombin time
UFH	Unfractionated heparin
ULN	Upper limit of normal
US	United States
VKA	Vitamin K antagonist (warfarin)
VTE	Venous thromboembolism. VTE is a continuum of disease, comprising distal DVT, proximal DVT, and PE.
VTE-P	Secondary prevention of venous thromboembolism
VTE-T	Treatment of venous thromboembolism

1. INTRODUCTION

AstraZeneca LP (AstraZeneca) submitted an original New Drug Application (NDA) for EXANTA® (ximelagatran) Tablets (ximelagatran also known as H 376/95) to the Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) Division of Gastrointestinal and Coagulation Drug Products in December 2003 (NDA 21-686). The NDA submission proposed that EXANTA, an oral pro-drug of the direct thrombin inhibitor melagatran, be approved for 3 indications (see Section 1.1).

A meeting of the Cardiovascular and Renal Drugs Advisory Committee has been scheduled for 10 September 2004 to review the safety and efficacy information included in the current application. This briefing document supports the Advisory Committee review.

A first Marketing Authorization Application (MAA) was submitted to the European Union (EU) in June 2002 for the single indication of prevention of venous thromboembolism (VTE) in patients undergoing hip or knee replacement surgery. This application is based on a program distinct from the North American program described in this document, and used a different dosing regimen of subcutaneous (sc) melagatran injection followed by oral ximelagatran. Ximelagatran was approved for this use in France on 23 December 2003. France acted as the Reference Member State in the European Mutual Recognition Procedure. The Mutual Recognition Procedure was completed in 15 EU countries in May 2004. Ximelagatran and melagatran were introduced into clinical practice in Germany on 21 June 2004. A second MAA for the long-term indications was submitted to France in December 2003 and is currently under review.

1.1 Proposed indications and dosing

1.1.1 Secondary prevention of VTE

EXANTA is indicated for the long-term secondary prevention of VTE after standard treatment for an episode of acute VTE.

It is recommended that patients who have received standard anticoagulant treatment for deep vein thrombosis (DVT) or pulmonary embolism (PE) be treated with EXANTA 24 mg twice daily (bid).

The pivotal trial conducted for this indication was THRIVE III (SH-TPV-0003) (see Table 10).

1.1.2 Prevention of VTE after knee replacement

EXANTA is indicated for the prevention of VTE in patients undergoing knee replacement surgery.

It is recommended that treatment be 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 of the day after surgery, but no sooner than 12 hours from the time of surgery.

The 2 pivotal trials conducted for this indication were EXULT A (SH-TPO-0010) and EXULT B (SH-TPO-0012) (see Table 10).

1.1.3 Prevention of stroke and systemic embolic events (SEEs) in atrial fibrillation (AF)

EXANTA is indicated for the prevention of stroke and thromboembolic complications associated with AF.

It is recommended that patients with AF be treated with EXANTA 36 mg bid.

The 2 pivotal trials conducted for this indication were SPORTIF III (SH-TPA-0003) and SPORTIF V (SH-TPA-0005) (see Table 10).

1.2 Epidemiology of thromboembolic disease

Thrombosis is a major cause of cardiovascular mortality. More than 60% of the 960000 cardiovascular deaths in the United States (US) in 1999 were caused by thrombotic disease (NHLBI 2002). VTE, a term that includes both DVT and PE, is the third most common cardiovascular disease after ischemic heart disease and stroke (US National Center for Health Statistics 2000), and is a major contributor to morbidity, mortality, and healthcare costs. The incidence in the total population is about 70 to 113 cases/100000 persons/year and increases with age, to as high as about 300 to 500 cases/100000 persons/year (age group 70 to 79 years) (White 2003). Approximately one-third of all patients with VTE present with symptomatic PE. In the US, approximately 400000 cases of DVT and approximately 160000 cases of PE are reported annually (InpatientView DVT 2002, InpatientView PE 2002, White 2003). VTE is a continuum of disease, comprising distal DVT, proximal DVT, and PE, albeit with an increasing level of medical risk. The rate of in-hospital death and death during 6 months follow-up period is 10.5% among patients with DVT and 14.7% among those with PE (Murin et al 2002). About 10% of PEs are rapidly fatal, and an additional 5% cause death later, despite diagnosis and treatment (Kearon 2003). While DVT and PE occur at different locations and show some differences in natural history, medical treatment is the same for both. Of patients with symptomatic DVT and symptomatic PE, approximately 50% of all symptomatic DVT cases also have concurrent PE and approximately 70% of all patients with symptomatic PE have evidence of co-existing lower extremity DVT (Meignan et al 2000, Murin et al 2002). In approximately 40% of VTE cases, DVT and PE are confirmed concomitantly. These facts have led medical experts to conclude that PE and DVT are different manifestations of a broad yet overlapping spectrum of disease called VTE.

The population at greatest risk for VTE is those undergoing major lower extremity orthopedic surgery and those who experience major trauma or spinal cord injury. The risk for DVT after total knee replacement (TKR) surgery is greatest within the first 2 weeks after surgery. Without treatment, the prevalence of total DVT at 7 to 14 days after TKR is between 40% and 84%, with proximal DVT rates between 9% and 20% (Geerts et al 2001).

Atrial fibrillation is the most common sustained cardiac arrhythmia, affecting 4% of those over 60 years of age and 10% of those aged over 80 years (Singer 1998). In patients with AF, altered atrial blood flow may lead to local thrombus formation, and embolization of thrombi from the left atrial appendage can cause stroke or SEEs. Atrial fibrillation is one of the strongest independent risk factors for stroke, increasing stroke incidence 5-fold to rates of approximately 5% per year for initial stroke and 12% for recurrent stroke (Wolf 1998). Ischemic stroke associated with AF is nearly twice as likely to be fatal as non-AF stroke, while recurrence is more frequent and 90% of surviving patients with stroke have some permanent functional deficit (Lin et al 1996). Factors increasing the risk of stroke in AF patients include: age >75 years, history of hypertension, previous stroke, transient ischemic attack (TIA) or SEE, or poor left ventricular function (Albers et al 2001).

1.3 Current anticoagulant treatment

Anticoagulants, agents that are targeted to inhibit pro-coagulant proteins in the coagulation cascade, are efficacious in preventing and treating thrombotic disease. Anticoagulation therapy has significantly reduced the morbidity and mortality for diseases associated with thrombosis. The most frequently used anticoagulants are unfractionated heparin (UFH), low molecular weight heparins (LMWHs), and vitamin K antagonists (VKAs, most commonly warfarin). More recently, injectable direct thrombin inhibitors (lepirudin, bivalirudin, argatroban), and an indirect Factor Xa inhibitor (fondaparinux, a synthetic pentasaccharide) have been introduced for limited clinical indications. Of all the anticoagulants, only warfarin can be administered orally and is regarded as the mainstay of routine chronic anticoagulation in patients at risk of VTE, stroke, or recurrent myocardial infarction (MI). Current recommendations for the use of anticoagulants in the treatment or prevention of VTE, and to prevent stroke in patients with AF, are summarized in Table 1.

Table 1 Published recommendations for anticoagulant treatment in the indications for which a claim is sought

Guideline	Indication for treatment	Recommended treatment
Antithrombotic Therapy for Venous Thromboembolic Disease (Hyers et al 2001)	Secondary prevention of DVT or PE	Warfarin (target INR 2.5; range, 2.0 to 3.0) Treatment for at least 12 months for recurrent idiopathic VTE or continuing risk factors
Prevention of Venous Thromboembolism (Geerts et al 2001)	Patients undergoing TKR surgery	Warfarin (target INR 2.5; range, 2.0 to 3.0) or LMWH Treatment for at least 7 to 10 days after surgery
Antithrombotic Therapy in Atrial Fibrillation[a] (Albers et al 2001, Fuster et al 2001)	Patients with nonvalvular AF and any high-risk factor, or >1 moderate-risk factor	Warfarin (target INR 2.5; range, 2.0 to 3.0) Long-term treatment

[a] Patients with nonvalvular AF and with 1 moderate-risk factor may receive ASA, 325 mg/d, or warfarin (target INR 2.5; range, 2.0 to 3.0) long-term treatment. Patients with nonvalvular AF and no high or moderate risk factors may receive ASA, 325-mg/d long-term treatment. Patients with rheumatic heart disease, prosthetic heart valves, prior thromboembolism, or persistent atrial thrombus may receive warfarin (INR range, 2.5 to 3.5, or higher) long-term treatment.

TKR Total knee replacement; INR International normalized ratio; LMWH Low molecular weight heparin; DVT Deep vein thrombosis; PE Pulmonary embolism; AF atrial fibrillation; ASA Acetylsalicylic acid; d Day; VTE venous thromboembolism.

1.4 Unmet medical need

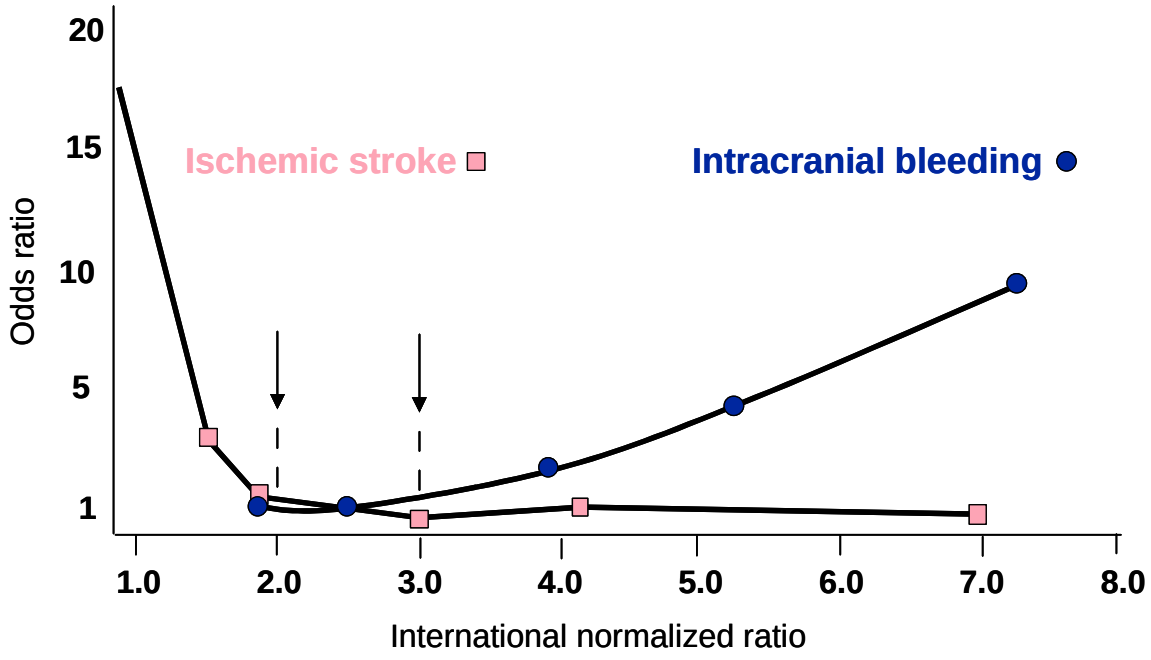
Warfarin is an efficacious anticoagulant, reducing the risk of stroke in AF patients by 62% and the recurrence of DVT and PE by 64% compared to placebo. However, achieving therapeutic efficacy and minimizing hemorrhagic risk requires maximizing the time spent in an optimal but narrow therapeutic range as measured by the international normalized ratio (INR). In addition, many factors influence the safety and efficacy of warfarin. These include: physiologic factors that affect the synthetic or metabolic fate of the vitamin K-dependent coagulation proteins (including genetic polymorphisms); and pharmacological factors, such as variable dietary intake of vitamin K, changes in gastrointestinal (GI) flora that affect availability of vitamin K, alcohol and drug interactions, and genetic variability in warfarin metabolism.

Other limitations of warfarin include its slow onset of effect (days), which requires bridging anticoagulation via the administration of a parenteral anticoagulant if rapid therapeutic anticoagulation is warranted or until therapeutic anticoagulation with warfarin can be achieved. A slow offset of action also requires management with vitamin K or fresh frozen plasma for excessive bleeding or hemorrhagic emergency. Finally, there is also the rare risk of the severe complication of warfarin-induced skin necrosis.

Due to the unpredictable anticoagulant response to warfarin, coagulation monitoring for dose adjustment must be performed daily until the therapeutic range has been achieved and then weekly or monthly depending on the stability of the patient's INR results (Ansell et al 2001). However, it is recommended that INR testing be done at least every 4 weeks after the INR remains stable for as long as the patient is taking warfarin (Ansell et al 2001). Despite careful monitoring and dose adjustment, patients in routine medical care are in the expected target INR range of 2.0 to 3.0 about 35% to 60% of the time (Samsa et al 2000, Ansell et al 2001). When managed in dedicated anticoagulation centers, the INR of patients remains within the therapeutic range, at best, from 61% to 68% of the time (Samsa et al 2000). Even in the highly structured setting of randomized clinical studies, the time in therapeutic range can vary from 48% to 83% (Ansell et al 2001).

Time out of therapeutic range has been associated with thromboembolism (subtherapeutic) and bleeding (supratherapeutic) (Hylek et al 2003) (Figure 2). Patients who do not achieve an INR of ≥2.0 are at increased risk of a VTE or stroke. Conversely, there is a risk of bleeding as the INR increases.

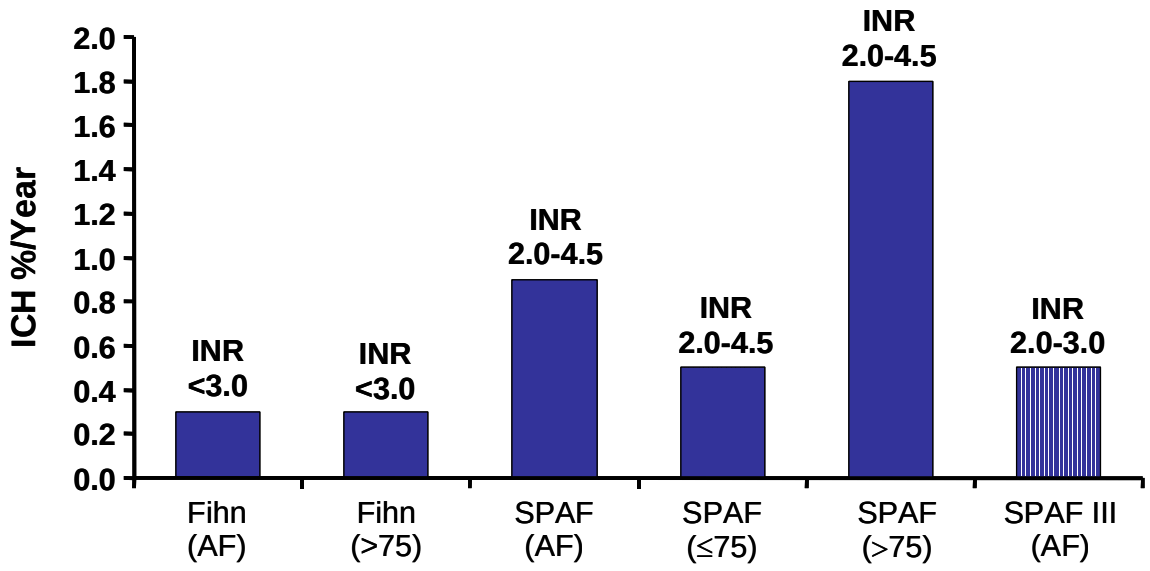
Figure 2 **INR and the risk of stroke or bleeding: the narrow therapeutic range of warfarin**



Singer & Hylek 1995, Hylek et al 1996.

In a large study using a coagulation clinic database, bleeding-related mortality increased with increasing INR (at INR 3.5 to 3.9, mortality from bleeding was 13.2/1000 patient years) (Odén and Fahlén 2002). Overall, the rate of major bleeding events for patients on warfarin is reported to be between 1% and 4% per year (Agnelli 2001, Kearon et al 1999, Schulman et al 1995). Intracranial hemorrhage rates, during long-term anticoagulation with warfarin, have also been reported to increase as the INR range increases (INR 2.0 to 4.5) (Levine et al 2001). This risk is increased further as the population ages (Figure 3).

Figure 3 **Intracranial hemorrhage during long-term anticoagulation with warfarin**



Adapted from Levine et al 2001 (Fihn et al 1993, Albers 1994, SPAF 1994 and 1998, Ezkowitz and Levine 1999).
Age group cut off: less than or equal to 75 years and greater than 75years.
ICH Intracranial hemorrhage, AF Atrial fibrillation, INR International normalized ratio, SPAF Stroke Prevention in Atrial Fibrillation Investigators.

Despite conclusive data demonstrating benefit from the use of anticoagulants, practice pattern evaluations consistently identify under-use of warfarin in patient populations that would benefit, and the impact is significant. Anticoagulation therapy can prevent more than 40000 strokes per year in the US (Agency for HealthCare Policy and Research 1995), yet 2 contemporary studies showed only 35% (Samsa et al 2000) and 40% (Stafford and Singer 1998) of eligible patients with no contraindications to warfarin received the recommended therapy. In a more recent study of Medicare patients published in 2003, only 57% of AF patients were discharged on anticoagulation therapy (Jencks et al 2003). Other studies have demonstrated similar results (Bungard et al 2000, Beyth et al 1996). Accounting for this, barriers inhibiting the prescribing and use of warfarin have been identified. Barriers pertaining to the patient include age, perceived embolic risk, and perceived risk for

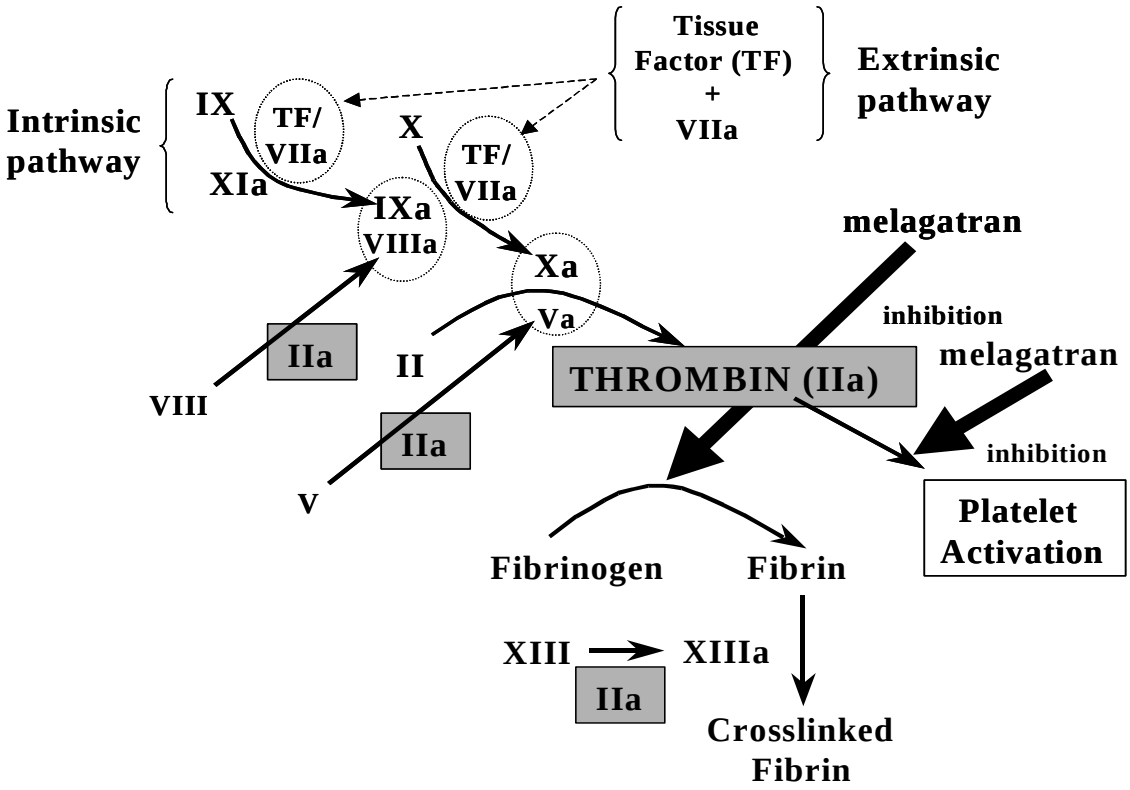
hemorrhage. The primary barrier pertaining to physicians prescribing warfarin is the weighting of benefit versus risk in each individual patient. Finally, the barriers pertaining to the Health Care System are the inconvenience of monitoring therapy and the need for further management (Bungard et al 2000).

Warfarin is an effective anticoagulant, but its challenges and management issues are significant: (1) warfarin administration requires complex management that is a challenge for the patient, healthcare provider, and healthcare system; (2) as a result, a large number of patients who would benefit from treatment with an anticoagulant long-term are not treated; and (3) treated patients have international normalized ratios (INRs) within the recommended target range only 35% to 68% of the time (Samsa et al 2000, Ansell et al 2001). The limitations of warfarin have a significant impact on patient acceptance of lifestyle change and compliance with complex warfarin regimens.

1.5 The rationale for the development of ximelagatran

The burden of thrombosis and the limitations of current anticoagulant treatments, indicate the need for an alternative oral anticoagulant. The development of an anticoagulant with: predictable, consistent, stable, and reproducible pharmacokinetics and pharmacodynamics; a low potential for interactions; and without a narrow therapeutic index, would fulfill this need. The development program for ximelagatran has been designed to offer an alternative oral anticoagulant to warfarin for major indications. Ximelagatran is the first new oral anticoagulant since warfarin was introduced into clinical medicine in the US in 1954. Ximelagatran is the prodrug of melagatran. Melagatran is a potent, reversible, competitive and direct inhibitor of thrombin. Melagatran inhibits the final key step in the coagulation cascade, the conversion of fibrinogen to fibrin, and also prevents thrombin from activating platelets, thus, inhibiting platelet aggregation (Figure 4). Unlike warfarin, melagatran is not dependent on vitamin K metabolism and, unlike heparins, melagatran does not require the co-factor antithrombin for antithrombotic activity.

Figure 4 The coagulation cascade



Ximelagatran has been developed as a new oral anticoagulant for several indications, of which the following 3 were proposed in NDA 21-686 and are discussed in this briefing document:

- An oral 24-mg bid fixed dose for the long-term secondary prevention of VTE after standard treatment for an episode of acute VTE
- An oral 36-mg bid fixed dose initiated post-operatively for the prevention of VTE in patients undergoing TKR surgery
- An oral 36-mg bid fixed dose for the prevention of stroke and systemic thromboembolic complications associated with AF.

Extensive clinical development of ximelagatran has been undertaken in these patient populations; more than 17000 subjects and patients have received ximelagatran during this development program, with just over 3500 patients being dosed for over 1 year. The development of ximelagatran was undertaken to provide an effective, safe therapy without the

need for extensive management of the drug during the course of treatment, ie, without coagulation monitoring or the need for dose adjustment.

2. OVERVIEW OF PRECLINICAL PHARMACOLOGY

The preclinical pharmacology program characterized the pharmacokinetics and pharmacodynamics of ximelagatran and its dominant active form, the direct thrombin inhibitor melagatran, in animal models.

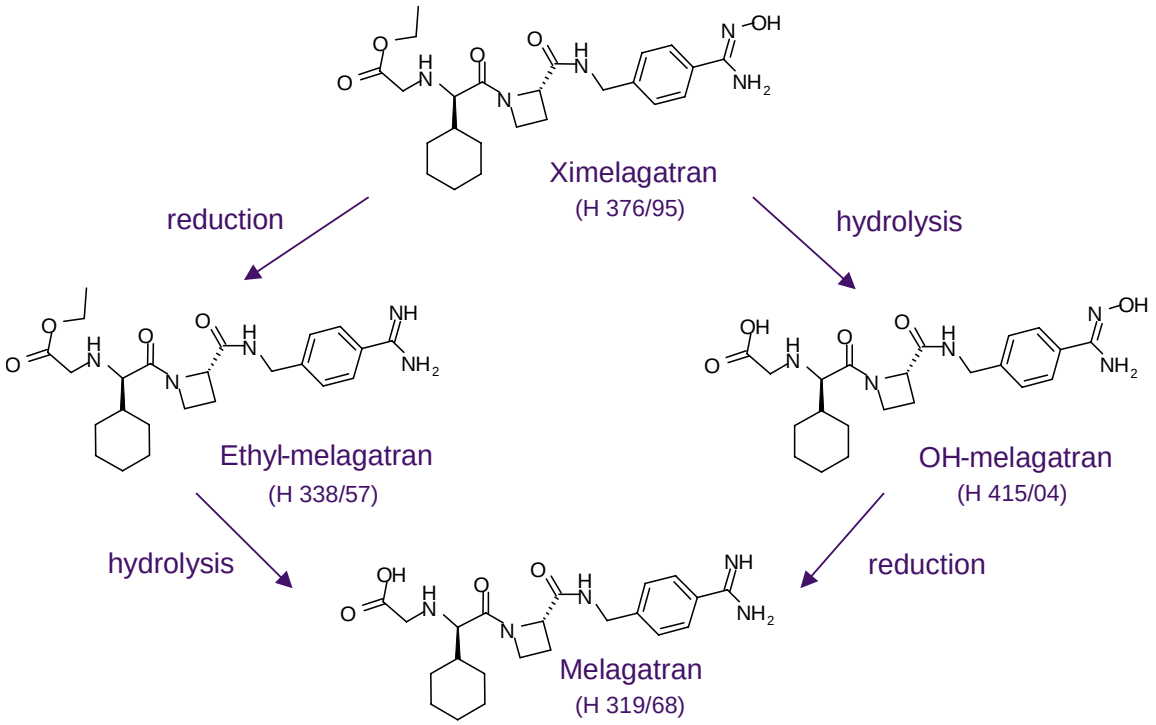
2.1 Introduction

Ximelagatran (H 376/95) is an orally available prodrug of melagatran. Melagatran (H 319/68) is a potent, small molecular direct inhibitor of the serine protease α-thrombin with competitive and reversible binding. Melagatran itself displays low and variable oral bioavailability; hence, ximelagatran was developed for oral delivery of melagatran.

2.1.1 Structure and physiochemical properties

After oral administration, ximelagatran is bioconverted to melagatran as the dominant active form. The conversion proceeds through 2 short-lived intermediates via hydrolysis of the ethyl ester group and reduction of the hydroxyamidine moiety. Hydrolysis of the esther occurs widely throughout the body via non-specific esterases resident in the tissues. The enzyme responsible for catalyzing the reduction is present in the liver, intestines, kidneys, and lungs. The structures of ximelagatran, melagatran, and the intermediates are shown in Figure 5.

Figure 5 Chemical structure of ximelagatran, melagatran and the intermediary metabolites H 338/57 and H 415/04



2.1.2 Mechanism of action

Melagatran is a potent inhibitor of α-thrombin with a Ki (enzyme inhibition constant) of 2 nmol/L. The prodrug ximelagatran and the OH-intermediate (H 415/04) are much less potent than melagatran (Ki: 370 and 610 nmol/L, respectively). The ethyl- intermediate (H 338/57) is equivalent to melagatran in potency, indicating that the free amidine group is important for inhibition of human α-thrombin. However, it only accounts for 10% of activity and has a brief half-life of approximately 30 minutes. The concentration of melagatran that reduces thrombin generation by 50% *in vitro* was shown to be 0.44 μmol/L. In addition, melagatran has been shown to inhibit clot-bound thrombin with an IC_{50} of 3.8 nmol/L.

Thrombin belongs to the family of serine proteases, which have a reactive serine residue at their active site and cleave their natural substrates at a lysine or arginine residue. Melagatran was shown not to inhibit other serine proteases (Table 2 and Table 3), with the exception of trypsin, for which the Ki was found to be approximately 4 nmol/L.

Table 2 Selectivity of melagatran versus some human serine proteases

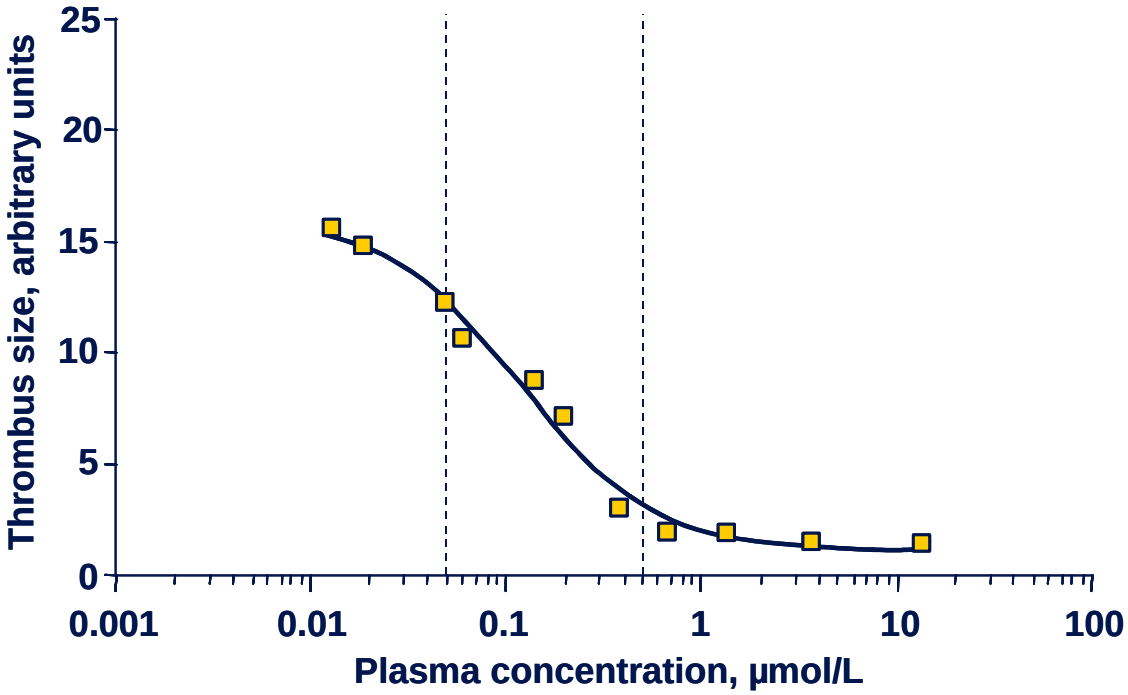
Enzyme	Potency (Ki melagatran at 37°C) (μmol/L)	Selectivity (Ki melagatran ratio vs thrombin)
α-thrombin	0.0020 (n=5)	1
Bovine trypsin	0.0036 (n=2)	1.8
plasmin	0.69 (n=2)	345
tc-tPA	0.88 (n=2)	440
Activated protein C	1.05 (n=3)	502
Plasma kallikrein	0.60 (n=2)	300
Urinary kallikrein	>600 (n=2)	>300000
Urokinase	6.30 (n=2)	3150
TF.FVIIa	4.26 (n=2)	2130
FXa	2.75 (n=2)	1375
FXIa	10.2 (n=2)	5100
FXIIa	6.46 (n=2)	3230

Table 3 Percent inhibition of chymotrypsin and elastase by melagatran, ximelagatran, H 338/57, and H 415/04

	% inhibition at 10 μM compound	
Compound	**Bovine chymotrypsin**	**Porcine elastase**
Melagatran	0.9	0.9
Ximelagatran	1.9	0.8
H 338/57	1.6	2.2
H 415/04	1.1	3.9

A significant antithrombotic effect of ximelagatran or melagatran in rat models of arterial (platelet rich) and venous (fibrin rich) thrombosis was found at melagatran plasma concentrations in the range of 0.05 to 0.5 μmol/L (Figure 6). The effect on tail bleeding time in this plasma concentration range was modest and was not additionally affected by acetylsalicylic acid (ASA).

Figure 6 Thrombus size in rats at various melagatran plasma concentrations



2.2 Hepatic effects of ximelagatran

The primary observations in preclinical toxicity studies with ximelagatran and melagatran in rats, dogs, minipigs, and rabbits are related to the pharmacological activity of the drug, since dose-limiting effects are related to bleeding in the animals. The studies have not revealed any significant treatment-related hepatic effects, based on macroscopic, microscopic and clinical chemistry examinations. In one study in rats, a few animals were preterminally sacrificed moribund or found dead due to hemorrhage resulting from high doses of ximelagatran. In these animals, post-mortem examination revealed centrilobular hepatic necrosis secondary to the hemorrhage. Such a finding is not uncommon in animals with hemorrhage as the cause of death.

2.3 Pancreatic effects of ximelagatran

A treatment-related increased incidence of multifocal acinar cell hyperplasia and multifocal acinar cell adenoma was seen in the pancreas of male and female rats, and a few cases of acinar cell carcinoma was seen in the pancreas of male rats. Similar effects have been seen in rats chronically given raw soy flour, which contains trypsin inhibitors. These pancreatic effects in the rat are considered the result of trypsin inhibition producing a sustained increase in plasma concentrations of cholecystokinin (CCK), resulting in chronic trophic pancreatic overstimulation through CCK receptors. Support for involvement of this mechanism in the

pancreatic observations in the carcinogenicity study comes from additional studies in rats, in which CCK levels were elevated for up to 1 year following chronic oral dosing with ximelagatran, and were associated with increased measures of proliferation in the pancreas (pancreatic protein, DNA, weight, and 5-bromodeoxyuridine labeling).

Control of pancreatic secretions in humans differs from that in the rat, as secretions are not dependent on direct signaling to the pancreas via CCK. Increased secretion of CCK in humans requires inhibition of other GI proteases, such as chymotrypsin or elastase, in addition to trypsin. Selective inhibition of trypsin alone is not sufficient to raise CCK levels in humans. Furthermore, the human pancreas does not express significant levels of CCKa receptors. Control of pancreatic secretions is instead mainly through cholinergic innervation. Lack of a trophic effect of ximelagatran on the pancreas is supported by: (1) *in vitro* studies showing that ximelagatran does not inhibit chymotrypsin or elastase to any appreciable extent; (2) studies in humans given study medication with a standard meal, in which plasma CCK levels were not increased following 3 months of dosing; (3) lack of increase in pancreas volume in humans following 12 months of study medication; and (4) analysis of pancreatic adverse events (AEs) in the Long-term exposure (LTE) Pool, showing no imbalance between ximelagatran and comparators.

No neoplastic changes were seen in the carcinogenicity study in mice with ximelagatran.

This information leads to the conclusion that the pancreatic effects seen in the rat carcinogenicity study are unique to the rat and do not represent an increased risk of pancreatic effects in humans.

2.4 Genotoxicity studies with ximelagatran

Ximelagatran tested weakly positive at high concentrations in the mouse lymphoma tyrosine kinase locus assay. It has tested negative in a battery of other genotoxicity assays, including the Ames test, the unscheduled DNA synthesis test in rat liver, and in the *in vivo* mouse micronucleus test. Melagatran and its intermediates, H 415/04 and H 338/57, tested negative in the mouse lymphoma assay, and melagatran was also negative in the Ames test, a cytogenetic test in human lymphocytes and in the *in vivo* mouse micronucleus test.

Based on these observations, it is concluded that ximelagatran and melagatran do not represent a risk of genotoxicity in humans.

2.5 Summary of ximelagatran preclinical properties

The findings from the preclinical investigations are consistent with the activity of melagatran as a potent, competitive and reversible, small molecular direct inhibitor of the serine protease α-thrombin, and that ximelagatran is an effective prodrug for systemic delivery of melagatran. Following oral dosing, ximelagatran is rapidly converted to melagatran via 2 short-lived intermediates, one the result of hydrolysis of the ester function and the other the product of reduction of the hydroxyamidine moiety. Oral ximelagatran and parenteral melagatran show

efficacy in models of venous (fibrin-rich) and arterial (platelet-rich) thrombus formation at melagatran plasma concentrations in the range of 0.05 to 0.5 μmol/L.

The primary observations in preclinical toxicity studies with ximelagatran and melagatran in rats, dogs, minipigs, and rabbits are related to bleeding, the expected pharmacological consequences of the drug action. No significant hepatic effects have been observed, and the pancreatic effects seen in carcinogenicity studies in the rat are considered unique to that species. Based on the weight of evidence in genotoxicity studies, ximelagatran is not thought to represent a risk for genotoxicity to humans.

3. CLINICAL PHARMACOLOGY

Oral administration of ximelagatran results in a rapid onset of action; with peak plasma melagatran concentrations occurring 2 to 3 hours post dosing. Anticoagulant plasma levels of ximelagatran are achieved within 1 hour of dosing and persist for 12 to 24 hours. The 4- to 5-hour elimination half-life of melagatran and stable and reproducible plasma concentrations of melagatran enables long-term, twice-daily, fixed dosing of ximelagatran without coagulation monitoring. Melagatran does not interact with food or alcohol and has a low potential for drug interactions. These properties, a rapid onset and offset of action, stable and reproducible systemic exposure with repeated dosing, and low potential for drug interactions, are important features of ximelagatran.

3.1 Introduction

The ximelagatran clinical pharmacology program included 60 individual Phase I studies as well as the collection of pharmacokinetic (PK) and pharmacodynamic (PD) data from many Phase II and Phase III studies. The following key topics were investigated within the clinical pharmacology program:

- The pharmacokinetics of melagatran after oral administration of ximelagatran to healthy volunteers
- The effect of age, gender, body weight, obesity, race, hepatic function, and renal function on melagatran pharmacokinetics
- The potential for pharmacokinetic interaction with intake of food and alcohol as well as with concomitant administration of other drugs
- The pharmacokinetics of melagatran in the target patient populations
- The PD effects of ximelagatran, including effects on coagulation time assays, alone and in combination with other drugs
- Exposure-response relationships for efficacy and safety parameters in the studied patient populations.

3.2 Human pharmacokinetics

Following oral administration, ximelagatran is rapidly absorbed and bioconverted to melagatran, with maximum melagatran plasma concentrations occurring approximately 2 to 3 hours post-dosing. As demonstrated in animal studies (Section 2.1.1), clinical studies showed bioconversion involves formation of 2 short-lived intermediates, ethyl melagatran (an active thrombin inhibitor) and hydroxy melagatran (an inactive thrombin inhibitor). Non-specific tissue esterases (not plasma esterases) are responsible for the hydrolysis of ximelagatran in humans. Cytochrome P450 (CYP) enzymes appear to be of no importance for the reduction.

Bioconversion of ximelagatran to melagatran was demonstrated in all subjects who received ximelagatran in the Phase I studies. There was no evidence of any altered bioconversion of ximelagatran to melagatran in patients with mild or moderate hepatic impairment, although there is no experience in those with severe hepatic impairment.

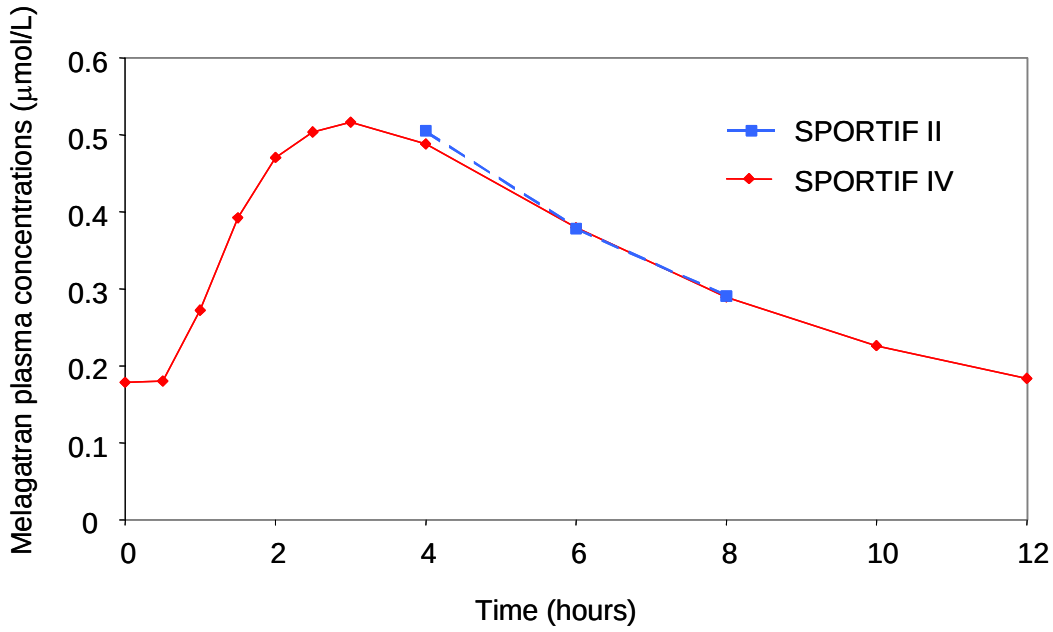
The volume of distribution of melagatran following parenteral administration of melagatran is approximately 0.2 to 0.3 L/kg, indicating limited extravascular distribution. The blood-plasma ratio for melagatran was 0.6, which shows that melagatran has low affinity for, and a low penetration into, red blood cells. Plasma protein binding of melagatran is low (<15%) and, therefore, there is very limited potential for displacement interactions with other drugs.

Plasma concentrations of melagatran (both AUC and C_{max}) have been shown to increase linearly in approximate proportion to dose, following 5 to 98 mg ximelagatran (up to 1.0 µmol/L melagatran). The bioavailability of melagatran following oral ximelagatran is approximately 20% and the variability (coefficient of variation; CV%) is about 20%. Following repeated oral dosing of ximelagatran in healthy volunteers, the CV% in melagatran AUC was about 15%. The variability within the volunteers over time was approximately 8%. There was no unexpected accumulation of melagatran plasma concentrations with repeated dosing. The lack of time and dose dependency in the pharmacokinetics indicated that melagatran plasma concentrations were stable and reproducible and enabled the initiation of Phase II clinical trials in patients with a fixed dose of ximelagatran and without routine coagulation monitoring.

In patients, steady-state plasma concentrations of melagatran are achieved within 24 hours, reflecting the 4- to 5-hour half-life. The variability of melagatran AUC in AF patients (CV = ~50%) is higher than that in healthy volunteers, largely due to a wider range of renal function among patients included in the Phase II/III studies. Thus, using a fixed oral dose of ximelagatran, the individual population-derived estimates of melagatran AUC indicate that melagatran exposure varied across the AF patient population by approximately 3- to 4-fold (5^{th} percentile 2.1 µmol h/L; 95^{th} percentile 6.2 µmol h/L). The pharmacokinetic model determined the variability within individual AF patients to be approximately 25% (CV%). This low degree of intra-patient variability indicates that melagatran plasma concentrations are stable and reproducible over time within an individual patient. In Figure 7, plasma melagatran concentrations in 153 AF patients are shown after 3 months of oral ximelagatran

(SPORTIF II, SH-TPA-0002) and again in 47 of the same patients (plus 2 additional patients, n=49 total) more than 1 year later (SPORTIF IV, SH-TPA-0004). These data indicate that the mean melagatran plasma concentrations are stable over time.

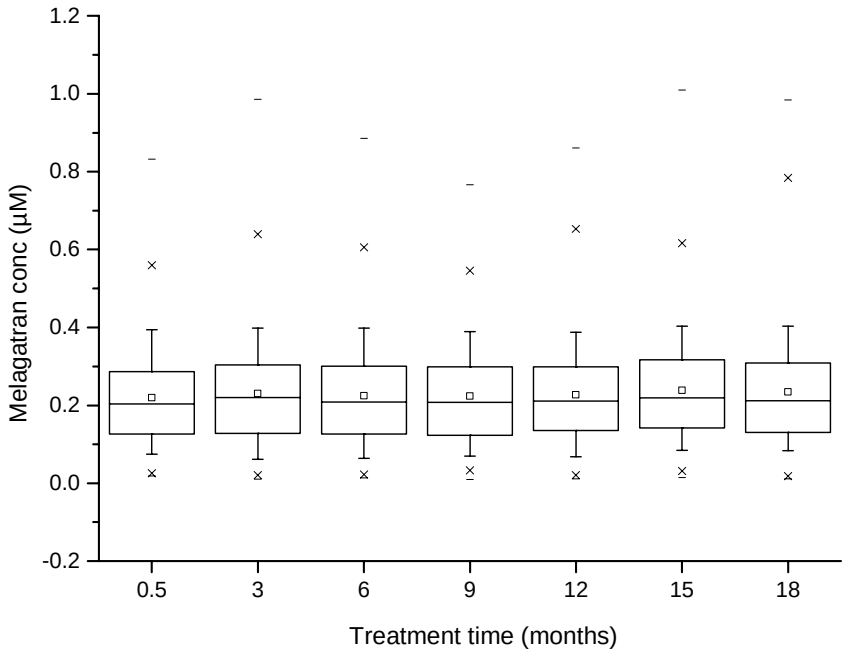
Figure 7 **Mean plasma concentration of melagatran (μmol/L) versus time in atrial fibrillation patients receiving 36 mg ximelagatran bid**



The observations from SPORTIF II (SH-TPA-0002) have been dose normalized to 36 mg ximelagatran. Approximately 13 to 16 months between sampling times in each patient. n=153 in SPORTIF II (SH-TPA-0002); n=49 in SPORTIF IV (SH-TPA-0004).

Stable and reproducible mean plasma concentrations of melagatran over an 18-month period were also observed in a cohort of patients receiving 24 mg oral ximelagatran for the secondary prevention of VTE in THRIVE III (SH-TPV-0003) (Figure 8).

Figure 8 **Plasma concentration of melagatran (μmol/L) versus time on treatment with ximelagatran in THRIVE III (SH-TPV-0003) patients receiving 24 mg ximelagatran bid**



Ximelagatran 24 mg bid given as long-term secondary prevention for up to 18 months after a 6-month standard of care anticoagulation treatment for VTE. Descriptive statistics of individual observations of mean melagatran plasma concentrations of 12-hour dosing interval are shown. The horizontal lines show the 1st, 2nd, and 3rd quartiles and the whiskers show the 5th and 95th percentiles (n=596). The symbols represent the mean (□), 1st and 99th percentiles (x), and minimum/maximum values (-).

After administration to 5 healthy male volunteers, a 50-mg oral dose of C^{14}-labeled ximelagatran was essentially completely recovered (96.3%) over a 7-day period. The major route of excretion of the total dose was via the feces (accounting for a mean of 71.1% of the dose). Most of the radioactivity in urine (25.2% of the dose), which was rapidly excreted and mainly recovered within 24 hours, was identified as melagatran (17% of the dose) while ximelagatran, H 338/57, and H 415/04 each accounted for only 1% to 2% of the dose. Unknown metabolites were identified in urine (<2%) and feces (<15%) that were more polar than ximelagatran and melagatran. The polar metabolites in feces are probably formed in the GI tract and are unlikely to be absorbed and have a systemic effect. A study in 12 healthy male volunteers using intravenous (iv) tritium-labeled melagatran indicated that of the 88% of melagatran recovered, 83% was found in urine, with the remaining 5% found in feces and presumably eliminated in bile. Although a significant amount of radioactivity is excreted in

the bile of rats and dogs following administration of radiolabeled ximelagatran, the degree of biliary excretion of ximelagatran has not been determined in humans. No metabolites of melagatran have been identified.

Renal clearance (7.16 L/h) accounts for ~80% of the total melagatran clearance (8.69 L/h) following iv dosing. Thus, melagatran is primarily excreted from the plasma via the kidneys. As the rate of renal clearance of melagatran is similar to glomerular filtration rate, this suggests that its elimination is via filtration with no net secretion or reabsorption, as might be expected for a polar compound with low plasma protein binding. The clearance of melagatran therefore correlates well with calculated creatinine clearance (CrCL).

Melagatran is excreted in trace amounts (approximately 0.0009% of ximelagatran dose) in human breast milk when oral ximelagatran is administered to lactating women.

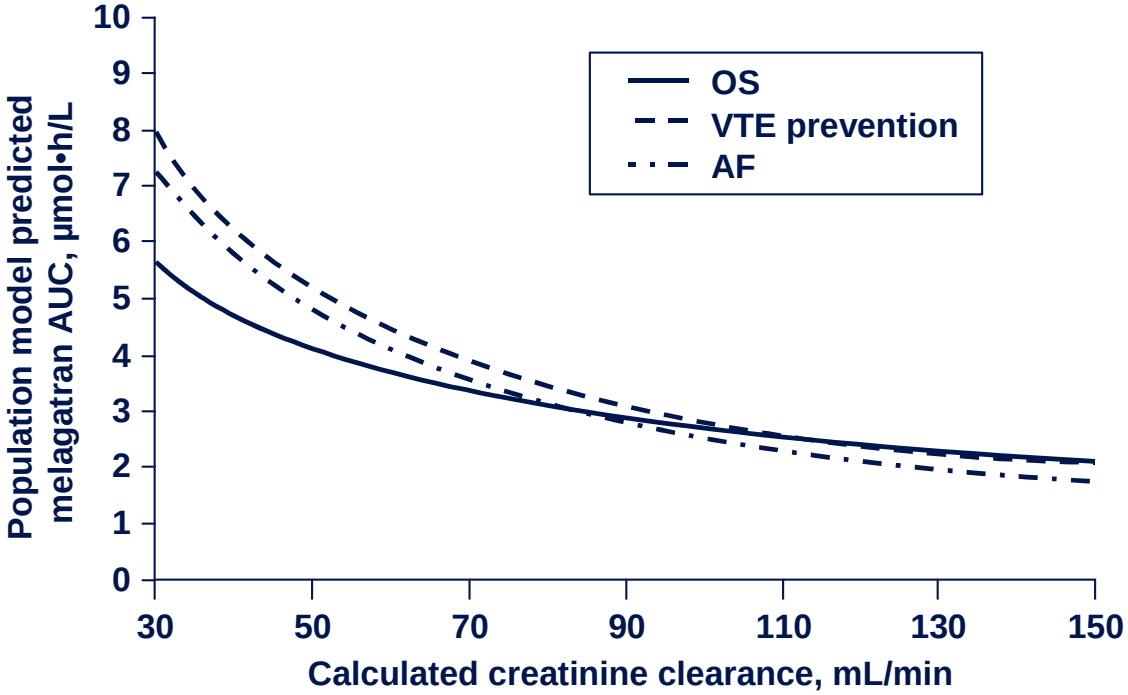
3.3 Special populations

A series of investigations have identified renal function as the most influential demographic factor on ximelagatran pharmacokinetics. There is no important independent influence of other intrinsic factors such as age, gender, body weight, obesity, race, or mild to moderate hepatic impairment on the pharmacokinetics of ximelagatran.

Renal function (assessed as calculated CrCL) has been identified as the most influential demographic factor for explaining melagatran exposure. Population pharmacokinetic analyses show that melagatran AUC values in patients with mild (CrCL 50 to 80 mL/min) and moderate (CrCL 30 to <50 mL/min) renal impairment are about 1.5 and 2.5 times higher, respectively, than in patients with normal renal function (CrCL >80 mL/min). The relationship between melagatran plasma concentrations and calculated CrCL is consistent across the 3 primary patient populations shown in Figure 9. The Phase II/III studies with oral ximelagatran include patients across a broad range of melagatran exposures and the influence of renal function on clinical outcome has been evaluated in these Phase II/III trials.

In subjects with severe renal impairment (CrCL <30 mL/min), the mean AUC and mean half-life of melagatran are increased approximately 5- and 3-fold, respectively, compared to subjects with normal renal function. Patients with severe renal impairment were therefore excluded from the Phase II and Phase III clinical studies. Melagatran is effectively cleared by the kidneys, and if needed, can be dialyzed. These results suggest that dialysis may be used to rapidly eliminate melagatran for reversal of anticoagulation in the event of overdose, unexpected accumulation because of severe renal dysfunction, or serious bleeding.

Figure 9 **Population-model predicted AUC of melagatran versus calculated creatinine clearance**



Population-model predicted melagatran AUC is shown for an oral dose of 36 mg ximelagatran for all patient populations irrespective of the actual doses given in the studies.
OS (Orthopedic surgery) patients (METHRO II, SH-TPO-0002); VTE prevention (THRIVE III, SH-TPV-0003); AF Atrial fibrillation patients (SPORTIF II, SH TPA-0002 and SPORTIF IV, SH-TPA-0004).
VTE Venous thromboembolism.

To study the influence of age on the pharmacokinetics of ximelagatran, a 20-mg dose of oral ximelagatran was administered to young (20 to 27 years old) and elderly (56 to 70 years old) volunteers. The oral bioavailability of melagatran was approximately the same for young and elderly subjects, suggesting no clinically relevant influence of age on the absorption and bioconversion of ximelagatran, while the AUC of melagatran was approximately 1.6-fold higher in the elderly compared to the young. The higher melagatran AUC in elderly subjects was mainly explained by the age-related decrease of renal function (calculated CrCL) leading to a reduced clearance of melagatran in the elderly volunteers.

Investigations into the influence of gender and body weight on the pharmacokinetics of ximelagatran also revealed that any detectable differences in females versus males or in low versus high body weight individuals was largely explained by body-weight related differences in renal function (as assessed by calculated creatinine clearance).

An investigation into the influence of obesity in 12 obese (body mass index [BMI] 32 to 39 kg/m^2) and 12 non-obese (BMI 21 to 26 kg/m^2) volunteers receiving a single 24-mg dose of ximelagatran revealed no influence of obesity on the AUC or C_{max} of melagatran.

The influence of race on the pharmacokinetics of ximelagatran was investigated in healthy male Asian, Black, and Caucasian volunteers (n=12/group). The bioconversion of ximelagatran to melagatran was rapid, with maximum plasma concentrations of melagatran observed approximately 1.6 hours after dosing, and melagatran was eliminated from plasma with half-lives in the range 2.8 to 3.0 hours (mean values per ethnic group). While the AUC of melagatran was similar in the Black and Caucasian volunteers, the AUC was 23% higher in Asians compared to Caucasians. After correction for differences in body weight, the AUC values were similar between the groups. The higher AUC in Asians was therefore attributed to lower body weight, and corresponding lower renal function (as assessed by calculated CrCL), compared to Caucasians.

Using population pharmacokinetic methodology, the geometric mean AUC of melagatran (derived from the individual Bayesian estimates of CL/F) in Japanese AF patients (4.24 μmol h/L) was found to be 18% higher than in the Caucasian patients (3.58 μmol h/L). This is a relatively small difference and there was a complete overlap for the ranges of the individual estimates of melagatran AUC in the Japanese and Caucasian patients. The population PK model attributed the higher melagatran exposure in the Japanese patients to the influence of body-weight related differences in renal function on melagatran clearance. The median calculated CrCL in the Japanese patients was 58 mL/min while it was 78 mL/min in the Caucasian patients.

Together, these data indicate that melagatran plasma concentrations are in general no more than 25% higher in Asians compared to Caucasians and this difference is largely explained by an on-average lower body weight and associated renal function (assessed as calculated CrCL) in Asians versus Caucasians. There is therefore, no independent effect of race on the pharmacokinetics of ximelagatran.

The influence of hepatic impairment on the absorption, bioconversion of ximelagatran to the active form melagatran, and excretion was investigated in a group of subjects with mild to moderate hepatic impairment (characterized by Child-Pugh scoring system as class A and B, respectively) and control subjects matched by age, body weight, and gender. Following a single dose of 24 mg ximelagatran, the subjects with hepatic impairment had slightly lower AUC and C_{max} of melagatran compared to control subjects. After adjusting for differences in calculated CrCL between the 2 groups, the AUC estimates were comparable. The results support that the absorption of ximelagatran and the bioconversion to its active form, melagatran, are not influenced for patients with mild to moderate hepatic impairment.

In summary, investigation into the effect of intrinsic factors on ximelagatran pharmacokinetics indicate that interindividual differences in exposure to melagatran could be largely accounted for by variation in renal function. There does not appear to be any important additional effect on melagatran exposure related to age, gender, body weight, obesity, race (Asian, Black, Caucasian), or mild or moderate hepatic impairment. Renal function (assessed as calculated

CrCL) is therefore the most important demographic factor influencing melagatran plasma concentrations.

3.4 Food, alcohol and drug interactions

Ximelagatran does not interact with food or alcohol. Ximelagatran also has a low potential for drug interactions as supported by a lack of CYP450 interactions, low plasma protein binding, and systemic melagatran being primarily excreted via glomerular filtration. No important drug interactions have been identified with a range of potential co-medications, although an interaction with erythromycin and azithromycin has been identified.

Systemic exposure to melagatran (AUC and C_{max}) following oral administration of ximelagatran tablets is not altered by food intake, although the time to reach maximum plasma concentrations of melagatran is delayed approximately 1 hour. The effect of alcohol on the pharmacokinetics of melagatran was investigated in young healthy subjects (n=26) receiving single oral doses of 36 mg ximelagatran with and without alcohol on 2 separate occasions (Table 4). There was no change in melagatran AUC or C_{max}, supporting that ethanol intake does not alter the pharmacokinetics of melagatran following oral ximelagatran.

In vitro investigations of ximelagatran, its intermediates, and melagatran revealed no evidence of metabolism by, or inhibition of, the following CYP450 isoenzymes: 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, or 3A4. A series of *in vivo* studies have also been performed in healthy volunteers using the following known CYP450 substrates and/or inhibitors: atorvastatin (3A4 substrate), diazepam (2C19 and 3A4 substrate), diclofenac (2C9 substrate), nifedipine (3A4 substrate), amiodarone (2C9, 2D6 and 3A4 inhibitor) (Table 4). These drugs did not significantly alter the exposure of melagatran and there was also no important influence on the pharmacokinetics of these drugs by ximelagatran. These data confirm the results of the CYP450 studies *in vitro*, and support that ximelagatran should not alter the metabolism of other drugs mediated by CYP2C9, CYP2C19 or CYP3A4. In addition, the metabolism of ximelagatran should not be altered by concomitant administration of drugs that are substrates or inhibitors for these isoenzymes. Based upon these data, the potential for drug-drug interactions via CYP450 isoenzymes appears low.

Table 4 ***In vivo*** **drug-interaction studies with ximelagatran and various concomitantly administered drugs**

Concomitant drug and oral dose	Ximelagatran dose	Melagatran AUC ratio (90% CI)[a]	Concomitant drug AUC ratio (90% CI)[b]	Pharmacokinetic interaction[c]
Alcohol 0.5-0.6 g/kg	36 mg	1.04 (1.0; 1.08)	ND	No
Amiodarone 600 mg	36 mg	1.21 (1.17; 1.25)	0.87 (0.69; 1.08)	No[d]
ASA 162 mg	36 mg	1.04 (0.97; 1.11)	ND	No
ASA 162 mg	72 mg	1.06 (0.99; 1.14)	ND	No
Atorvastatin 40 mg	36 mg	0.97 (0.94; 1.01)	1.01 (0.94; 1.10)	No
Clopidogrel 75 mg	24 mg	1.02 (0.95; 1.11)	0.98 (0.95; 1.01)[e]	No
Diazepam 0.1 mg/kg iv	24 mg	0.99 (0.93; 1.06)	0.99 (0.95; 1.04)	No
Diclofenac 50 mg	24 mg	1.00 (0.93; 1.08)	0.99 (0.85; 1.16)	No
Digoxin 0.5 mg	36 mg	1.02 (0.98; 1.07)	1.04 (0.96; 1.12)	No
Erythromycin 500 mg	36 mg	1.82 (1.64; 2.01)	ND	Yes
Nifedipine 60 mg	24 mg	1.01 (0.97; 1.06)	1.05 (0.95; 1.17)	No

[a] Ximelagatran plus concomitant drug versus ximelagatran alone.
[b] Concomitant drug plus ximelagatran versus concomitant drug alone.
[c] No drug interaction indicated by 90% CI of AUC within 0.8–1.25. Due to the high variability of amiodarone, a 90% CI for AUC within 0.7–1.43 was accepted.
[d] 90% CI for melagatran C_{max} was outside 0.8–1.25 interval. AUC 90% CI for amiodarone was outside 0.7-1.43 interval.
[e] The active form of clopidogrel is not measurable, thus, the inactive metabolite SR 26334 was measured.
AUC Area under the curve, CI Confidence interval; ND Not determined; iv Intravenous.

The pharmacokinetics of digoxin, which depends on renal excretion as the primary route of elimination, were not altered upon co-administration with ximelagatran and the exposure of melagatran was not altered by the concomitant administration of digoxin (Table 4).

No PK interactions were observed with concomitant administration of ximelagatran and ASA or clopidogrel (Table 4). The effects on capillary bleeding times (CBTs) with these combinations are discussed in Section 3.5.1.

A PK interaction between ximelagatran and erythromycin has been observed (Table 4). Concomitant administration of erythromycin and ximelagatran to healthy subjects resulted in an increase of melagatran exposure to 1.8-times the level of melagatran following oral ximelagatran alone. Although erythromycin is an inhibitor of CYP3A4, this isoenzyme is not likely to be the site of the interaction with ximelagatran as both *in vitro* and *in vivo* studies have shown that ximelagatran and melagatran are not substrates of CYP3A4. Studies in rats using parenteral dosing of ximelagatran and erythromycin suggested that erythromycin inhibited biliary excretion of melagatran. It is not clear if this is representative of the interaction in humans as ximelagatran and erythromycin were administered orally in the

human study. The mechanism of the interaction is under further investigation. The clinical significance of this interaction is not known. The 80% increase in melagatran levels is, however, less than a 2-fold increase and is within the approximately 3- to 4-fold range of melagatran plasma concentrations observed in the patient population.

Two additional drug interaction studies involving antibiotics have been recently performed in response to the erythromycin interaction study findings. In the first study, ximelagatran was coadministered with therapeutic doses of amoxicillin, ciprofloxacin, or doxycycline (Table 5). In the second study, ximelagatran was coadministered with therapeutic doses of azithromycin or cefuroxime (Table 5). All antibiotics were administered either once or twice daily for 5 days with ximelagatran administered as a single dose on Days 1 and 5.

Table 5 ***In vivo*** **drug-interaction studies with ximelagatran and various concomitantly administered antibiotics**

Concomitant drug and dose	Ximelagatran dose	Melagatran AUC ratio (90% CI)[a]	Pharmacokinetic interaction[b]
Amoxicillin 750 mg bid	36 mg	0.98 (0.90; 1.07)	No
Azithromycin 500 mg loading dose	36 mg	1.60 (1.40; 1.82)	Yes
Azithromycin 250 mg od	36 mg	1.41 (1.24; 1.61)	Yes
Cefuroxime 250 mg bid	36 mg	1.16 (0.97; 1.38)	Yes
Ciprofloxacin 750 mg bid	36 mg	0.98 (0.89; 1.07)	No[c]
Doxycycline 200 mg loading dose	36 mg	0.99 (0.88; 1.11)	No
Doxycycline 100 mg od	36 mg	1.03 (0.88; 1.22)	No

[a] Ximelagatran plus concomitant drug versus ximelagatran alone on Day 5 of dosing with antibiotic except for AUC during loading doses, which were on Day 1 of dosing with antibiotic.
[b] No drug interaction indicated by melagatran AUC 90% CI within 0.8–1.25.
[c] C_{max} 90% CI for melagatran was slightly below 0.7–1.43 interval. As AUC was unchanged, the decrease in C_{max} is not believed to be of concern.
bid Twice daily, od Once daily; AUC Area under the curve; CI Confidence interval.

The data indicate that, although smaller than the interaction with erythromycin, azithromycin increased melagatran levels by 60%, or 1.6 times, following a 500-mg loading dose and by 40% following the 250-mg daily maintenance dose of azithromycin. Importantly, cefuroxime resulted in a minimal increase (16%) in melagatran levels while amoxicillin, ciprofloxacin, and doxycycline showed no interaction with ximelagatran. The only important PK interactions identified with ximelagatran are therefore with the macrolide antibiotics erythromycin and azithromycin. The lack of important interactions with the 4 other antibiotics studied indicates that there are alternative antibiotics for use if needed.

In support of these data from clinical pharmacology studies, population PK analyses in the long-term treatment studies indicated no significant influence on melagatran exposure detected in patients receiving oral ximelagatran and a wide range of concomitant medications including: digoxin, ACE inhibitors, organic nitrates, loop diuretics, β-blockers, calcium

channel blockers (including dihydropyridine derivatives and verapamil), amiodarone, angiotensin II antagonists and HMG CoA reductase inhibitors (statins).

3.4.1 Drug interaction analyses for bleeding events and alanine aminotransferase (ALT) elevations

Analysis of event rates describing the bleeding risk and the hepatic effect (occurrence of ALT >3x the upper limit of normal [ULN]) associated with the use of ximelagatran, in patients in the chronic indications taking amiodarone or a macrolide antibiotic in combination with ximelagatran compared to patients taking ximelagatran alone, showed no indication of a clinically relevant interaction. In each case, there was no signal for increased event rates between patients treated with the combination compared to those treated with ximelagatran alone.

3.4.1.1 Bleeding events

Event rate estimates for bleeding events in patients receiving, or not receiving amiodarone are presented in Table 6. Out of 252 patients receiving amiodarone and ximelagatran, there were no major bleeding events while the event rates per 100 patient years for major bleeding events in patients receiving ximelagatran alone was 2.8%. Out of 239 patients receiving comparator and amiodarone the event rate per 100 patient years for major bleeding events was higher (5.5%) than for comparator alone (2.6%).

Event rates per 100 patient years for major and minor bleeding events were 33.5% for ximelagatran alone compared with 22.6% for ximelagatran in combination with amiodarone. For the comparator, event rates per 100 patient years for major and minor bleeding events were 28.8% compared to 29.1% for comparator and amiodarone.

Table 6 Event rate estimates for major and major/minor bleeding events in patients treated with ximelagatran or comparator alone or in combination with amiodarone

	Ximelagatran	Ximelagatran + amiodarone	Comparator + amiodarone	Comparator
	n=6696	n=252	n=239	n=5991
Major bleeding events				
Number of events	134	0	15	150
% of patients reporting events	2.0	0.0	6.3	2.5
Number of patient-years of exposure	4834	151	271	5760
Event rate per 100 patient year (%)	2.8	0	5.5	2.6
Major and minor bleeding events				
Number of events	1617	34	79	1657
% of patients reporting events	24.2	13.5	33.1	27.7
Number of patient-years of exposure	4834	151	271	5760
Event rate per 100 patient year (%)	33.5	22.6	29.1	28.8

These data do not suggest an increased incidence of major, or major and minor bleeding, when ximelagatran is combined with amiodarone.

Event rate estimates for bleeding events in patients receiving, or not receiving, macrolide antibiotics are presented in Table 7. Out of 233 patients receiving macrolide antibiotics and ximelagatran, there were no major bleeding events while the event rate per 100 patient years for major bleeding events in patients receiving ximelagatran alone was 2.7%. Out of 208 patients receiving comparator and macrolide antibiotics the event rate per 100 patient years for major bleeding events was higher (7.8%) than for comparator alone (2.7%).

Event rates per 100 patient years for major and minor bleeding events were 33.1% for ximelagatran alone compared with 35.2% for ximelagatran in combination with macrolide antibiotics. For the comparator, event rates per 100 patient years for major and minor bleeding events were 217.7% compared to 28.7% for comparator and macrolides.

Table 7 Event rate estimates for major and major/minor bleeding events in patients treated with ximelagatran or comparator alone or in combination with macrolides

	Ximelagatran	Ximelagatran + macrolides	Comparator + macrolides	Comparator
	n=6715	n=233	n=208	n=6022
Major bleeding events				
Number of events	133	0	3	158
% of patients reporting events	2.0	0.0	1.4	2.6
Number of patient-years of exposure	4870	17.1	38.6	5790
Event rate per 100 patient year (%)	2.7	0.0	7.8	2.7
Major and minor bleeding events				
Number of events	1614	6	84	1664
% of patients reporting events	24.0	2.6	40.4	27.6
Number of patient-years of exposure	4870	17.1	38.6	5790
Event rate per 100 patient year (%)	33.1	35.2	217.7	28.7

In the pivotal trials, approximately 20% (37/233) of the patients taking macrolide antibiotics concomitantly with ximelagatran were taking erythromycin.

These data no not suggest an increased incidence of major, or major and minor bleeding, when ximelagatran is combined with macrolide antibiotics.

3.4.1.2 ALT elevations

Event rate estimates for ALT >3x ULN in patients receiving, or not receiving, amiodarone are presented in Table 8. Event rates per 100 patient years for ALT >3x ULN were 11% for ximelagatran alone compared with 3.3% for ximelagatran in combination with amiodarone.

Table 8 Event rate estimates for ALT >3x ULN in patients treated with ximelagatran or comparator alone or in combination with amiodarone

	Ximelagatran	Ximelagatran + amiodarone	Comparator + amiodarone	Comparator
	n=6696	n=252	n=239	n=5991
Number of events	531	5	1	74
% of patients reporting events	7.9	2.0	0.4	1.2
Number of patient-years of exposure	4834	151	271	5760
Event rate per 100 patient year (%)	11.0	3.3	0.4	1.3

Event rate estimates for ALT >3x ULN in patients receiving, or not receiving, macrolides are presented in Table 9. Event rates per 100 patient years for ALT >3x ULN were 10.9% for ximelagatran alone compared with 0% for ximelagatran in combination with a macrolide.

Table 9 Event rate estimates for ALT >3x ULN in patients treated with ximelagatran or comparator alone or in combination with macrolides

	Ximelagatran	Ximelagatran + macrolides	Comparator + macrolides	Comparator
	n=6715	**n=233**	**n=208**	**n=6022**
Number of events	530	0	3	72
% of patients reporting events	7.9	0.0	1.4	1.2
Number of patient-years of exposure	4870	17.1	38.6	5790
Event rate per 100 patient year (%)	10.9	0.0	7.8	1.2

These data no not suggest an increased incidence of ALT >3x ULN when ximelagatran is administered with amiodarone or macrolide antibiotics.

These data suggest that concomitant administration of ximelagatran with amiodarone or macrolide antibiotics does not increase the incidence of bleeding or ALT >3x ULN. The PK changes observed in the presence of amiodarone (21% increase in melagatran AUC) or macrolide antibiotics (up to 80% increase in melagatran AUC) do not appear to translate into any increased risk of bleeding or ALT >3x ULN.

3.4.2 Summary of drug interactions

In summary, oral ximelagatran has a low risk of significant drug interactions for the following reasons:

- The mechanism of action of ximelagatran is not vitamin-K dependent
- The plasma protein binding of melagatran is low
- The primary route of elimination of systemic melagatran is via glomerular filtration
- Ximelagatran is not metabolized by, and does not inhibit, CYP450 isoenzymes
- Evidence from population PK analyses suggest no significant influence of the most commonly used concomitant medications in the long-term dosing patient studies.

3.5 Human pharmacodynamics

Oral administration of ximelagatran to humans results in statistically significant melagatran-induced inhibition of thrombin activity, thrombin generation, platelet activation and thrombus formation, with statistically significant pharmacologically active plasma concentrations as low as 0.03 μmol/L, slightly below the 0.05 μmol/L level detected in rats.

In human experimental models of thrombosis, a direct relationship was observed between the concentration of melagatran in plasma and inhibition of thrombus formation, thrombin generation, and platelet activation. No hysteresis was observed. 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 at 2 hours after dosing in healthy subjects. Pharmacologically active concentrations of melagatran (>0.03 μmol/L) are detected in plasma as early as 30 to 60 minutes following an oral dose of 24 or 36 mg ximelagatran and, based on concentrations detected at 12 hours, are predicted to remain for 12 to 24 hours following 24 or 36 mg oral ximelagatran. If there is a need for more rapid reversal of the effect, the elimination of melagatran can be accelerated using dialysis in patients with reduced renal function. As with other direct thrombin inhibitors, there are currently no non-blood-product hemostatic agents available that have demonstrated clinical value in reversing the anticoagulant effects of ximelagatran.

If a dose of ximelagatran is missed, low but pharmacologically active concentrations of melagatran should remain for 12- to 24-hours following a dose of 24 or 36 mg oral ximelagatran.

The 12- to 24-hour offset of action following the last dose of ximelagatran supports the use of a twice-daily dosing regimen.

3.5.1 Capillary bleeding time prolongation

Melagatran was found to prolong CBT by up to approximately 35% (to ~9 minutes) from baseline (~7 minutes) at therapeutic concentrations. The CBT following 2 days of ASA (450 mg ASA on Day 1 followed by 150 mg ASA on Day 2) was ~10 minutes (~3 minutes above baseline). When melagatran and ASA were co-administered, the CBT was approximately ~12 minutes (~5 minutes above baseline) indicating an additive effect of melagatran and ASA on the CBT. A slightly less than additive effect following co-administration of 24 mg oral ximelagatran and 50 mg of the non-steroidal anti-inflammatory drug (NSAID) diclofenac was observed. CBTs of ~7, ~7.5, and ~8 minutes following ximelagatran, diclofenac or the combination, respectively, were observed. The baseline CBT was ~5 minutes. A more than additive, or synergistic, effect following co-administration of 24 mg oral ximelagatran and 75 mg clopidogrel (for 13 days) was observed. CBTs of ~6, ~12, and ~26 minutes were observed following ximelagatran, clopidogrel, and the combination, respectively. The baseline CBT was ~5 minutes.

Although CBT is not directly predictive of bleeding risk, these results support the use of caution in concomitant administration of ximelagatran with ASA, NSAID or other antiplatelet

agents, and probably also with other agents that affect hemostasis, such as other anticoagulants or fibrinolytics.

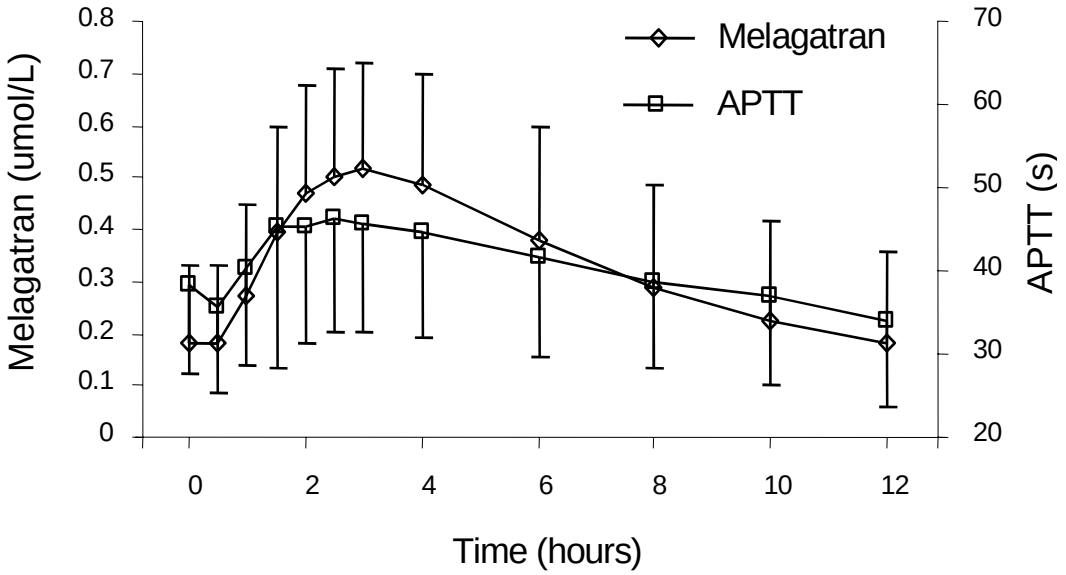
3.5.2 Coagulation time assays

Ximelagatran prolonged conventional coagulation time assays to varying degrees and with varying sensitivity. The assays including activated partial thromboplastin time (APTT), activated clotting time (ACT), prothrombin time/international normalized ratio (PT/INR) and thrombin time (TT). The variability in the sensitivity of assay reagents to melagatran and the non-standardized nature of the assays limit their clinical usefulness. These coagulation time assays are, therefore, unsuitable for assessing the effect of ximelagatran in patients.

The APTT and ACT are prolonged in a non-linear manner and are relatively insensitive to melagatran. The PT/INR, which is the only globally standardized coagulation time assay and is used to monitor warfarin therapy, is particularly insensitive to melagatran. The TT is very sensitive to melagatran but conventional TT assays are maximally prolonged at the lower end of the normal range of melagatran plasma concentrations observed in patients. Results using these assays varied depending on the commercial assay reagent used. The ecarin clotting time is prolonged by melagatran in a linear manner but is an experimental assay that is not widely available.

Following administration of 36 mg oral ximelagatran under fasting conditions, maximal prolongation of the APTT is observed 2 to 3 hours after dosing. The rather flat relationship between the APTT and melagatran plasma concentrations at steady-state concentrations of melagatran in AF patients means that absolute APTT levels change by only approximately 12 seconds from trough to peak melagatran plasma concentrations following oral ximelagatran 36 mg (Figure 10). Although the APTT is not a sensitive indicator of extent of effect, evidence of a prolongation of the APTT is an indication of the presence of an anticoagulant effect following oral ximelagatran.

Figure 10 Plasma melagatran concentrations and APTT levels at steady state following 36 mg oral ximelagatran



APTT Activated partial thromboplastin time.

3.5.3 Exposure-response analyses in patient studies

In the PK evaluation of data collected in clinical studies across different patient populations, the estimated interindividual variability of melagatran AUC following oral treatment with ximelagatran was about 50% (expressed as CV%). Thus, although the intraindividual variability was only about 25% in AF patients, the melagatran exposure varied across the patient population such that there was about a 3- to 4-fold difference between the 5^{th} and 95^{th} percentiles of the individual population-derived estimates of melagatran AUC with a fixed oral dose regimen of ximelagatran.

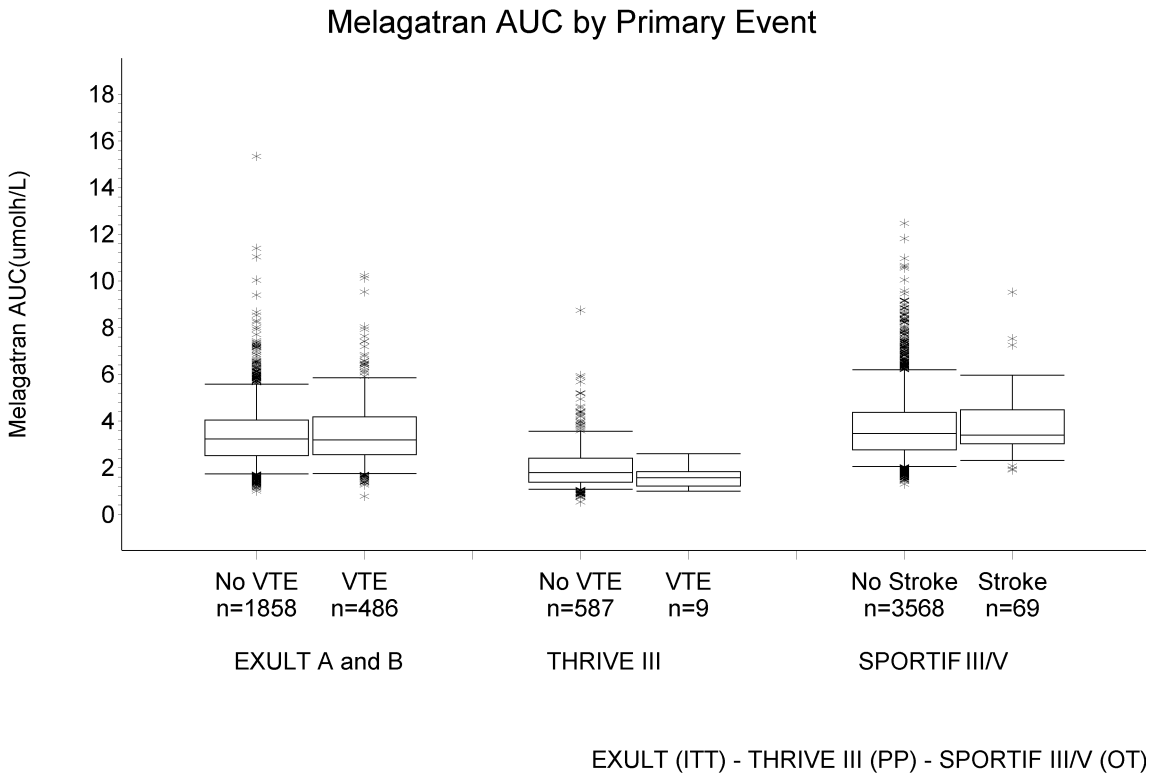
To understand whether the 3- to 4-fold range of melagatran plasma concentrations observed in patients had any impact on the efficacy or safety of oral ximelagatran, the relationships between population model predicted melagatran exposure and the clinical endpoints were investigated in the Phase III studies for orthopedic surgery, secondary prevention of VTE, and AF patient populations. No samples were collected at the time of an event.

Melagatran exposure (AUC) was predicted in individual patients using a population PK model. The exposure predictions represent the average melagatran exposure in an individual patient over time. As melagatran plasma concentrations are stable and reproducible over time, these exposure estimates are believed to be representative of an individual patient's plasma levels over time. However, the actual concentrations at the time of a clinical event may have differed from these predicted exposures (eg, a patient may not have taken their study drug on the day of the event). The relationships between melagatran AUC and the occurrence of

clinical efficacy endpoint events or bleeding events were investigated. The methodology used for these analyses was in accordance with recent FDA guidance, but it is recognized that the analyses are exploratory and that there are confounding factors that may influence potential exposure-response relationships.

An analysis of predicted melagatran exposure with the presence or absence of efficacy endpoints in secondary prevention of VTE, orthopedic surgery (OS), and AF did not show any statistically significant relationships with melagatran exposure (Figure 11). The analysis did not indicate a relationship between melagatran exposure and bleeding in the OS patient population. In the long-term dosing population, an increasing exposure to melagatran was associated statistically with an increased likelihood of bleeding (pooled LTE hazard ratio 1.38 [95% CI: 1.28 to 1.50; $p<0.0001$]). However, while melagatran exposure increases with decreasing calculated CrCL, ximelagatran was associated comparable, or less, bleeding than the comparator across CrCL sub-groups in the LTE Pool (Figure 34). This highlights a potential confounding factor in this exposure-response analysis since the apparent trend of increased likelihood of bleeding with increasing melagatran exposure was not associated with increased bleeding versus the comparator. As can be seen in Figure 12, while the median melagatran exposures are higher in patients with major bleeding events compared to those without, the distribution of melagatran AUC in patients with a clinical event was largely within the range of melagatran AUC values in patients without a clinical event. Thus, at the studied fixed oral dose regimens of ximelagatran, melagatran exposure is not predictive of a clinical event on an individual basis. As there is no apparent separation in the distribution of melagatran concentrations in patients who did or did not experience a major bleeding event, monitoring melagatran plasma concentrations or a surrogate of melagatran concentrations (such as a coagulation time assay) would not help identify those at increased risk of bleeding.

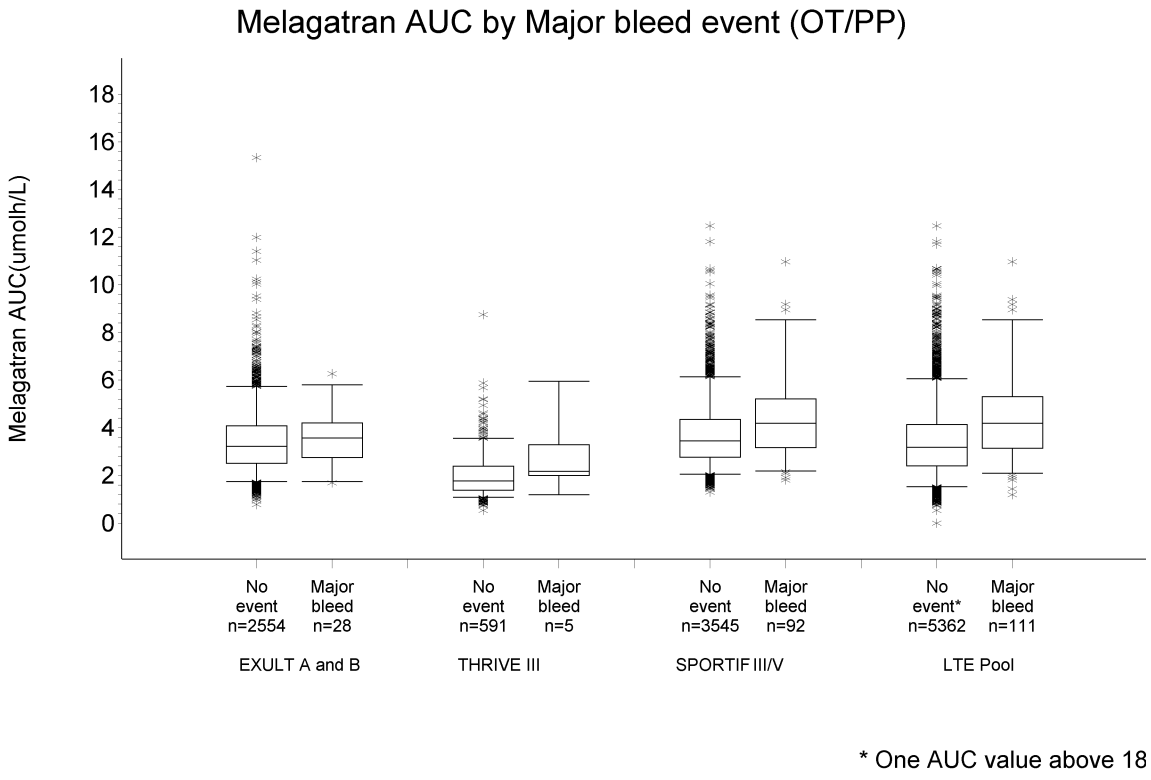
Figure 11 Relationship between population-model predicted melagatran AUC and VTE or stroke/SEE



Relationships investigated using an on treatment (OT) analysis for EXULT A and EXULT B (SH-TPO-0010 and SH-TPO-0012) and SPORTIF III and V (SH-TPA-0003 and SH-TPA-0005), and a per protocol (PP) analysis for THRIVE III (SH-TPV-0003).

AUC Area under the curve; VTE Venous thromboembolism; SEE Systemic embolic event.

Figure 12 Relationship between population-model predicted melagatran AUC and major bleeding events in long-term treatment trials



Relationships investigated using an OT analysis for EXULT A and B (SH-TPO-0010 and -0012) and SPORTIF III and V (SH-TPA-0003 and -0005), and a PP analysis for THRIVE III (SH-TPV-0003). Long-term exposure (LTE) pool includes SPORTIF III and SPORTIF V (SH-TPA-0003 and SH-TPA-0005), ESTEEM (SH-TPC-0001), and THRIVE II/V and III (SH-TPV-0002/0005 and -0003).
AUC Area under the curve, OT On-treatment, PP Per protocol.

3.6 Summary of ximelagatran clinical pharmacology

The clinical pharmacology program characterized the pharmacokinetics and pharmacodynamics of both ximelagatran and its dominant active form, the direct thrombin inhibitor melagatran. Overall, there was stable and reproducible systemic exposure to melagatran, with no time or dose dependency in pharmacokinetics. As systemic melagatran is cleared mainly by glomerular filtration, renal function (calculated CrCL) is the most influential demographic factor for explaining melagatran exposure and largely explained any small differences in exposure among special populations. Ximelagatran has a low potential for drug interactions. Interactions with erythromycin and azithromycin have been observed that results in increased systemic exposure to melagatran; however, the PK interactions were not associated with increased bleeding or increased incidence of ALT >3x ULN. Interaction studies with other antibiotics (amoxicillin, cefuroxime, ciprofloxacin, and doxycyline) showed

no important interactions. Onset of anticoagulant effect is rapid, within the first hour of dosing, plasma concentrations are stable over the duration of treatment, and the effect declines rapidly (within 12 to 24 hours) after treatment is discontinued. Although a statistical relationship between increasing exposure of melagatran and increased likelihood of bleeding events was identified in the long-term treatment indications, overall bleeding with ximelagatran was equal to or better than well-controlled warfarin and plasma concentrations of melagatran were not predictive of bleeding events for individual patients. A maximal, or threshold, melagatran concentration above which bleeding rates are unacceptable has not been identified with the fixed oral dose regimens of ximelagatran investigated. Oral administration of 24 mg or 36 mg ximelagatran results in a 3- to 4-fold range of melagatran exposure, with low within patient variability, and anticoagulant concentrations of melagatran are maintained throughout the dosing interval. In total, the clinical pharmacology findings support the use of a fixed bid-dosing regimen without coagulation monitoring in the patient populations studied in the clinical program.

4. OVERVIEW OF THE XIMELAGATRAN CLINICAL PROGRAM

The development program for ximelagatran has been designed to offer an oral alternative anticoagulant to warfarin. Ximelagatran has been evaluated in various patient populations in large, controlled, worldwide, primarily outcome-based, clinical studies. The studies were designed to demonstrate that fixed-dose ximelagatran, without coagulation monitoring or dosage adjustment, offers superiority to placebo (secondary prevention of VTE), superiority to warfarin (prevention of VTE after TKR surgery), and non-inferiority to warfarin (prevention of stroke and SEE in AF).

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 30698 subjects were randomized. A total of 17365 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 1 year (up to 2.5 years in the pivotal AF studies and up to 5 years in one ongoing AF safety study). The clinical development program for ximelagatran is briefly summarized in Table 10.

Although the safety data from the studies conducted for the treatment of VTE (THRIVE II&V, SH TPV-0002 and SH-TPV-0005) are integrated into the LTE Pool, the efficacy data were not included in the efficacy section of this document because approval for these indications is not being sought at this time. Summaries of the Phase III studies THRIVE II&V (THRIVE Treatment, SH TPV-0002 and SH-TPV-0005) and ESTEEM (SH-TPC-0001) are provided in Appendix A.

Table 10 Scope of the clinical development program for ximelagatran

Phase I studies	**60 studies**
Phase II and III studies other than the pivotal studies for the proposed indications (2 detailed below)	**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	Dose	Treatment goal	Target patient population	Study name (number)	Number of patients randomized
Long-term secondary prevention of VTE after standard treatment for an episode of acute VTE.	Oral 24 mg bid	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.	THRIVE III (SH-TPV-0003)	1233
Prevention of VTE in patients undergoing knee replacement surgery.	Oral 36 mg bid	Reduce the incidence of developing VTE (DVT or PE) following orthopedic surgery.	Patients undergoing primary TKR.	EXULT A (SH-TPO-0010) EXULT B (SH-TPO-0012)	4604
Prevention of stroke and other thromboembolic complications associated with atrial fibrillation.	Oral 36 mg bid	Reduce the incidence of stroke and systemic embolic events.	Patients with nonvalvular atrial fibrillation at increased risk for stroke.	SPORTIF III (SH-TPA-0003) SPORTIF V (SH-TPA-0005)	7329
Other studies, referred to in the safety section of this document, for indications not being sought in this application					
NA (Phase III)	Oral 36 mg bid	Reduce the incidence of recurrent symptomatic VTE (DVT and PE) events.	Patients with acute, symptomatic, objectively confirmed VTE.	THRIVE II&V (SH-TPV-0002 and SH-TPV-0005)[a]	2528
NA (Phase II)	Oral 36 mg bid	Reduce the incidence of death, myocardial infarction, and severe recurrent ischemia	Patients with a recent history of myocardial damage.	ESTEEM (SH-TPC-0001)[a]	1900

[a] THRIVE II&V (SH-TPV-0002/0005) was a Phase III pivotal study, ESTEEM (SH-TPC-0001) was a Phase II therapeutic exploration study. Summaries of the Phase III studies THRIVE II&V (THRIVE Treatment, SH TPV-0002 and SH-TPV-0005) and ESTEEM (SH-TPC-0001) are provided in Appendix A.

VTE Venous thromboembolism; DVT Deep vein thrombosis; PE Pulmonary embolism; TKR Total knee replacement, NA Not applicable.

4.1 Key design aspects of the Phase III pivotal studies

The design of the clinical studies varied among the 3 indications, but some important features are common to most of them, and are described below:

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

Patient population: Principal investigators recruited patients who satisfied the selection criteria from their primary or referral clinical practices. The patient population investigated in each of the pivotal trials was based on inclusion and exclusion criteria that incorporated the appropriate target population for the indications being studied in each of the trials: patients suitable for establishing the value of prolonged ximelagatran prophylaxis in preventing the recurrence of VTE; patients scheduled for elective primary unilateral or bilateral TKR surgery; and patients with AF at moderate to high risk of stroke, for whom guidelines recommend warfarin prophylaxis dose-adjusted to an INR 2.0 to 3.0. Inclusion criteria also limited participation to adults who provided informed consent, there being no basis for pediatric dosing of ximelagatran at this time.

Other inclusion and exclusion criteria were aimed at ensuring patient safety and reducing the number of patients at risk of being prematurely withdrawn from the study, eg, patients for whom a high risk of bleeding would contraindicate anticoagulation therapy. Melagatran depends on renal excretion as the primary route of elimination. For this reason, subjects with severe renal insufficiency (calculated CrCL <30 mL/min) were excluded. The exclusion of patients with elevated liver enzymes (>2x ULN) acted to decrease factors confounding subsequent liver enzyme increases associated with ximelagatran exposure. The remaining clinical exclusion criteria aimed to provide optimal compliance and to ensure as complete a follow-up as possible. These criteria impacted minimally on the suitability of the patients included in the study as representative of the target treatment population.

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

Maintaining a blinded INR: To preserve the blind, it was necessary to set up a mechanism whereby INR results were transmitted to the IVRS without being seen by study personnel. The IVRS reported the actual INR value for those patients randomized to warfarin treatment, or a sham value for those patients randomized to the ximelagatran treatment. The range of the shammed INRs for the ximelagatran group was narrower than that of true INRs for warfarin patients because the shamming algorithm maintained the range between narrower limits, 1.1 and 4.0. This range limit was implemented to prevent reporting of shammed INRs that would lead to unnecessary hospitalization of patients randomized to ximelagatran. This range limit helped protect the study blind.

Outcome-based efficacy variables: The assessment of clinical efficacy is based on the occurrence of clinical events that were largely outcome-based, including thrombotic events and death (Table 11).

Table 11 Efficacy objectives and outcome variables/endpoints relating to each objective for the Phase III pivotal trials

Study	Objective	Outcome variable/endpoint
THRIVE III SH-TPV-0003 Secondary prevention of VTE	**Primary** To assess whether the oral thrombin inhibitor ximelagatran given as prolonged prophylaxis after a 6 month anticoagulation treatment for VTE reduces the recurrence rate of symptomatic objectively confirmed VTE event compared to placebo (time to event)	Time to symptomatic objectively confirmed VTE event during up to 18 months of treatment or until premature discontinuation of the study (ITT population)
	Secondary To estimate all-cause mortality	Time to death from any cause, during up to 18 months of treatment or until premature discontinuation of the study (ITT population)
EXULT A SH-TPO-0010 and EXULT B SH-TPO-0012 Prevention of VTE after TKR surgery	**Primary** To determine the better of the 2 doses of ximelagatran for the prevention of VTE using 2 different doses (24 mg and 36 mg) given twice daily by oral administration, starting as early as possible on the morning after the day of surgery, to patients undergoing primary elective TKR.	Incidence of total VTE (ie, distal and/or proximal DVT and/or symptomatic PE, with objective adjudication committee confirmation) and/or all-cause mortality during the treatment period (ITT population).
	Secondary To compare ximelagatran with warfarin, targeting of INR 2.5, for proximal DVT and/or PE and/or all-cause mortality during the study drug treatment period.	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).
	To compare ximelagatran with warfarin, targeting of INR 2.5, for the incidence of DVT and/or PE and/or all-cause mortality according to on-site evaluations during the study drug treatment period.	Incidence of total VTE and/or all-cause mortality during the treatment period (ITT population).

Table 11 Efficacy objectives and outcome variables/endpoints relating to each objective for the Phase III pivotal trials

Study	Objective	Outcome variable/endpoint
SPORTIF III SH-TPA-0003 and SPORTIF V SH-TPA-0005 Prevention of stroke and SEE in AF	**Primary**	
	To determine whether the efficacy of ximelagatran is non-inferior compared to that of dose-adjusted warfarin, aiming for an INR 2.0 to 3.0, for the prevention of strokes (fatal and non-fatal) and SEE in patients with chronic AF.	Time to first occurrence of the composite of stroke and SEE (ITT population)
	Secondary	
	To compare the efficacy of ximelagatran to that of dose-adjusted warfarin, aiming for an INR 2.0 to 3.0, for the combined endpoint of prevention of death, non-fatal strokes, non-fatal SEE, and non-fatal AMI.	Time to first occurrence of the composite of the following: all-cause mortality/stroke/SEE/AMI (OT analysis)
	To compare the efficacy of ximelagatran to that of dose-adjusted warfarin, aiming for an INR 2.0 to 3.0, for the combined endpoint of prevention of ischemic strokes, TIA, and SEE.	Time to first occurrence of any one of the following: ischemic stroke/SEE/TIA (OT analysis)

VTE Venous thromboembolism, ITT Intention-to-treat, TKR Total knee replacement, DVT Deep vein thrombosis, PE Pulmonary embolism, AF Atrial fibrillation, SEE Systemic embolic event, AMI Acute myocardial infarction, OT On-treatment, TIA Transient ischemic attack.

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. Hence, even in the study in which the treatments were not blinded (SPORTIF III, SH-TPA-0003), subjectivity and potential bias in the evaluation of endpoint events was reduced. Appendix B provides the definitions for adjudicated major and minor bleeding events for the pivotal trials.

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

4.2 Development of dose selection

4.2.1 Background

Dose response using cardiovascular outcomes as endpoints is a challenge because of the low event rates that require large clinical trials to detect differences between treatments. For an

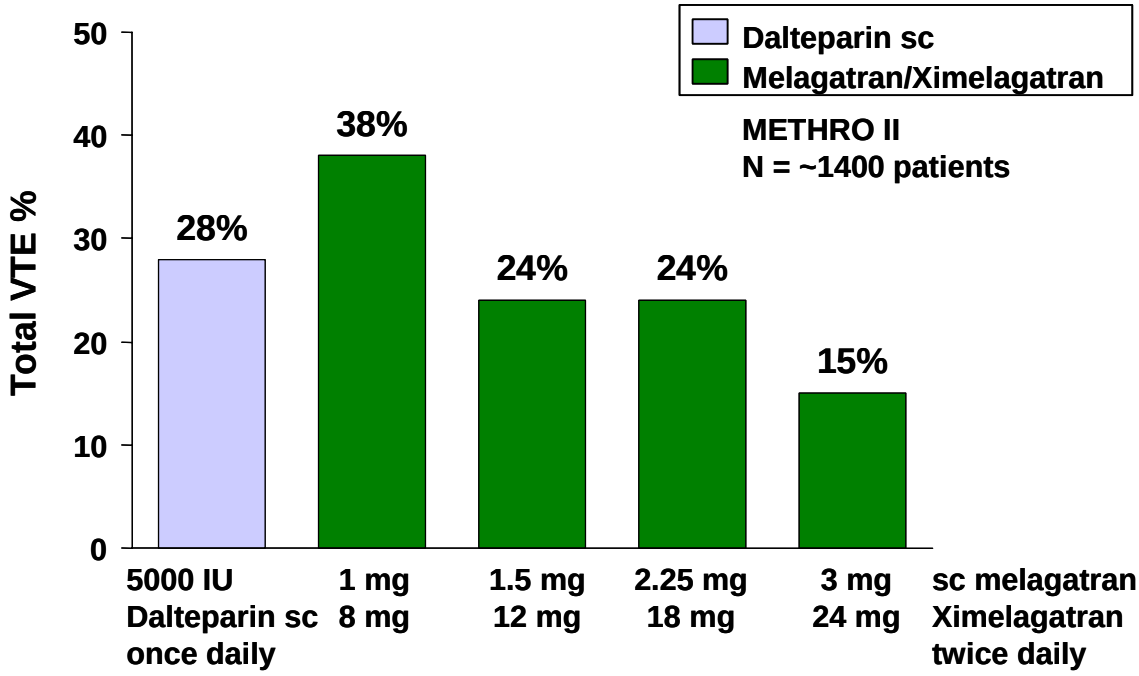
anticoagulant, the main efficacy and safety measures lie along the same pharmacological continuum: agents reduce the risk of thrombosis, while running the risk of increasing bleeding. Dose selection of any new anticoagulant has to achieve an optimal balance between efficacy and bleeding across the patient types and indications sought.

4.2.2 Ximelagatran dose selection for the Phase III studies

Selection of the dosage for ximelagatran was initially guided by data from animal studies in which melagatran showed good antithrombotic effect and no increase in bleeding time over a plasma concentration range of 0.05 to 0.5 μmol/L (see Section 2). Initial studies in humans focused on investigating the safety, tolerability, PK, PD, and efficacy of these plasma concentrations in Phase I studies with ximelagatran at doses from 5 mg to 98 mg. Oral ximelagatran was well tolerated and no serious adverse events (SAEs) were reported during treatment. Ximelagatran, administered at 98-mg single dose, resulted in concentrations of melagatran up to 1.0 μmol/L and was well tolerated (see Section 3.2). The maximum pre specified coagulation time prolongation was achieved at this dose, fulfilling the mandated study stopping criteria; a 2.5-fold increase in APTT. The PK properties of melagatran following oral ximelagatran in Phase I studies in healthy volunteers supported the selection of twice-daily dosing: peak melagatran concentrations were achieved at 2 to 3 hours, following an oral dose of 24 mg or 36 mg ximelagatran and melagatran plasma concentrations remained above 0.05 μmol/L for up to 12 hours or longer.

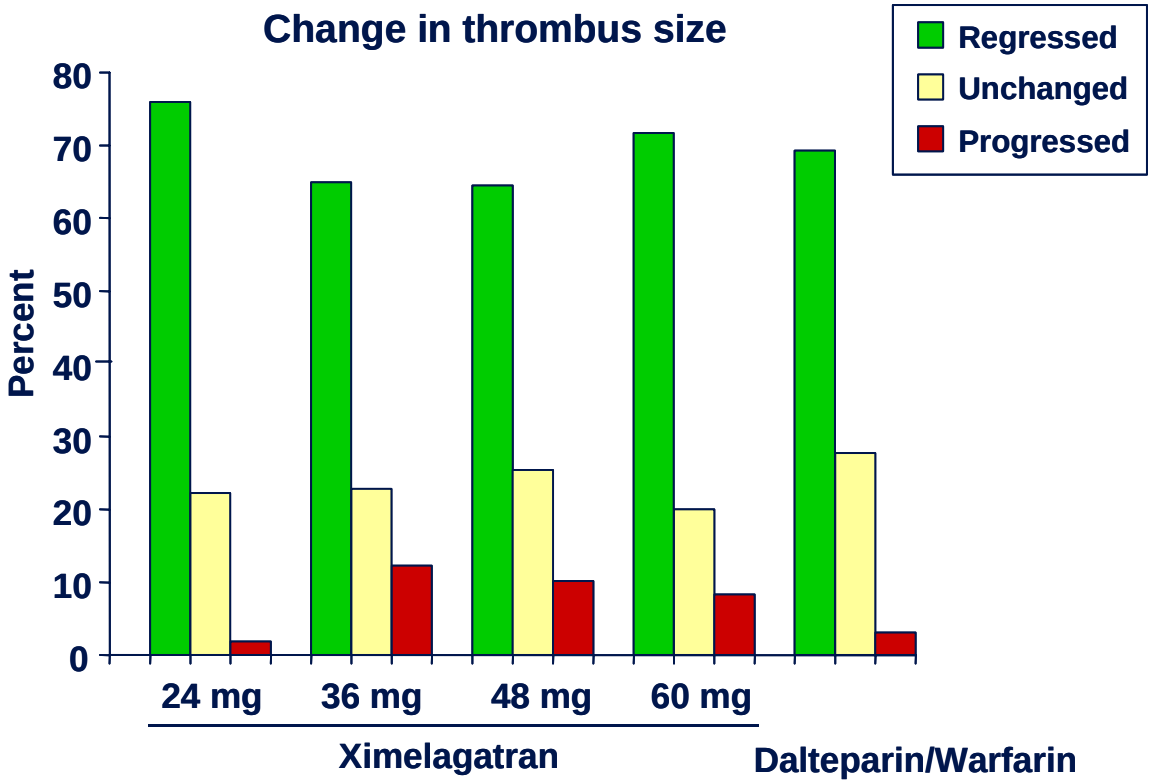
METHRO I (SH-TPO-0001) was the first Phase II study performed with the goal of providing a basis for dose selection in future pivotal studies of efficacy and safety. Initiated in OS patients as VTE prophylaxis, it tested a treatment regimen of sc melagatran followed by oral ximelagatran. The next Phase II study (METHRO II, SH-TPO-0002) of VTE prophylaxis in OS patients tested combinations of initial melagatran sc doses, followed by oral ximelagatran for 8 to 11 days, which were shown to be efficacious, safe, and well tolerated. A dose-response relationship for efficacy, with oral ximelagatran doses ranging from 8 mg bid to 24 mg bid, was shown in this study. The 8-, 12- and 18-mg doses were not as effective as the 24-mg dose compared with dalteparin and were not developed further (Figure 13).

Figure 13 **Dose-response relationship for efficacy, with oral ximelagatran doses ranging from 8 mg bid to 24 mg bid in METHRO II (SH-TPO-0002)**



A Phase II dose-finding study in 331 patients with acute DVT (THRIVE I, SH-TPV-0001) compared safety and efficacy outcomes of 4 different doses of twice-daily ximelagatran (24, 36, 48 and 60 mg) and standard anticoagulant treatment (dalteparin/warfarin). Efficacy in that study was evaluated with a surrogate endpoint, venographic estimation of thrombus extension (Marder score), after 2 weeks treatment. The efficacy of ximelagatran was similar to that in the dalteparin/warfarin group for all doses, indicating a flat dose-response relationship regarding thrombus extension (Figure 14).

Figure 14 **Dose-response relationship and progression/regression of thrombus with oral ximelagatran doses ranging from 24 mg bid to 60 mg bid in THRIVE I (SH-TPV-0001)**



Based on the evidence that 24 mg provided effective anticoagulation with an acceptable safety profile, the Phase III study program was initiated using 24 mg bid oral ximelagatran. The following subsections summarize the dose selection in each of the proposed indications.

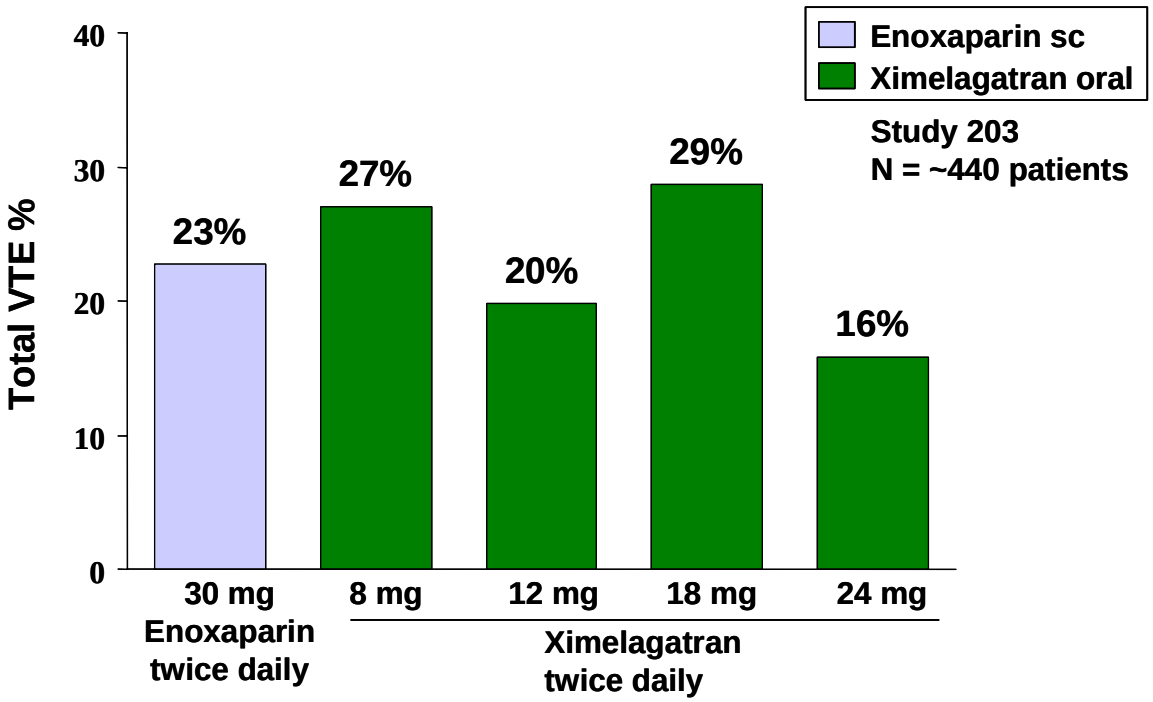
4.2.2.1 Prevention of VTE after knee replacement surgery

An "oral only" program was conducted in North America, using post-operative administration of oral ximelagatran. While the overall purpose of the oral only and European sc + oral programs was similar, the designs were substantially different in key respects, reflecting different medical practices in the 2 regions in which these regimens were pursued. Further information on the EU OS program leading up to the 3 Phase III TKR surgery studies can be found in Appendix C.

The first North American Phase II dose-ranging study, SH-TPO-0004, suggested that the 24-mg oral bid dose of ximelagatran would be appropriate in TKR surgery patients. Oral ximelagatran 8, 12, 18, and 24 mg bid was investigated for 6 to 12 days. The 24-mg oral ximelagatran dose was again shown to be the most effective dose with a reassuring safety

profile (Figure 15). The 24 mg oral dose of ximelagatran was thereafter progressed into Phase III clinical studies for the prevention of VTE in knee replacement surgery patients.

Figure 15 **Dose-response relationship for efficacy, with oral ximelagatran doses ranging from 8 mg bid to 24 mg bid in SH-TPO-0004**



The initial Phase III study, PLATINUM KNEE (SH-TPO-0006), in TKR surgery patients, confirmed that 24 mg bid was numerically more effective than warfarin in preventing VTE, but again the difference was not statistically significant (p=0.07). The incidence of VTE in the warfarin group was 25%, but the study had been powered based on an assumed incidence of 35%.

EXULT A (SH-TPO-0010) was designed both to re-test whether ximelagatran 24 mg oral bid was superior to well-controlled warfarin (target INR 2.5), and to determine if the efficacy of ximelagatran could be improved by increasing the dose to 36 mg bid, without compromising safety. The results with 36 mg bid were first compared to warfarin and showed superior efficacy while revealing no difference in bleeding rates. The results with the 24-mg bid dose were then compared to warfarin. These results showed that ximelagatran 24 mg bid was numerically better than warfarin, but again did not show statistically superior efficacy to warfarin. Based on these results, ximelagatran 36 mg bid was chosen for the second pivotal study, EXULT B (SH-TPO-0012).

4.2.2.2 Secondary prevention of VTE

Based on the results of the Phase II trial, METHRO II (SH-TPO-0002), the secondary prevention of VTE (the first chronic indication evaluated) compared ximelagatran 24 mg bid to placebo in the long-term (up to 18-months) secondary prevention of VTE (THRIVE III, SH-TPV-0003). This dose was believed to be high enough to fulfill the efficacy objectives and low enough to minimize the risk of AEs, particularly bleeding, during long-term prophylactic treatment.

4.2.2.3 Prevention of stroke and SEEs in AF

Effects on thrombus growth and thrombus formation, respectively, across the concentrations and doses evaluated in the Phase II studies, influenced the selection of 20-mg, 40-mg, and 60-mg doses for twice-daily ximelagatran in the Phase II AF study (SPORTIF II, SH-TPA-0002). These doses were expected to bracket the plasma concentrations seen in earlier Phase I trials and the Phase II METHRO II (SH-TPO-0002) trial.

The low stroke rate in the anticoagulant-treated population would have necessitated a very large dose-finding study to detect a statistical difference between treatments based on prevention of stroke as an endpoint. Therefore, dose selection for the Phase III studies was based mainly on consideration of risk in the patient population and of safety criteria.

SPORTIF II (SH-TPA-0002) suggested better safety in the 20-mg and 40-mg dose groups than in the 60-mg dose group, with more minor bleeding events at the 60-mg dose. No differences in efficacy were observed but, based on the experience in OS, the 40-mg dose was chosen over the 20-mg dose because a higher dose of ximelagatran was considered appropriate given the greater severity of risk of stroke. Thus, the long-term follow-up study SPORTIF IV (SH-TPA-0004) proceeded at the 40-mg dose. Replacement of the 40-mg dose with 36 mg occurred following a decision within the ximelagatran clinical program to dose in multiples of 12 mg. The 2 pivotal studies, SPORTIF III (SH-TPA-0003) and SPORTIF V (SH-TPA-0005) used ximelagatran 36 mg bid.

4.2.2.4 Summary of ximelagatran dose selection

An extensive program of studies in a number of indications has demonstrated that ximelagatran is effective at doses of 24 mg bid and 36 mg bid, with no increased risk of bleeding. Doses less than 24 mg have proven to be less effective and doses greater than 36 mg bid have provided no incremental efficacy in the patient populations studied.

5. EFFICACY OF XIMELAGATRAN IN THE PREVENTION OF THROMBOTIC DISEASE

5.1 Introduction

The clinical efficacy program included 22 Phase II and Phase III studies, incorporating 5 pivotal, primarily outcome-based, trials in 3 patient populations. Each pivotal study was the largest ever conducted in its indication and included representative patient populations at risk of life-threatening thromboembolic events. During these 5 pivotal trials, more than 13000 patients were exposed to ximelagatran, of which almost 60% were randomized in North America, including the US, Canada, and Mexico (Table 12). This section presents the effectiveness of ximelagatran as an anticoagulant in these 5 Phase III pivotal trials in comparison to the current standard of treatment in each of the indications being sought. These studies have demonstrated that at a fixed-dose and without coagulation monitoring or dosage adjustment, ximelagatran is an effective oral anticoagulant compared to placebo and comparators in the 3 indications being sought.

Table 12 Number (%) of patients by country or region in each pivotal study (ITT population)

	VTE secondary prevention (THRIVE III)	VTE prophylaxis following surgery (EXULT A and EXULT B)		Stroke prophylaxis (SPORTIF III and SPORTIF V)		
Country or region	**SH-TPV-0003 (n=1223)**	**SH-TPO-0010 (n=2285)**	**SH-TPO-0012 (n=2299)**	**SH-TPA-0003 (n=3407)**	**SH-TPA-0005 (n=3922)**	**Total (n=13136)**
US	–	949 (42)	931 (41)	–	3266 (83)	5146 (39)
Canada	34 (3)	845 (37)	618 (27)	–	656 (17)	2153 (16)
Mexico	62 (5)	184 (8)	285 (12)	–	–	531 (4)
South America[a]	44 (4)	84 (4)	382 (17)	–	–	510 (4)
Europe[b]	982 (80)	–	–	2787 (82)	–	3769 (29)
Rest of world[c]	101 (8)	223 (10)	83 (4)	620 (18)	–	1027 (8)

[a] Argentina and Brazil.
[b] Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Italy, Norway, Poland, Portugal, Republic of Ireland, Russia, Spain, Sweden, United Kingdom.
[c] Hong Kong, Japan, Malaysia, Philippines, Taiwan, Australia, New Zealand, Israel, South Africa.
ITT Intention-to-treat, VTE Venous thromboembolism; US United States.

5.2 Ximelagatran for the extended secondary prevention of VTE

There is one pivotal trial for this indication: THRIVE III (SH-TPV-0003).

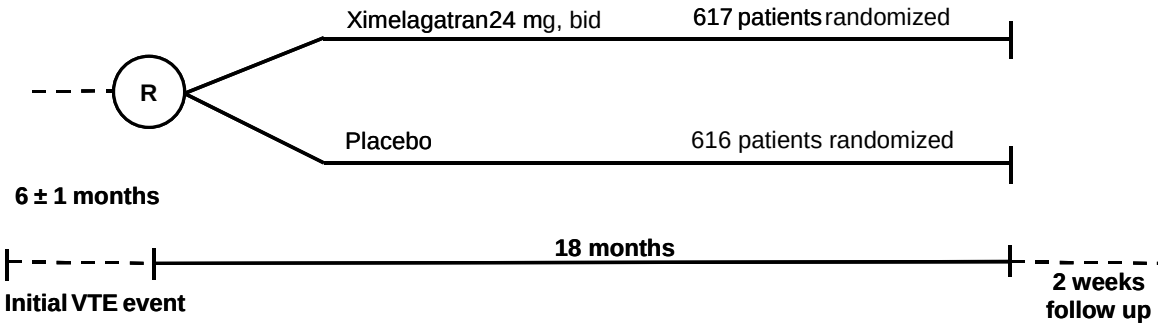
5.2.1 THRIVE III (SH-TPV-0003)

The overall objectives of this clinical program were to document that patients with a previous VTE would benefit from extended prophylactic treatment with ximelagatran after having completed a period of anticoagulant treatment for an episode of VTE, and to determine if oral ximelagatran can provide the efficacy and safety needed for prolonged anticoagulation. At the time the THRIVE III study was designed and initiated (1999), the optimal duration of oral anticoagulant prevention after a VTE event was a matter of debate. Clinical trial results at the time showed that at least 3 months of anticoagulation after a first episode of VTE led to lower recurrence rates than did shorter terms of treatment (Schulman et al 1995, Kearon et al 1999), and that oral anticoagulation continued for an indefinite period after a secondary episode of VTE was associated with a much lower rate of recurrence during 4 years of follow-up than treatment for 6 months (Schulman et al 1997). A major drawback to this therapy was an annual 3% to 4% risk of major bleeding events (Schulman et al 1995, Kearon et al 1999, Agnelli et al 2001), and the inconvenience of ongoing coagulation monitoring. ACCP Consensus Conference Recommendations then, and currently, advocate antithrombotic therapy of an acute episode of VTE for 3 to 6 months (Hyers et al 1998, Hyers et al 2001).

The clinical development program for the long-term, secondary prevention of VTE consisted of one therapeutic, confirmatory pivotal study, THRIVE III (SH-TPV-0003), designed to show superiority of oral ximelagatran to placebo. US regulatory guidance details certain characteristics of a single pivotal study that can contribute to the conclusion that the study adequately supports an effectiveness claim. Such characteristics include a high degree of statistical significance, consistency across subsets, and a large multicenter study with no single center dominating the overall results. All of these characteristics were present in this study. Furthermore, the THRIVE III (SH-TPV-0003) study is supported by accumulating evidence of substantial risk of recurrence beyond 6 months (Schulman et al 1997, Heit et al 2001) and that there is benefit to extended anticoagulation therapy (Ridker et al 2003, Kearon et al 2003).

THRIVE III (SH-TPV-0003) was a double-blind, randomized, placebo-controlled, parallel-group multicenter study comparing the efficacy and safety of oral ximelagatran 24 mg bid with placebo over a period of up to 18 months in patients who had completed 6 months of anticoagulant treatment for an episode of VTE. The primary objective was to assess whether ximelagatran reduced the recurrence rate of symptomatic, objectively confirmed VTE events compared to placebo (time to event analysis). An independent Adjudication Committee blinded to treatment allocation, to ensure objective evaluation and the use of uniform diagnostic criteria, assessed all clinical endpoints. The study flow-chart is presented in Figure 16.

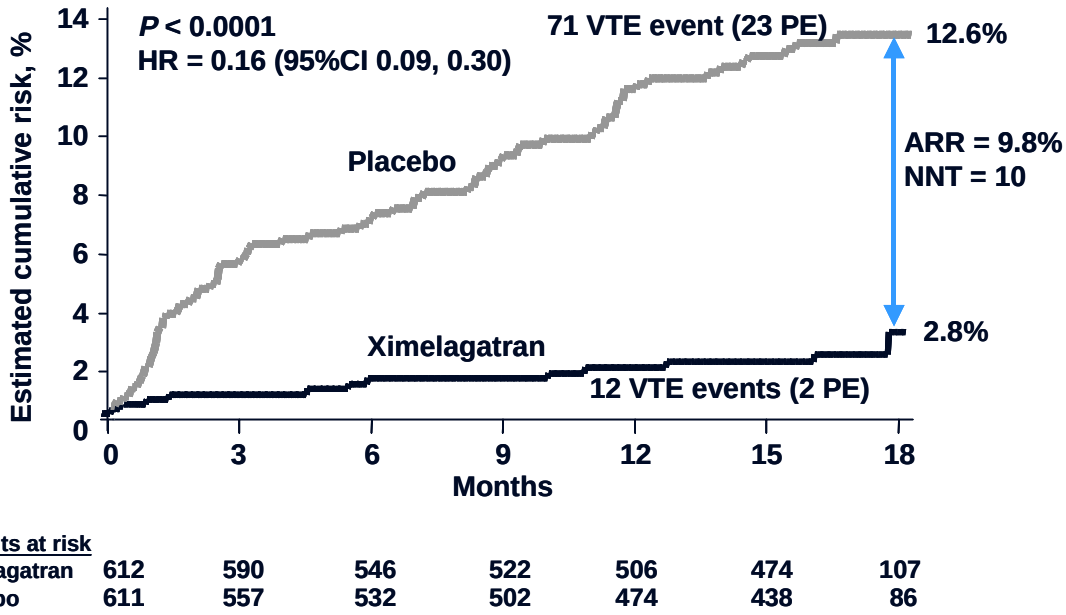
Figure 16 Study design – THRIVE III (SH-TPV-0003)



THRIVE III (SH-TPV-0003) randomized patients in 12 European countries, 2 countries in South America, and in Canada, Mexico, Israel, and South Africa. A total of 1233 patients were randomized, 1223 patients received study drug, with 903 completing the study on the study drug (468 on ximelagatran and 435 on placebo). Efficacy and safety were analyzed in 612 and 611 patients treated with ximelagatran and placebo, respectively. Overall, the treatment groups were comparable for demographic characteristics, baseline parameters, treatment compliance, and use of concomitant medication. Slightly more than 50% of the patients were male, 93% were Caucasian, and the mean age was 57 years (range 18 to 90). Approximately 20% of the patients had some level of renal impairment (CrCL <80 mL/min). This study had no centers in the US; however, the treatment of VTE is uniform globally and demographic results and rates of VTE events for patients enrolled in Canada (n=34) and Mexico (n=62) were consistent with the overall study. Two published studies, investigating long-term prophylactic treatment with warfarin, randomized patient populations in North America and Europe (Kearon et al 2003, Ridker et al 2003). The baseline demographics observed in these 2 studies are similar to those recorded in the THRIVE III (SH-TPV-0003) patient population; mean age in the 3 studies was in the mid fifties, there was an even distribution between males and females, mean BMI was comparable, and a majority of the patients were Caucasian.

THRIVE III (SH-TPV-0003) successfully demonstrated that prophylactic treatment with ximelagatran at a fixed dose of 24 mg bid considerably reduces the risk of recurrent VTE as compared to placebo (estimated cumulative risk 2.8% with ximelagatran versus 12.6% for placebo through up to 18 months of prophylactic treatment; hazard ratio 0.16; 95% CI: 0.09 to 0.30; p<0.0001) (Figure 17). The 9.8% absolute reduction of VTE events corresponds to a NNT of 10, ie, only 10 patients would need to be treated with ximelagatran for up to 18 months to prevent one recurrence of DVT or PE. Ximelagatran also significantly reduced the rate of the composite endpoint all-cause mortality and/or recurrent VTE (hazard ratio 0.23; 95% CI: 0.14 to 0.39; p<0.0001).

Figure 17 **VTE events (primary endpoint), cumulative risk versus time after randomization, THRIVE III (SH-TPV-0003), ITT population**



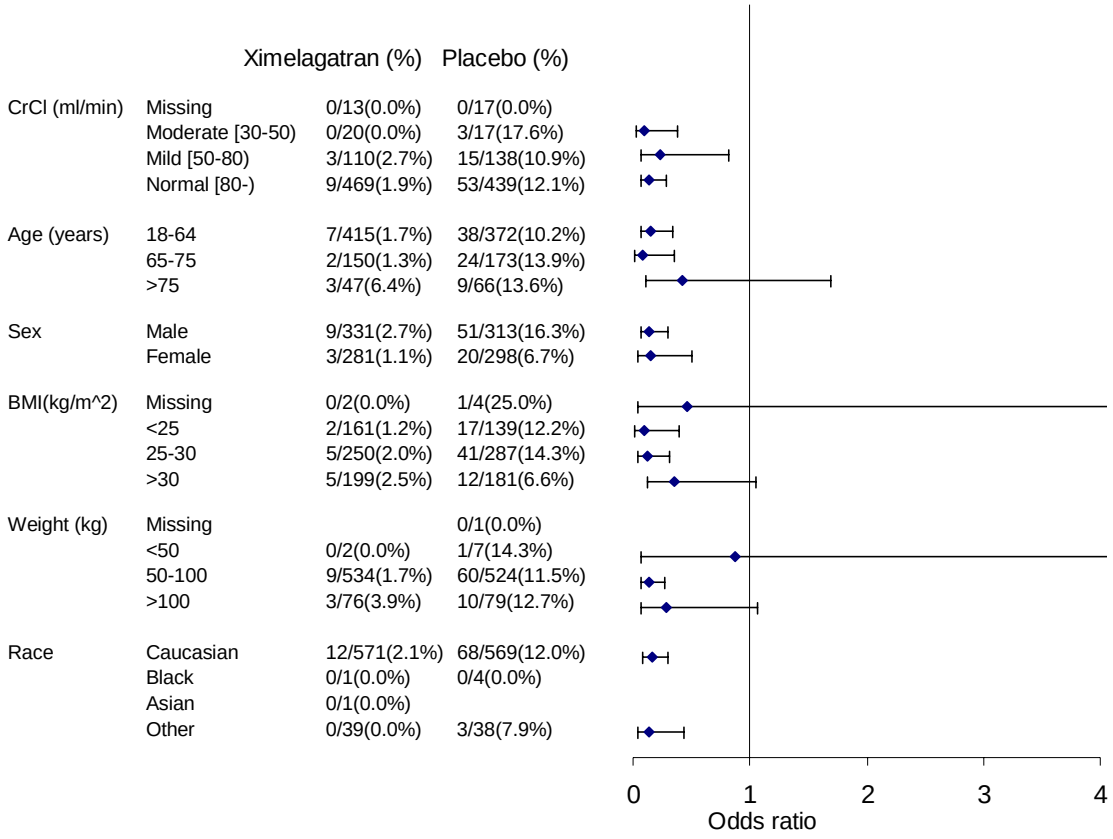
HR Hazard ratio, VTE Venous thromboembolism, ARR Absolute risk reduction, NNT Number needed to treat, PE Pulmonary embolism; CI Confidence interval.

Death by any cause occurred in 6 and 7 patients in the ximelagatran and placebo groups, respectively (hazard ratio 0.83; 95% CI: 0.28 to 2.46; p=0.73). Three deaths due to VTE occurred in the placebo group and none in the ximelagatran group.

Initially, THRIVE III (SH-TPV-0003) was designed with a 2-week follow-up period for all patients. Subsequently, an amendment to the study protocol mandated follow-up of prematurely discontinued patients for VTE events and death during the remainder of the 18-month study period. The combined data were analyzed as a complementary intention-to-treat (ITT) population analysis. The results of the complementary ITT population analyses were consistent with the results of the primary ITT population analyses. The complementary ITT population analyses sets estimated the cumulative risk of an event (VTE and/or death) during up to 18 months of prophylactic treatment at 3.2% and 12.7% for patients on ximelagatran and placebo, respectively. The estimated hazard ratio between treatments according to the complementary ITT population analyses was 0.30 (95% CI: 0.19 to 0.46; p<0.0001).

The efficacy of ximelagatran over placebo was consistent across all subgroups (Figure 18). Superiority was shown for all subgroups with a sample size >50 patients for both subgroups except BMI >30 kg/m2 and weight >100 kg, although the efficacy benefit was maintained in that group as well.

Figure 18 VTE events according to subgroup factors, comparison between treatments with 95% CI, ITT population (THRIVE III, SH-TPV-0003)



The prophylactic treatment regimen of 24 mg oral ximelagatran bid offers a significant, clinically meaningful reduction in the recurrence rate of VTE events compared to placebo during long-term therapy after previous anticoagulant treatment for an episode of VTE. This study supports the use of oral ximelagatran 24 mg bid, without routine coagulation monitoring and without dose adjustment, for the long-term secondary prevention of VTE after standard treatment for an episode of acute VTE.

5.3 Ximelagatran for the prevention of VTE after knee replacement surgery

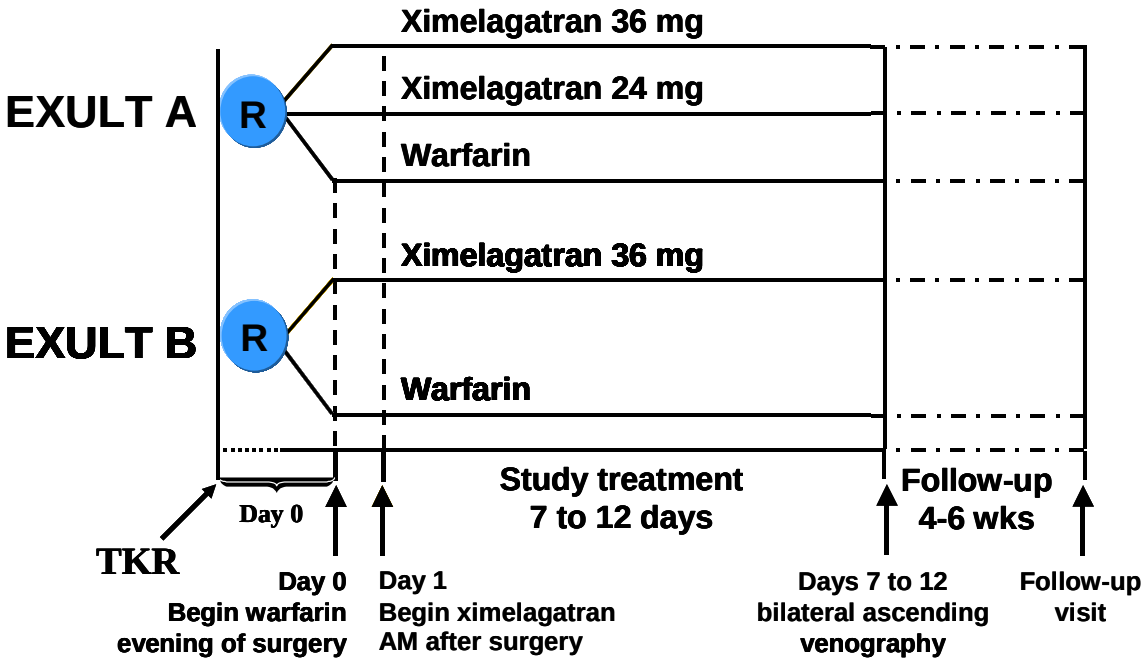
Three double-blind, randomized trials, the initial Phase III study (PLATINUM KNEE, SH-TPO-0006) and the 2 pivotal studies EXULT A (SH-TPO-0010) and EXULT B (SH-TPO-0012), evaluated short-term prophylaxis with ximelagatran 24 mg bid and 36 mg

bid compared to warfarin for the prevention of VTE in patients undergoing knee replacement surgery. EXULT A (SH-TPO-0010) and EXULT B (SH-TPO-0012) are presented in Section 5.3.1 and PLATINUM KNEE (SH-TPO-0006) in Section 5.3.2.

5.3.1 EXULT A and EXULT B (SH-TPO-0010 and SH-TPO-0012)

AstraZeneca evaluated an oral-only regimen of ximelagatran tablets compared to warfarin in 2 large Phase III, double-blind, multicenter, randomized clinical studies in patients undergoing primary elective TKR surgery: EXULT A (SH-TPO-0010) and EXULT B (SH-TPO-0012). A total of 4604 patients were randomized in these 2 studies. Of these, 1927 were randomized to receive ximelagatran 36 mg bid, 762 to ximelagatran 24 mg bid, and 1915 to well-controlled warfarin (target INR of 2.5; range 1.8 to 3.0). The pivotal trials, EXULT A (SH-TPO-0010) and EXULT B (SH-TPO-0012), are the largest TKR-only studies, conducted to date, with the highest reported percentage of evaluable efficacy endpoints available for analysis. These 2 studies are described in this section and the study flow chart is presented in Figure 19.

Figure 19 Study design – EXULT A (SH-TPO-0010) and EXULT B (SH-TPO-0012)



During the EXULT trials (SH-TPO-0010 and SH-TPO-0012) ximelagatran was administered for 7 to 12 days after surgery with follow-up at 4 to 6 weeks after surgery. Ximelagatran was initiated in the morning of the day after surgery to ensure achievement of post-operative hemostasis. Warfarin was begun the evening of the day of surgery with the aim of achieving an INR of 2.5 as soon as possible. The primary endpoint was a composite of the combined incidence of total VTE (including venographic assessment of both the distal and proximal

veins plus symptomatic, objectively confirmed DVT and/or PE) and/or all-cause mortality during the treatment period. An independent Adjudication Committee blinded to treatment allocation, to ensure objective evaluation and the use of uniform diagnostic criteria, assessed all clinical endpoints.

In the Phase III studies of the oral-only TKR surgery program, warfarin was selected as the active comparator because warfarin is a Grade 1A recommended therapy for the prevention of DVT after orthopedic surgery (ACCP Guidelines, Geerts et al 2001) and is the most commonly prescribed agent (used by more than 50% of surveyed practicing orthopedic surgeons) for post TKR surgical prophylaxis in North America (Anderson et al 2003, Mesko et al 2001, Gross et al 1999). When choosing the comparator for this program of trials, the reported benefit-risk of warfarin was considered. The primary advantages of warfarin to OS practice are oral administration and slower onset to reach maximal effect, allowing time for surgical hemostasis to develop but providing prophylaxis soon after. Orthopedic surgeons are especially concerned about bleeding and wound complications. Warfarin is associated with less bleeding events when compared to LMWHs (Hull et al 1993, RD Heparin Arthroplasty Group 1994, Hamulyak et al 1995, Leclerc et al 1996, Heit et al 1997, Fitzgerald et al 2001). Warfarin as an oral VKA is a logical comparator to ximelagatran for orthopedic surgeons who prefer this method of anticoagulation for VTE prevention following TKR surgery.

Initiation of warfarin therapy the evening of the day of surgery was selected because it is a common starting time in clinical practice and is one of the recommended regimens in previously published studies (Francis et al 1997, Leclerc et al 1996, RD Heparin Arthroplasty Group 1994, Hull et al 1993). The target INR for warfarin (INR of 2.5) was selected because it is the INR target recommended by the ACCP Consensus Conference guidelines drawn from clinical trials (Geerts et al 2001). The target INR range (1.8 to 3.0) was selected because of surgeons' preferences for a slightly reduced INR lower range limit in clinical practice to prevent bleeding and is supported by recent studies documenting the use of lower INR ranges in post-surgery patients (Messieh et al 1999, Robinson et al 1997, RD Heparin Arthroplasty Group 1994).

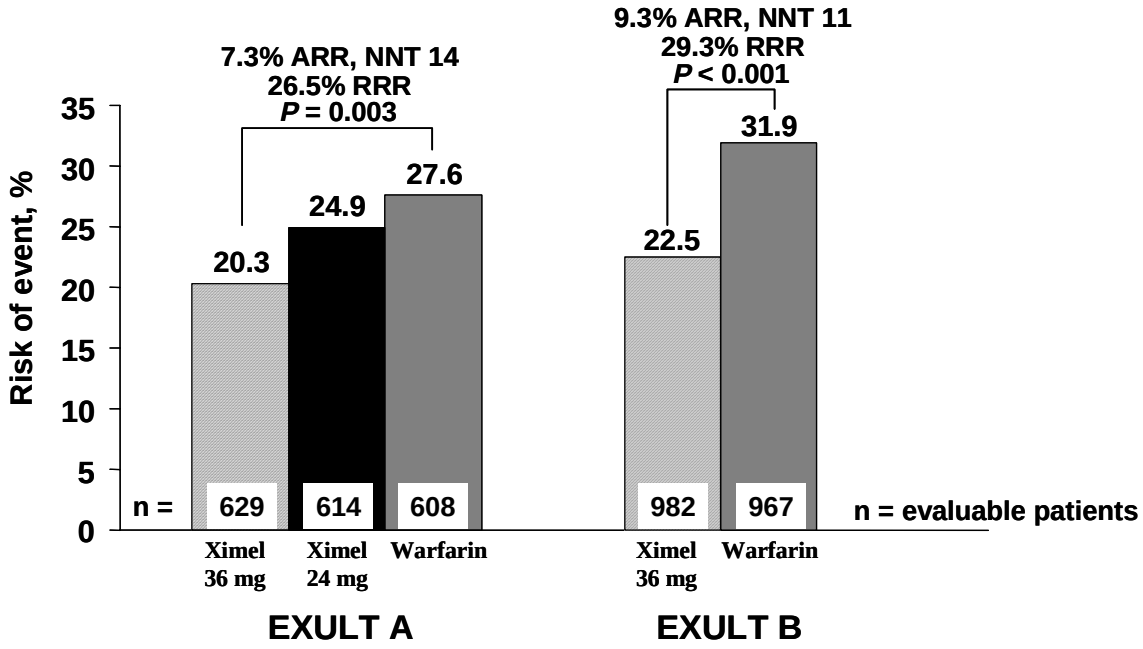
The well-defined endpoint of venographic DVT is an established approach in testing the efficacy of a new prophylactic anticoagulant after orthopedic surgery (Leclerc et al 1992, Colwell et al, 1995, Bauer et al 2001). Based on published studies and the pathophysiology of VTE, post-operative, asymptomatic, venographically confirmed DVT would propagate to proximal DVT in 7% to 32% of these patients (Ohgi et al 1998, Lohr et al 1995 & 1991, Lagerstedt et al 1985, Haas et al 1992, Philbrick and Becker 1988), and to PE in up to 5% of these patients (Haas et al 1992, Lohr et al 1991). The clinical relevance of distal DVT is significant in patients undergoing orthopedic surgery and was a pre-specified endpoint in the design of the Phase III TKR surgery studies.

EXULT A (SH-TPO-0010) and EXULT B (SH-TPO-0012) randomized patients in the US, Canada, Israel, Mexico, and Brazil, with over 75% of the patients randomized in North America. In EXULT A (SH-TPO-0010), a total of 2301 patients were randomized, 1537 to ximelagatran (24 mg n=762, 36 mg n=775) and 764 to warfarin. Demographic and baseline

characteristics were well matched across the 3 treatment groups. Slightly more than 60% of the patients were female, 96% were Caucasian, and the mean age was 68 years (range 32 to 89). Approximately 30% of the patients had some level of renal impairment (CrCL <80 mL/min). EXULT B (SH-TPO-0012) randomized a total of 2303 patients, 1152 to ximelagatran and 1151 to warfarin. Demographic and baseline characteristics were well matched across the treatment groups. Approximately 62% were female, 94% were Caucasian, and the mean age was 67 years (range 26 to 91). Approximately 30% of the patients had some level of renal impairment (CrCL <80 mL/min). The demographics of the randomized population, in both studies, were representative of the target population for this indication (Premier Health Informatics 2003, InpatientView 2002).

The 2 pivotal studies, EXULT A (SH-TPO-0010) and EXULT B (SH-TPO-0012), demonstrated efficacy superior to well-controlled warfarin. Each of these 2 trials met its primary objective: statistically significant improvements with oral ximelagatran 36 mg bid over well-controlled warfarin in preventing the composite of VTE (including both DVT and PE) and all-cause mortality in patients undergoing primary elective TKR surgery. The frequency of total VTE and/or all-cause mortality in EXULT A (SH-TPO-0010) was 24.9% (ximelagatran 24 mg), 20.3% (ximelagatran 36 mg) and 27.6% (warfarin). In EXULT B (SH-TPO-0012), the frequency rates were 22.5% for the ximelagatran group and 31.9% for the warfarin group. Absolute risk reductions (ARRs) of 7.3% ($p=0.003$) and 9.3% ($p<0.001$) were demonstrated with oral ximelagatran 36 mg bid compared to well-controlled warfarin in EXULT A (SH-TPO-0010) and EXULT B (SH-TPO-0012), respectively (Figure 20).

Figure 20 **Total VTE and mortality in TKR - EXULT A (SH-TPO-0010) and EXULT B (SH-TPO-0012)**



VTE Venous thromboembolism (includes both distal and proximal deep vein thrombosis, plus pulmonary embolism), TKR Total knee replacement; ARR absolute risk reduction; NNT number needed to treat; RRR relative risk reduction; Ximel ximelagatran.

In EXULT A (SH-TPO-0010), no statistical significance was seen with ximelagatran 24 mg versus well-controlled warfarin, although the VTE rate was numerically lower for ximelagatran 24 mg (24.9%) than for warfarin (27.6%). The rate of the composite secondary endpoint of proximal DVT, PE, and all-cause mortality was numerically lower for ximelagatran 36 mg (2.7%) and 24 mg (2.5%) than for warfarin (4.1%), but the difference was not statistically significant (p=0.171 and 0.104, respectively). When local venography assessments were analyzed for EXULT A (SH-TPO-0010), the incidence of total VTE and all-cause mortality was statistically significantly lower in the ximelagatran 36-mg group (29.6%) compared with the warfarin group (37.7%) (p=0.002), but not when comparing the ximelagatran 24-mg group with warfarin (33.4%) (p=0.108). Symptomatic DVT and PE were uncommon overall, and did not differ among the groups. The number of symptomatic DVTs during the treatment period with ximelagatran 36 mg and 24 mg, and warfarin was 7 (1.1%), 5 (0.8%), and 9 (1.5%), respectively. In the ximelagatran groups, 1 (36 mg) and 1 (24 mg) symptomatic DVTs occurred during the follow-up period. In the warfarin group no symptomatic DVTs occurred during the follow-up period. The number of symptomatic PEs during the treatment period, with ximelagatran 36 mg and 24 mg, and warfarin was 2 (0.3%), 2 (0.3%), and 0 (0.0%), respectively. During the follow-up period, the corresponding

numbers were 0, 1, and 1. The low number of events and comparable numbers between the treatment groups during follow-up (4 to 6 weeks) indicates no withdrawal or rebound phenomena following short-term exposure to ximelagatran.

In EXULT B (SH-TPO-0012), the rate of the composite secondary endpoint of proximal DVT, PE, and all-cause mortality was numerically lower for ximelagatran 36 mg (3.9%) than for warfarin (4.1%), but the difference was not statistically significant (p=0.802). When local venography assessments were analyzed for EXULT B (SH-TPO-0012), the incidence of total VTE and all-cause mortality was statistically significantly lower in the ximelagatran 36-mg group (30.1%) compared with the warfarin group (35.8%) (p=0.007). Symptomatic DVT and PE were uncommon overall, and did not differ between the groups. The number of symptomatic DVTs during the treatment period with ximelagatran 36 mg and warfarin was 8 (0.8%) and 15 (1.6%), respectively. During the follow-up period the numbers were 3 and 1, respectively. The number of symptomatic PEs during the treatment period with ximelagatran 36 mg and warfarin was 2 (0.2%) and 5 (0.5%); 1 PE occurred during follow-up in the ximelagatran group and 0 in the warfarin group. Again, the low number of events and comparable numbers between the treatment groups during follow-up (4 to 6 weeks) indicates no withdrawal or rebound phenomena following short-term exposure to ximelagatran.

In the pooled EXULT A (SH-TPO-0010) and EXULT B (SH-TPO-0012) analyses, the incidence of total VTE and/or all-cause mortality among patients undergoing TKR surgery 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 a relative risk reduction (RRR) of 28.1% and a number needed to treat (NNT) to obtain a benefit (1/ARR) of 12 (95% CI: 9 to 18).

A high percentage of the randomized patients (80.7% in EXULT A [SH-TPO-0010] and 84.8% in EXULT B [SH-TPO-0012]) completed the protocol treatments, assessments, and had evaluable venograms for independent objective evaluation, ensuring an accurate and unbiased comparison for the efficacy and safety outcomes. Among the patients assigned to warfarin in the EXULT trials (SH-TPO-0010 and SH-TPO-0012), the INR value was ≥1.8 in approximately 65% of patients by post-operative Day 3 (mean INR 2.4) and in approximately 75% of patients by the day of venography (mean INR 2.4). There were no differences in mean INR values between patients with and without VTE when compared for each day.

Eight patients died during EXULT A (SH-TPO-0010): 2 in the ximelagatran 24-mg treatment group, 4 in the ximelagatran 36-mg treatment group, and 2 in the warfarin treatment group. Of the 8 deaths, one occurred in each of the treatment groups during the study treatment period. Ten patients died during EXULT B (SH-TPO-0012): 7 in the ximelagatran 36-mg treatment group and 3 in the warfarin treatment group. Six of the 10 deaths occurred while patients were receiving treatment (4 in the ximelagatran group and 2 in the warfarin group).

Subgroup analyses of the 36-mg Pool and 24-mg Pool, and PK exposure-response analyses, did not reveal a subgroup with significantly different efficacy from the entire population. No subgroup indicated that a different dose might be necessary (Figure 21 and Figure 22). There

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

Figure 21 **Efficacy events according to subgroup factors for the 36-mg Pool, comparison between treatments with 95% CI, ITT population (EXULT A [SH-TPO-0010] and EXULT B [SH-TPO-0012])**

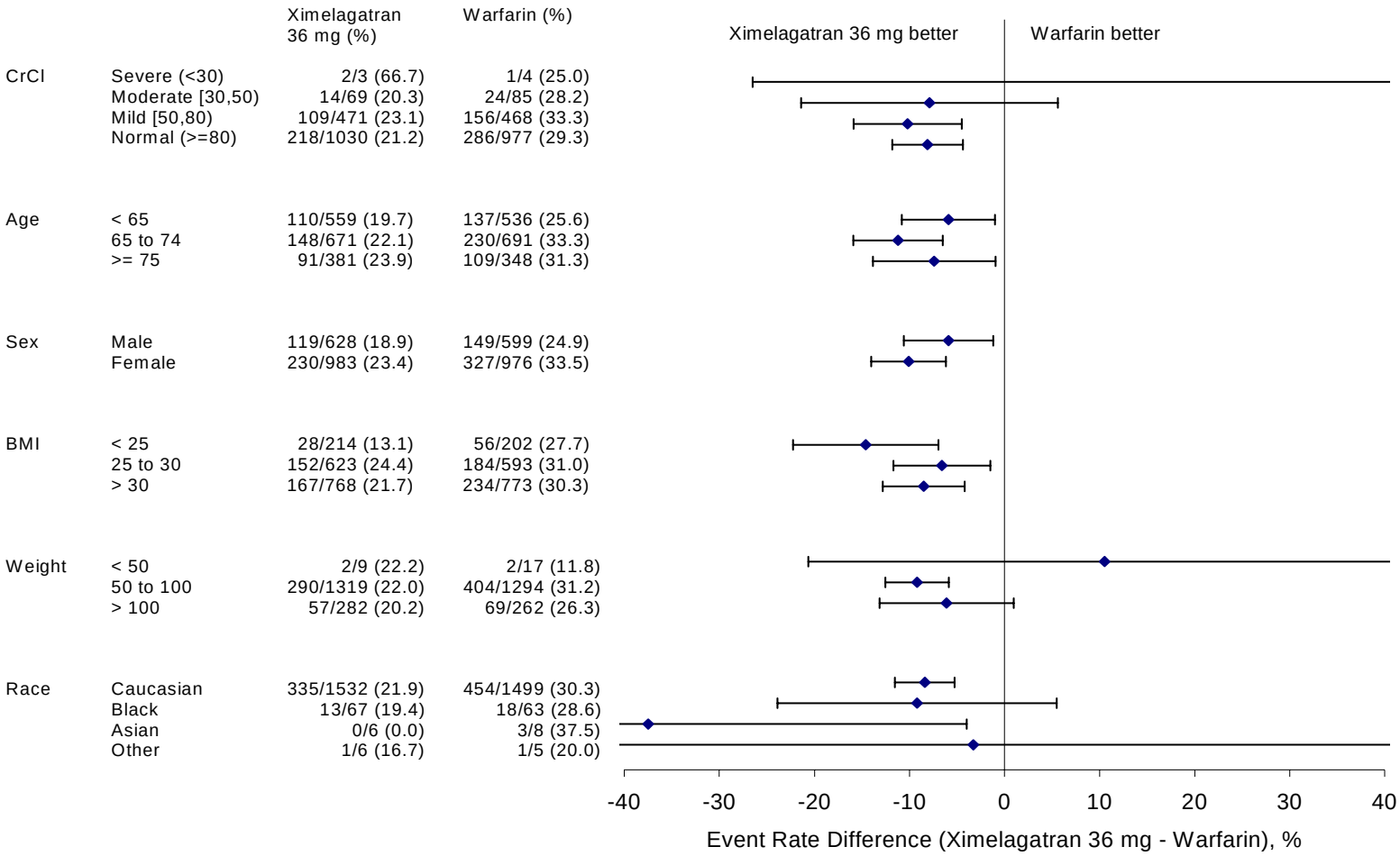
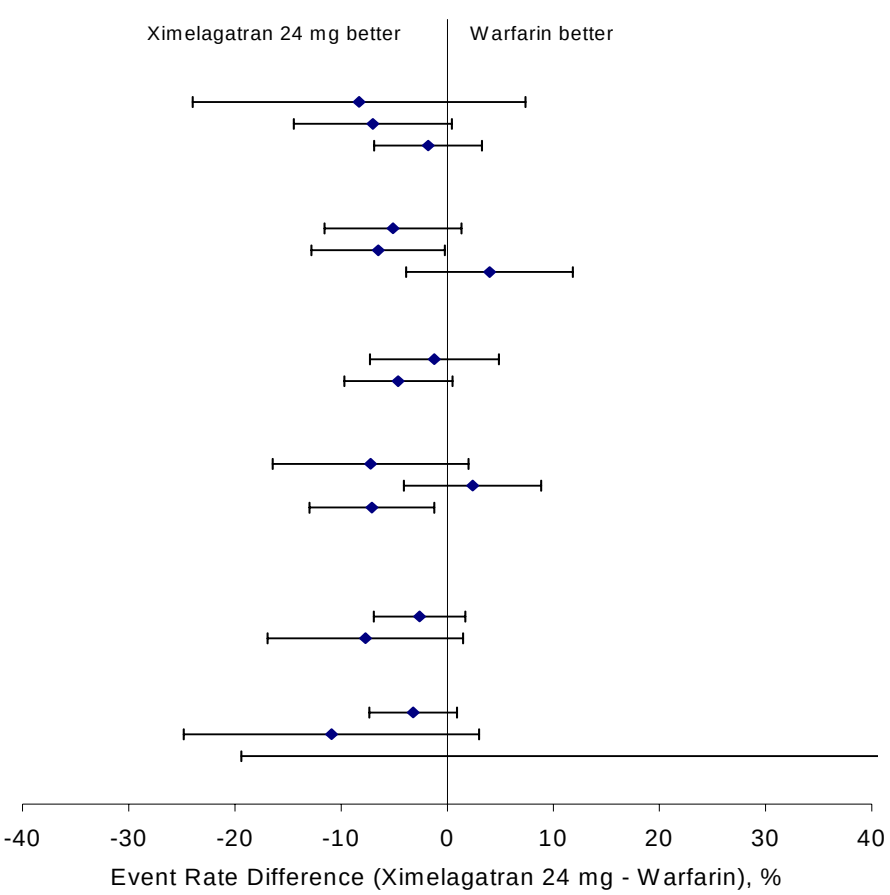


Figure 22 **Efficacy events according to subgroup factors for the 24-mg Pool, comparison between treatments with 95% CI, ITT population (EXULT A [SH-TPO-0010] and PLATINUM KNEE [SH-TPO-0006])**

		Ximelagatran 24 mg (%)	Warfarin (%)
CrCl	Severe (<30)	0/2 (0.0)	0/3 (0.0)
	Moderate [30,50)	9/54 (16.7)	12/48 (25.0)
	Mild [50,80)	54/257 (21.0)	73/261 (28.0)
	Normal (>=80)	121/541 (22.4)	130/539 (24.1)
Age	< 65	46/276 (16.7)	63/289 (21.8)
	65 to 74	84/372 (22.6)	106/364 (29.1)
	>= 75	61/236 (25.8)	47/215 (21.9)
Sex	Male	71/341 (20.8)	75/340 (22.1)
	Female	120/543 (22.1)	141/528 (26.7)
BMI	< 25	16/123 (13.0)	25/124 (20.2)
	25 to 30	81/331 (24.5)	73/331 (22.1)
	> 30	90/424 (21.2)	114/403 (28.3)
Weight	< 50	0/5 (0.0)	0/6 (0.0)
	50 to 100	154/706 (21.8)	171/700 (24.4)
	> 100	34/169 (20.1)	45/162 (27.8)
Race	Caucasian	186/840 (22.1)	208/820 (25.4)
	Black	3/41 (7.3)	8/44 (18.2)
	Asian	1/2 (50.0)	0/4 (0.0)
	Other	1/1 (100.0)	0/0 (0.0)



Oral ximelagatran 36 mg bid was superior to well-controlled warfarin in reducing the incidence of the composite endpoint of total VTE and all-cause mortality in patients undergoing primary elective TKR surgery. These studies support the use of oral ximelagatran 36 mg bid for 7 to 12 days after surgery (beginning the morning of the day after surgery) in the prevention of VTE in patients undergoing knee replacement surgery.

5.3.2 PLATINUM KNEE (SH-TPO-0006)

The initial, Phase III, double-blind, double-dummy, parallel-group, multicenter study was conducted in this indication to assess the efficacy of oral ximelagatran 24 mg bid begun at least 12 hours after surgery versus oral warfarin begun the evening of the day of surgery, and titrated to a target INR 2.5 (INR range 1.8 to 3.0) in preventing VTE in patients undergoing TKR surgery. Treatment duration was 7 to 12 days, with follow-up at 4 to 6 weeks after surgery. The primary objective was to establish superior efficacy of ximelagatran compared with warfarin for the prevention of VTE in TKR patients after unilateral or bilateral TKR surgery. Efficacy was assessed by the number of patients in each treatment group with confirmed distal and/or proximal DVT and or symptomatic PE during the treatment period as determined by the independent Adjudication Committee.

A total of 680 patients were randomized in PLATINUM KNEE (SH-TPO-0006), 348 patients to ximelagatran 24 mg and 332 patients to well-controlled warfarin. Demographic and baseline characteristics were well matched across the treatment groups. Approximately 64% were female, 92% were Caucasian, and the mean age was 68 years (range 24 to 90).

In the PLATINUM KNEE study (SH-TPO-0006), the rate of total VTE was numerically lower for ximelagatran (19.2%) than for warfarin (25.7%), but the difference was not statistically significant (p=0.07). For the secondary endpoint, the rate of proximal DVT and/or PE was numerically lower for ximelagatran (3.3%) than for warfarin (5.0%), but the difference was not statistically significant (p=0.316).

Although this study concluded that patients treated with oral ximelagatran 24 mg bid had numerically lower rates of VTE than those treated with well-controlled warfarin, the difference did not reach statistical significance. Based on these findings, the program was developed further with EXULT A (SH-TPO-0010) and EXULT B (SH-TPO-0012), designed to confirm these results and study the ximelagatran dose of 36 mg bid.

5.4 Ximelagatran for the prevention of stroke and SEEs in AF

In this third objective of the clinical development program, AstraZeneca conducted 2 independent, pivotal trials, nearly identical in design, to evaluate fixed-dose oral ximelagatran relative to well-controlled warfarin in the prevention of all strokes (ischemic and hemorrhagic) and systemic embolism, in patients with nonvalvular AF. SPORTIF III (SH-TPA-0003) and SPORTIF V (SH-TPA-0005) are the largest clinical trials to date for this indication.

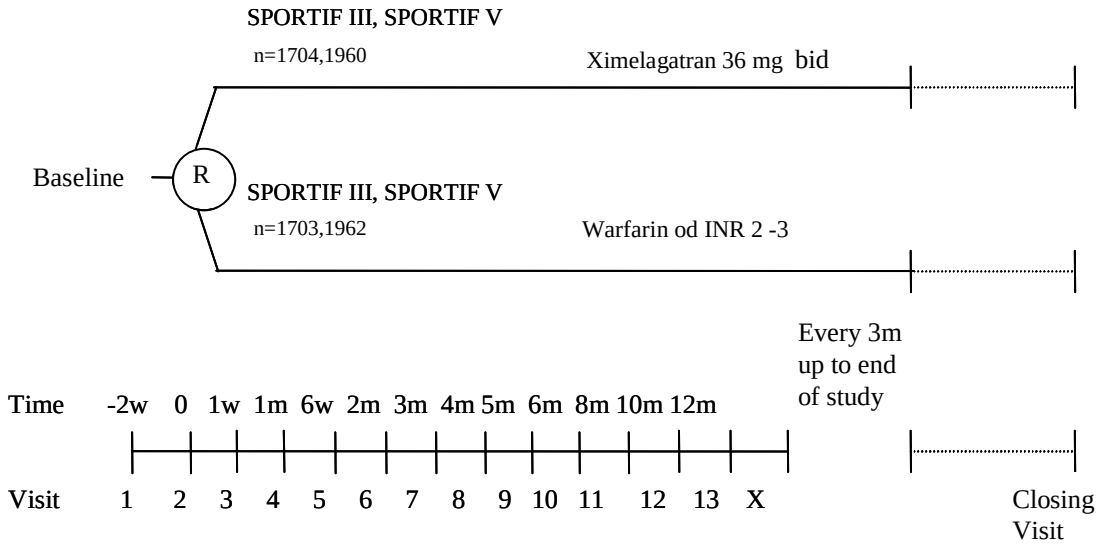
5.4.1 SPORTIF III and SPORTIF V (SH-TPA-0003 and SH-TPA-0005)

Patients entering each of the SPORTIF trials had persistent or paroxysmal AF and fulfilled the ACCP Guideline criteria for oral anticoagulant prophylaxis (Albers et al 2001), ie, the presence of one or more of the following:

- History of prior stroke, TIA, or systemic embolism
- Age at least 75 years
- History of hypertension
- Congestive heart failure or poor left ventricular function
- Age at least 65 years AND coronary artery disease
- Age at least 65 years AND diabetes mellitus.

Most prior stroke prevention trials in AF utilized an open-label format, because of the difficulties of blinding anticoagulation tests and dosage adjustments. SPORTIF III (SH-TPA-0003), conducted open-label, included 2 levels of blinding to treatment to decrease potential bias of the open-label design. First, local study-affiliated neurologists blinded to treatment assessed primary endpoints. Second, an independent, central Adjudication Committee blinded to treatment evaluated all study endpoint events. To conduct SPORTIF V (SH-TPA-0005) in double-blind fashion, patients received double-dummy study medications, ie, either warfarin and placebo ximelagatran, or ximelagatran and placebo warfarin. Blinding of INR values occurred by transmission of test results, determined by either central laboratory or point-of-care machine with encryption, to a separate, centralized service that faxed real or sham INR values to the site based on treatment group. SPORTIF V (SH-TPA-0005) utilized the same independent, central Adjudication Committee for study endpoints that SPORTIF III (SH-TPA-0003) used. Figure 23 outlines the study designs of SPORTIF III (SH-TPA-0003) and SPORTIF V (SH-TPA-0005).

Figure 23 Study design - SPORTIF III (SH-TPA-0003) and SPORTIF V (SH-TPA-0005)



w weeks; m months; R randomization.

Many patients were already receiving warfarin anticoagulation for stroke prophylaxis at study entry. These patients discontinued warfarin therapy in sufficient time to achieve an INR of 2.0 or less at the time of study randomization. All patients randomized, whether dosed or not, constituted the ITT population, which formed the basis for the primary analysis. Because the primary analysis proceeded in non-inferiority fashion (see Section 5.4.2), an on-treatment (OT) analysis of the identical cohort, that discounts events occurring beyond 30 continuous or 60 cumulative days without study treatment, accompanies the ITT analysis.

SPORTIF III (SH-TPA-0003) randomized patients in 23 countries; Australia, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hong Kong, Hungary, Iceland, Ireland, Italy, Japan, Malaysia, New Zealand, Norway, Poland, Philippines, Portugal, Spain, Sweden, Taiwan and United Kingdom. The dynamic allocation system used in SPORTIF III (SH-TPA-0003) randomized 1704 patients to ximelagatran and 1703 patients to warfarin. The 2 treatment groups displayed nearly identical demographic profiles, with 69% male, 88% Caucasian, and mean age of 70 years (range 29 to 92). Most patients (92%) had persistent AF; 79% had AF for more than 1 year. Approximately 70% of patients had 2 or more risk factors for stroke in addition to AF. At enrollment, 73% had been receiving a VKA and 21% ASA. Nine percent (9%) of patients withdrew from SPORTIF III (SH-TPA-0003) prematurely; the most common cause for withdrawal was death. Patients spent a median of 18 months in the trial, with 94% completing at least 12 months, for a total of 4941 patient years.

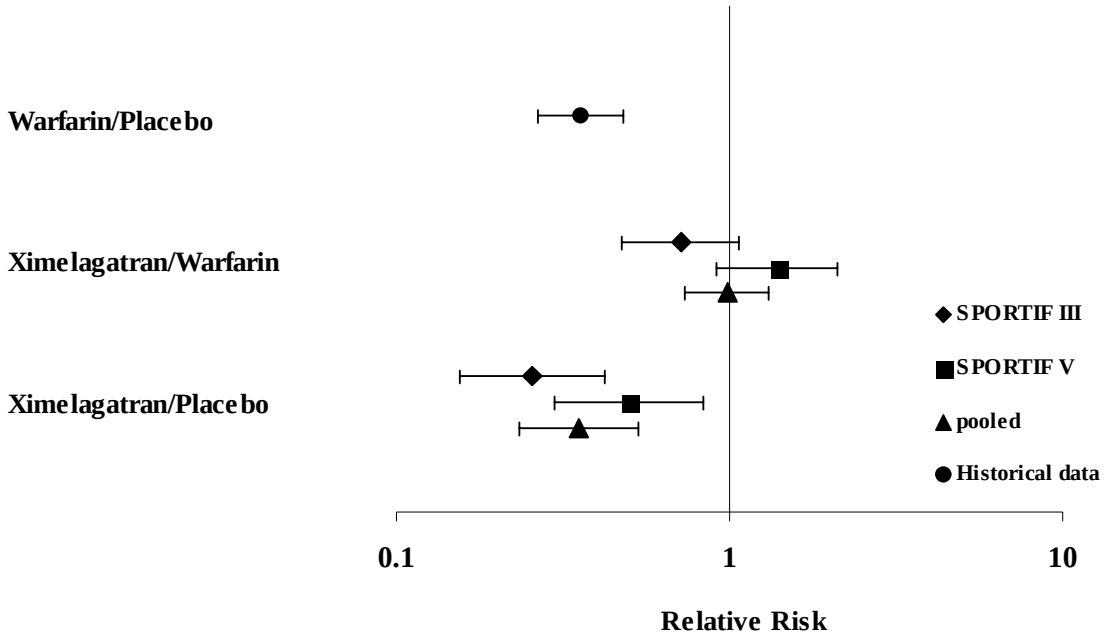
SPORTIF V (SH-TPA-0005) randomized patients in the US and Canada. The dynamic allocation system in SPORTIF V (SH-TPA-0005) randomized 1960 patients to ximelagatran and 1962 patients to warfarin. The 2 treatment groups displayed nearly identical demographic profiles, with 69% male, 96% Caucasian, and mean age of 72 years (range 30 to 97). Most patients (86%) had persistent AF; 84% had AF for more than 1 year. Approximately 74% of patients had 2 or more risk factors for stroke in addition to AF. At enrollment, 84% had been receiving a VKA and 20% ASA. SPORTIF V (SH-TPA-0005) did not enroll Black patients in proportion to that group's representation in the US population, despite particular efforts to include such subjects. However, in a large cohort of patients with heart failure, Blacks had 49% lower odds of having AF (Ruo et al 2004). This racial imbalance in the incidence of AF would directly impact recruitment, and partially explains the racial distribution in SPORTIF V (SH-TPA-0005). Fifteen percent (15%) of patients withdrew from SPORTIF V (SH-TPA-0005) prematurely; the most common cause of withdrawal was death. Patients spent a median of 20.5 months in the trial, with 94% completing at least 12 months, for a total of 6405 patient years duration.

The ximelagatran- and warfarin-treated cohorts displayed nearly identical demographic profiles in each pivotal trial. The patients randomized reflect well the target population of those people with nonvalvular AF requiring anticoagulation for stroke prophylaxis, ie, elderly, predominantly male, and many with modestly impaired renal function. More than one-fifth had had a prior stroke, TIA, or systemic embolism. Patients commonly suffered from concomitant cardiovascular diseases such as hypertension, coronary artery disease, congestive heart failure, and diabetes mellitus.

The INR control in the warfarin treatment groups of SPORTIF III (SH-TPA-0003) and SPORTIF V (SH-TPA-0005) were within the range of 2.0 to 3.0 for 66% and 68% of the study period, respectively confirms that the warfarin-treated cohorts received well-controlled warfarin management and constituted appropriate comparator groups for ximelagatran.

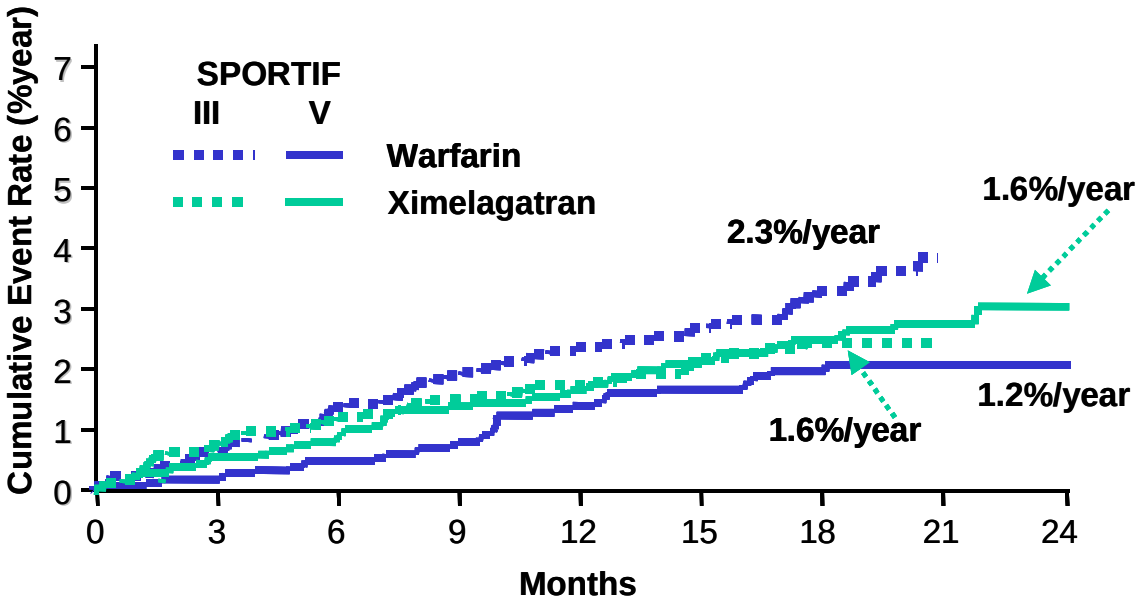
Establishing efficacy of ximelagatran over placebo in AF patients was a prerequisite for the analysis of non-inferiority versus warfarin. Since no direct data were available to compare ximelagatran and placebo, historical data from published studies comparing warfarin to placebo were used. A meta-analysis, using original data from the 6 prior stroke prevention studies was performed (BAATAF 1990, Connolly et al 1991, EAFT 1993, Ezekowitz et al 1992, Petersen et al 1989, SPAF 1991), using an identical primary outcome (all stroke and SEE) to the SPORTIF program. An advantage over placebo was to be declared if the upper limit of the 2-sided 95% CI around the estimated risk ratio for ximelagatran relative to placebo was less than unity. Both SPORTIF trials (SH-TPA-0003 and SH-TPA-0005) demonstrated superiority to placebo (Figure 24). In SPORTIF III (SH-TPA-0003), ximelagatran exhibited a 75% relative risk reduction (95% CI: 58% to 85%) relative to placebo. In SPORTIF V (SH-TPA-0005), ximelagatran exhibited a 50% relative risk reduction (95% CI: 17% to 70%) relative to placebo.

Figure 24 **Indirect efficacy comparison of ximelagatran versus placebo using historical data of previous warfarin trials and SPORTIF III (SH-TPA-0003), SPORTIF V (SH-TPA-0005) and pooled analysis (ITT population)**



In SPORTIF III (SH-TPA-0003), primary events occurred at a rate of 2.3% per year for warfarin and 1.6% per year for ximelagatran. In SPORTIF V (SH-TPA-0005), the corresponding rates were 1.2% per year and 1.6% per year (Figure 25). The warfarin group rates of 1.2% and 2.3% per year fall within the range of warfarin rates in previous trials of stroke prevention: 0.61% to 4.14% per year. For comparison, the pooled placebo rate in prior stroke trials for patients at similar risk was more than 8% per year.

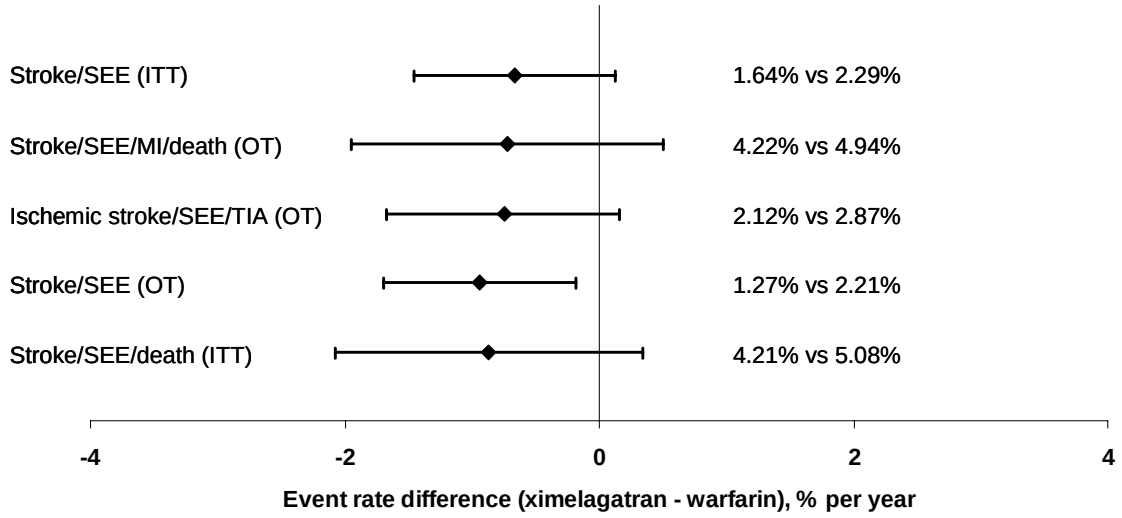
Figure 25 **Cumulative proportion of patients with stroke and/or SEE over time – estimated Kaplan-Meier curves (ITT population) (SPORTIF III, SH-TPA-0003 and SPORTIF V, SH-TPA-0005)**



SEE Systemic embolic event, ITT Intention-to-treat.

SPORTIF III (SH-TPA-0003) met its primary objective with a wide margin: 40 patients sustained primary events (1.6% per year) in the ximelagatran group compared with 56 (2.3% per year) in the warfarin group, yielding an event rate difference of –0.66% per year (95% CI: –1.45% to 0.13% per year), well within the pre-specified 2% non-inferiority margin (Figure 26). Of these patients, 4 in the ximelagatran group and 9 in the warfarin group had hemorrhagic strokes. Sensitivity analyses, as well as secondary analyses, tested the robustness of the primary results (Figure 26). In all instances, these analyses provided results consistent with the primary outcome results. In particular, primary events plus all-cause mortality, analyzed by ITT, yielded an event rate difference of –0.87% per year (95% CI: –2.09 to 0.34) (Figure 26).

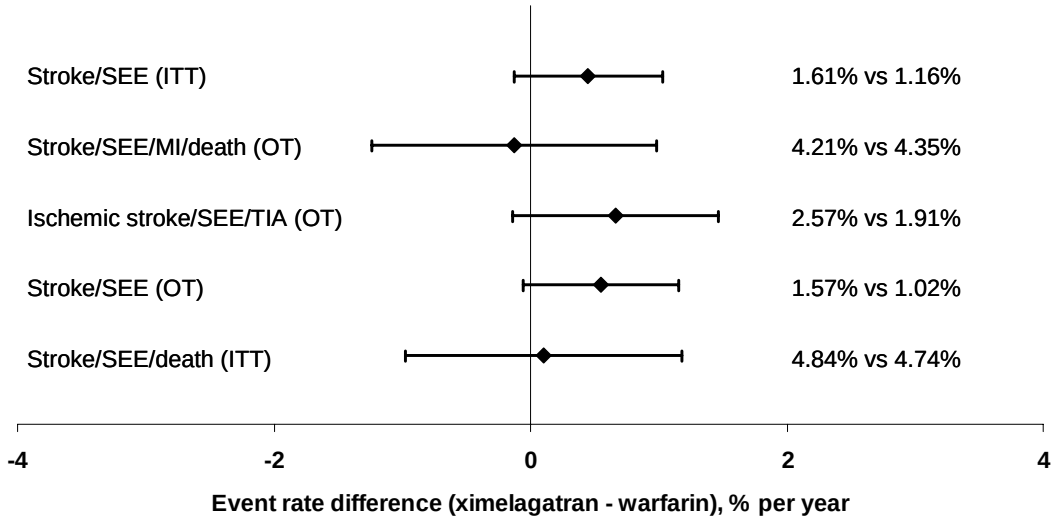
Figure 26 **Summary of primary efficacy results, sensitivity analyses and secondary efficacy results for SPORTIF III (SH-TPA-0003)**



ITT Intention-to-treat, OT On-treatment, SEE Systemic embolic events, MI Myocardial infarction, TIA Transient ischemic attack.

SPORTIF V (SH-TPA-0005) met its primary objective: 51 patients sustained primary events (1.6% per year) in the ximelagatran group compared with 37 (1.2% per year) in the warfarin group, yielding an event rate difference of 0.45% per year (95% CI: -0.13% to 1.03% per year), well within the pre-specified 2% non-inferiority margin (Figure 27). Of these patients, 2 in each treatment group had hemorrhagic strokes. Sensitivity analyses, as well as secondary analyses, tested the robustness of the primary results (Figure 27). In all instances, these analyses provided results consistent with the primary outcome results. In particular, primary events plus all-cause mortality, analyzed by ITT, yielded an event rate difference of 0.10% per year (95% CI: -0.97% to 1.2%) (Figure 27).

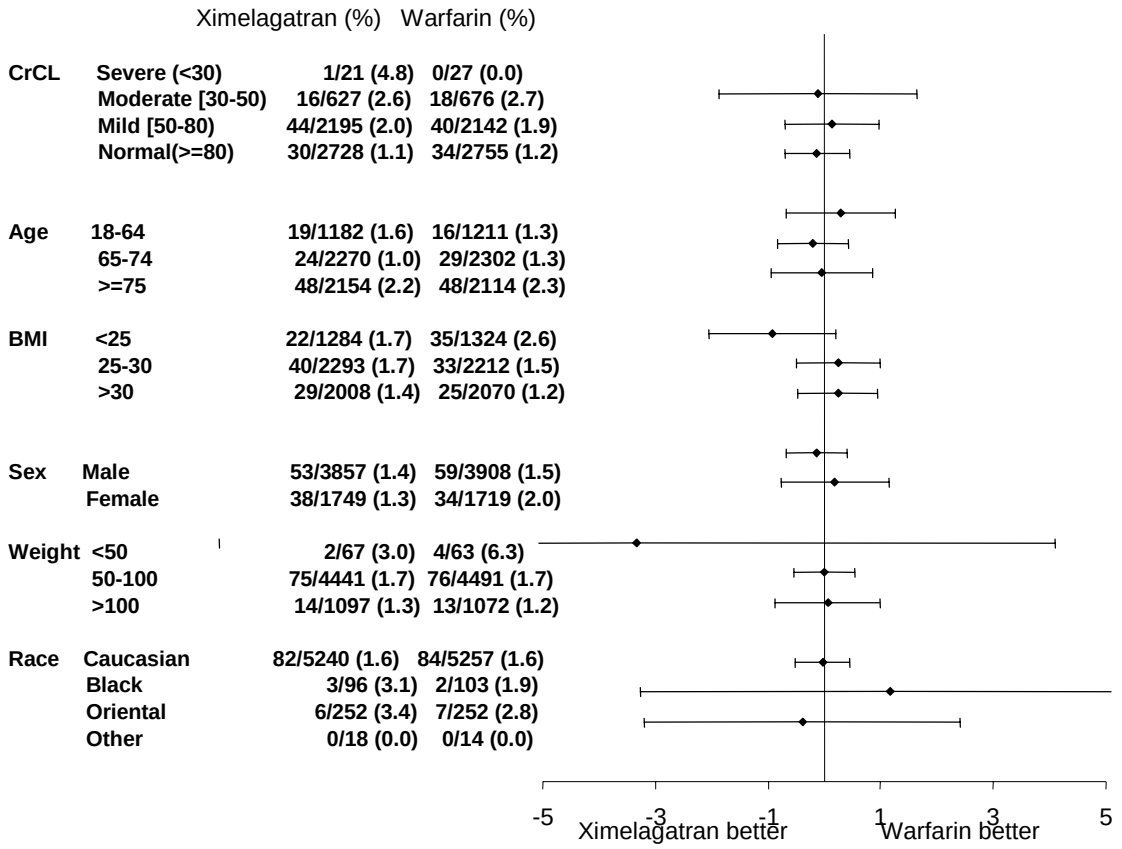
Figure 27 Summary of primary efficacy results and sensitivity analyses for SPORTIF V (SH-TPA-0005)



ITT Intention-to-treat, OT On-treatment, SEE Systemic embolic events, MI Myocardial infarction, TIA Transient ischemic attack.

Pooling data from SPORTIF III (SH-TPA-0003) and SPORTIF V (SH-TPA-0005) may reveal effects in subpopulations not otherwise seen in analogous analyses in the individual trials. Figure 28 demonstrates no subpopulations at risk for decreased efficacy for the primary outcome; including males, patients aged over 65 years, the obese, and those with normal renal function.

Figure 28 Efficacy in atrial fibrillation subgroups (ITT population) (SPORTIF III, SH-TPA-0003 and SPORTIF V, SH-TPA-0005)



Note: Bars for CI not depicted for subgroups with fewer than 50 patients.
BMI Body mass index; CrCL Creatinine clearance; ITT Intention-to–treat.

Oral ximelagatran 36 mg bid was non-inferior to well-controlled warfarin in reducing the incidence of stroke and SEE. All sensitivity analyses and other composite endpoints demonstrate this result to be robust. These studies support the use of oral ximelagatran 36 mg bid for long-term treatment in the prevention of stroke and thromboembolic complications in this patient population.

5.4.2 Validity of the non-inferiority analyses

In a meta-analysis of 6 controlled clinical studies (BAATAF 1990, Connolly et al 1991, EAFT 1993, Ezekowitz et al 1992, Petersen et al 1989, SPAF 1991), the incidence of stroke (excluding SEEs) in chronic nonvalvular AF patients who received placebo was 6.0% per year (Hart et al 1999). Patients who received warfarin achieved an overall risk reduction of 62%

from this rate (95% CI: 48% to 72%). Warfarin is an effective anticoagulant; therefore, it is reasonable to establish efficacy versus warfarin in this indication.

SPORTIF III (SH-TPA-0003) and SPORTIF V (SH-TPA-0005) were designed as non-inferiority trials with a pre-specified absolute non-inferiority margin. AstraZeneca planned this design in collaboration with an Executive Steering Committee (ESC) and DSMB composed of leaders of prior stroke prevention trials and statisticians with expertise in non-inferiority trials.

In selecting the non-inferiority margin, AstraZeneca considered what difference in event rates would be clinically tolerable, accounting for the overall clinical profile of warfarin. The designers of the SPAF-III trial, dealing with a population at similar risk for stroke, powered that trial to detect a 2%/year event rate difference, yielding an upper confidence bound of 3%/year. For the SPORTIF trials, AstraZeneca chose a more conservative upper confidence bound of 2%/year for the largest event rate difference allowing success of these non-inferiority trials. The 2%/year absolute non-inferiority margin is clinically relevant, was pre-specified, and was conservatively chosen.

The non-inferiority margin was selected to represent an upper CI. As a result, the observed difference in event rates between treatments for each SPORTIF trial was required to be much smaller than 2%/year to satisfy this criterion. In addition, a putative placebo comparison was added as a prerequisite to non-inferiority analysis in each of the SPORTIF trials. The non-inferiority analysis was to be done only if ximelagatran was found to be statistically superior to placebo. This prerequisite analysis adds robustness to the conclusions drawn from the subsequent non-inferiority analysis.

Each SPORTIF trial independently established non-inferiority to warfarin. In SPORTIF III (SH-TPA-0003), ximelagatran demonstrated both superiority to placebo (relative risk 26%; 95% CI: 16% to 42%), and a treatment difference to warfarin within the non-inferiority margin (event rate difference -0.66%/yr; 95% CI: -1.45%/yr to 0.13%/yr). In SPORTIF V (SH-TPA-0005), ximelagatran demonstrated both superiority to placebo (relative risk 50%; 95% CI: 30% to 83%), and a treatment difference to warfarin within the non-inferiority margin (event rate difference 0.45%/yr; 95% CI: -0.13%/yr to 1.03%/yr). These results are robust to sensitivity analyses. The analysis of SPORTIF using an OT approach confirms the results of the primary analysis: SPORTIF III (SH-TPA-0003) event rate difference –0.94%/yr; 95%CI: –1.70%/yr to –0.18%/yr; SPORTIF V (SH-TPA-0005) event rate difference 0.55%/yr; 95%CI: –0.06%/yr to 1.16%/yr. As expected, in each trial, the OT approach generated confidence intervals of the difference in event rates that are placed slightly more distant from zero than the ITT results. Each trial still independently maintained non-inferiority to warfarin.

The addition of all-cause mortality to the primary event cluster also confirms the results of the primary analysis. In SPORTIF III (SH-TPA-0003), analysis of this endpoint yielded an event rate difference of –0.87%/yr (95% CI: –2.09%/yr to 0.34%/yr). In SPORTIF V (SH-TPA-0005), analysis of this endpoint yielded an event rate difference of 0.10%/yr

(95% CI: –0.97%/yr to 1.2%/yr). This further demonstrates the robustness of the non-inferiority results and suggests that the treatments provide similar benefit to patients.

The SPORTIF trials were designed using a robust, well-defined non-inferiority approach. SPORTIF III (SH-TPA-0003) and SPORTIF V (SH-TPA-0005) independently established the efficacy of ximelagatran, in comparison to warfarin using these non-inferiority analyses. Results of the primary analysis held for subpopulations and for sensitivity analyses.

5.5 Summary of ximelagatran efficacy

Fixed-dose oral ximelagatran demonstrated anticoagulant efficacy in 3 diverse populations and clinical settings without coagulation monitoring or dose-adjustment. First, in comparison to placebo for long-term prophylaxis of VTE after treatment for an acute DVT or PE; second, as superior to warfarin in preventing VTE after TKR surgery; and third, non-inferiority to the risk reduction achieved by warfarin in preventing stroke and SEEs in patients with nonvalvular AF. The pivotal studies demonstrated the effectiveness of oral ximelagatran as an anticoagulant.

6. SAFETY

6.1 Introduction

The safety of ximelagatran has been evaluated in an extensive clinical program, including 30698 subjects of whom 17365 received ximelagatran or melagatran. Patients from the US accounted for approximately one-quarter of this number. In the short-term treatment population, more than 8500 patients undergoing hip or knee replacement surgery received ximelagatran for up to 12 days (Section 6.2). 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 1 year (Section 6.3).

All 22 Phase II and III patient studies were controlled, thus enabling comparison with a large cohort of patients exposed mainly to the reference anticoagulant warfarin but also to placebo in a smaller group of patients. In addition, more than 25% of the patients were above 75 years of age. The size, extent of exposure, and demographic diversity of the populations studied in the clinical program allow a thorough assessment of the safety profile of ximelagatran. For all patient groups in the pivotal studies, ximelagatran was always given as a fixed dose (24 mg bid or 36 mg bid), without dose adjustment for gender, age, weight, CrCL or other intrinsic patient factors, and without coagulation monitoring.

6.1.1 Pooling strategy

The clinical studies within the program fall into 3 groups based on the clinical context and population studied, and on the duration of exposure to the drug (≤35, >35 days). The patient populations that comprise these 3 groups (Phase I population, surgical population, and non-surgical population) are mutually exclusive (ie, no patient is included in more than one population), have distinctly different characteristics, and would be expected to have

different safety profiles due to their baseline conditions and their duration of exposure to the drug.

There were no unexpected findings in the Phase I studies (1285 subjects in 60 studies), therefore, the following safety evaluation will focus on 2 primary safety populations:

- Surgical patients: those patients receiving short-term treatment for <35 days, typically up to 12 days.

- Non-surgical patients: those patients who were to be dosed for ≥35 days and up to 2.5 years in SPORTIF V (SH-TPA-0005) and 5 years (4 years at cut-off for the NDA) in SPORTIF II (SH-TPA-0002) and SPORTIF IV (SH-TPA-0004), combined.

The surgical population (15456 patients) consists of 2 sets of patients: the Warfarin-comparison Pool (38% of the surgical safety population) and the Dose-levels Pool (early US studies and the European Phase II and III studies). The 2 pools were established because significant differences in medical practice exist. The "oral only" program, conducted in North America, and the "sc + oral" program, conducted in Europe, developed separately after the METHRO II study (SH-TPO-0002) was completed. The Warfarin-comparison Pool provides the data to support the use of oral-only ximelagatran 36 mg bid as a late post-operative regimen in elective TKR surgery using warfarin as the comparator. The European OS program represents patients who received either preoperative or early post-operative sc melagatran followed by oral ximelagatran in patients undergoing TKR or total hip replacement (THR) surgery. Data for the European OS program (Dose-levels Pool) can be found in Appendix C.

The non-surgical population (13147 patients) consists of the Phase II and III studies with chronic dosing and is termed the Long-term exposure Pool (LTE Pool). The LTE Pool consists of 4 disease-based populations with thrombotic risk: patients with AF, patients receiving treatment for VTE or extended secondary prophylaxis of VTE, and patients with post acute coronary syndrome (ACS).

The creation of 2 distinct safety populations was based on the following rationale:

- Surgery presents a unique hemostatic challenge, and the safety profile immediately after surgery, in particular the risk of bleeding and wound complications related to the surgical procedure, differs from that in non-surgical patients.

- Pooling the surgical population with the long-term treated non-surgical populations would artificially increase the denominators in the estimation of the frequency of rare, long-term events in the non-surgical population and of the post-operative events in the surgical population, hence, underestimating the incidence of such events.

- Finally, each population is large enough to allow a reasonable pre-marketing assessment of the safety profile of ximelagatran.

6.2 Surgical population

Three Phase III trials in elective TKR surgery constitute the Warfarin-comparison Pool (5236 patients), the 2 EXULT trials (SH-TPO-0010, SH TPO-0012) and a Phase III trial evaluating 24 mg versus warfarin (PLATINUM KNEE, SH-TPO-0006). In the Warfarin-comparison Pool, 1913 patients undergoing TKR surgery were exposed to ximelagatran 36 mg, 1097 patients were exposed to ximelagatran 24 mg, and 2226 patients were exposed to well-controlled warfarin (INR 2.0 to 3.0). The safety population included all randomized patients who received at least one dose of study medication (active or placebo); therefore, the population numbers are different to those presented in the efficacy section for the ITT populations.

6.2.1 Demographics and drug exposure

Within the Warfarin-comparison Pool, all treatment groups were well balanced regarding demographic characteristics (Table 13). Nearly all of the patients (>94%) were Caucasian and there were more females (>60%) than males. Approximately two-thirds of patients were 65 years or older, although there was a wide range of ages in the program (24 to 91 years of age). More than 85% of the patients had a BMI ≥25 kg/m^2. Approximately 35% of the patients had some degree of renal impairment; defined as CrCL <80 mL/min and a total of 16 patients had severe renal impairment (CrCL <30 mL/min) in violation of entry criteria. Ximelagatran (as melagatran) depends on renal excretion as the primary route of elimination. For this reason, subjects with severe renal insufficiency were intended to be excluded from the Phase III clinical trials.

Table 13 Demographic description: The Warfarin-comparison Pool

Demographic characteristic	Warfarin-comparison Pool							
	Ximelagatran 36 mg (n=1913)		Warfarin[a] (n=1897)		Ximelagatran 24 mg (n=1097)		Warfarin[a] (n=1081)	
	n	%	n	%	n	%	n	%
Age, years								
Mean	60.8		61.0		60.7		61.8	
Range	26-91		32-89		24-90		26-89	
Age in years								
<65	647	33.8	633	33.4	354	32.3	353	32.7
65 to 74	797	41.7	824	43.4	449	40.9	447	41.4
≥75	469	24.5	440	23.2	294	26.8	281	26.0
Race								
Caucasian	1810	94.6	1804	95.1	1038	94.6	1020	94.4
Black	88	4.6	80	4.2	52	4.7	57	5.3
Asian	7	0.4	9	0.5	4	0.4	4	0.4
Other	8	0.4	4	0.2	3	0.3	0	0.0
Gender								
Male	720	37.6	709	37.4	416	37.9	415	38.4
Female	1193	62.4	1188	62.6	681	62.1	666	61.6
BMI, kg/m^2								
<25	261	13.6	243	12.8	139	12.7	160	14.8
25-30	712	37.2	684	36.1	396	36.1	378	35.0
>30	933	48.8	961	50.7	554	50.5	533	49.3
Missing	7	0.4	9	0.5	8	0.7	10	0.9
CrCL, mL/min								
<30	4	0.2	5	0.3	3	0.3	4	0.4
≥30 to <50	88	4.6	116	6.1	67	6.1	61	5.6
≥50 to <80	584	30.5	552	29.1	322	29.4	336	31.1
≥80	1189	62.2	1173	61.8	667	60.8	656	60.7
Missing	48	2.5	51	2.7	38	3.5	24	2.2

[a] 752 patients (from EXULT A, SH-TPO-0010) included in both the 36-mg Pool and the 24-mg Pool.
BMI Body mass index; CrCL Creatinine clearance.

6.2.2 Adverse events

More than half of all patients experienced at least one AE, with similar incidences between the ximelagatran and warfarin groups in both the 36-mg and 24-mg Pools (Table 14). The overall frequency of AEs by intensity was similar across the treatment groups. Most events were of mild or moderate intensity.

Within both the 36-mg and 24-mg Pools, the frequency of non-fatal SAEs was slightly higher in each ximelagatran treatment group than in their respective warfarin groups during treatment. Non-fatal SAEs were reported at a frequency of 3.7% versus 3.1% for warfarin in the 36-mg group, and at 3.5% versus 2.6% for warfarin in the 24-mg group.

Adverse events leading to discontinuation of study drug (DAEs) were slightly 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 post-operative complication the most common reason for a DAE.

Except for numerically higher incidence of postoperative complications in the ximelagatran groups, there were no appreciable differences among treatment groups in the incidence of AEs at the investigator-reported term level (Table 14). Post-operative complications were mostly related to bleeding and were reported at a slightly higher frequency in the ximelagatran groups (17% at 36 mg, 23% at 24 mg) than in the warfarin groups (15% and 20%, respectively).

Table 14 Number (%) of patients with the most commonly reported AEs: The Warfarin-comparison Pool (exposed safety population, during treatment)

	Warfarin-comparison Pool							
	Ximelagatran 36 mg		Warfarin[a]		Ximelagatran 24 mg		Warfarin[a]	
Investigator-reported term[b]	**(n=1913)**		**(n=1897)**		**(n=1097)**		**(n=1081)**	
Total no. of patients with AEs	*1113*	*(58.2)*	*1055*	*(55.6)*	*720*	*(65.6)*	*663*	*(61.3)*
Post-operative complications	333	(17.4)	285	(15.0)	251	(22.9)	215	(19.9)
Fever	133	(7.0)	134	(7.1)	119	(10.8)	97	(9.0)
Nausea/nausea (aggravated)	119	(6.2)	94	(5.0)	79	(7.2)	87	(8.0)
GGT increased	107	(5.6)	79	(4.2)	48	(4.4)	45	(4.2)
Constipation	72	(3.8)	76	(4.0)	57	(5.2)	76	(7.0)
Hypokalemia	65	(3.4)	66	(3.5)	46	(4.2)	54	(5.0)
Pruritus	62	(3.2)	75	(4.0)	40	(3.6)	49	(4.5)
Urinary retention	61	(3.2)	53	(2.8)	54	(4.9)	44	(4.1)
Dizziness/vertigo	43	(2.2)	38	(2.0)	45	(4.1)	43	(4.0)

Note: AEs reported with a frequency of at least 4.0% in any column are presented. The events are sorted by the ximelagatran 36-mg column.

[a] 752 patients (from EXULT A, SH-TPO-0010) included in both the 36-mg Pool and the 24-mg Pool.

[b] Patients can appear in more than one category.

AE adverse event; GGT Gamma glutamyl transferase.

Two categories of AEs have been identified to be of special interest in the safety profile of short-term ximelagatran: (1) coronary artery disease and (2) bleeding, as expected for an anticoagulant. Coronary artery disease is presented in Section 6.2.2.1 and an evaluation of bleeding is reported in Section 6.2.3.

6.2.2.1 Coronary artery disease

The most common SAE leading to death in the Warfarin-comparison Pool was acute myocardial infarction (AMI). AMI was reported as a fatal SAE in 7 patients; 3 occurred in the ximelagatran 36-mg group (1 event on treatment) and 4 occurred in the warfarin group (2 events on treatment).

MI was also among the most commonly reported non-fatal SAEs in the Warfarin-comparison Pool. During treatment 5 (0.3%) patients in the ximelagatran 36-mg bid group had an MI reported as a non-fatal SAE; 1 (0.1%) patient was reported in the warfarin group. After

treatment, the numbers were 2 (0.1%) and 0, respectively. Similar numbers were reported in the ximelagatran 24-mg Pool.

Overall, the risk of AMIs in the ximelagatran groups was low, but higher than the comparator groups for both pools. There were no consistent findings for other less severe expressions of coronary artery disease. Overall, there was no clear or consistent pattern that indicated a safety concern with respect to coronary artery disease.

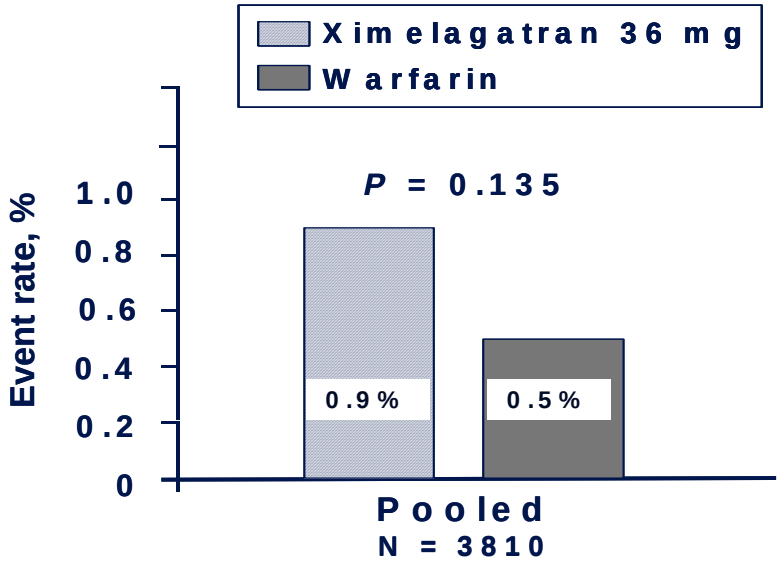
6.2.3 Evaluation of bleeding in the surgical population

Bleeding was evaluated in the surgical population with several different measures. In addition to the usual collection of bleeding AEs reported by investigators, a pre-specified objective assessment of bleeding was performed through the measurement of adjudicated major and minor bleeding events. Assessments of transfusion need (% transfused, volume transfused) and bleeding at the wound were also performed. The latter included investigator-reported interventions for wound bleeding, intra-articular hematoma, bruising and wound appearance.

6.2.3.1 Adjudicated bleeding events

Major and minor bleeding events were a pre-specified secondary endpoint in the EXULT studies (SH-TPO-0010, SH-TPO-0012) and SH-TPO-0006. As with the efficacy endpoints , the bleeding events were adjudicated by an independent, blinded Adjudication Committee (see Appendix B for the definition of major and minor events for the EXULT trials). The OT adjudicated major bleeding event results are presented below for the pooled EXULT A (SH-TPO-0010) and EXULT B (SH-TPO-0012) trials. Major bleeding occurred in 0.9% of patients treated with ximelagatran 36 mg, compared with 0.5% of patients treated with warfarin (Figure 29). Similar results were observed for ximelagatran 24 mg bid pooled data compared with warfarin. Adjudicated major and minor bleeding events on-treatment occurred in 5.1% of patients treated with ximelagatran 36 mg and 4.1% of patients treated with warfarin. The corresponding number of patients for ximelagatran 24 mg was 5.7% compared to 4.7% in the warfarin-treated patients. There were no statistically significant differences noted between these groups.

Figure 29 **Adjudicated major bleeding events - Pooled EXULT A (SH-TPO-0010) and EXULT B (SH-TPO-0012): exposed safety population (on-treatment)**



6.2.3.2 Bleeding adverse events

In the bleeding adverse event analysis, results of all three studies, EXULT A (SH-TPO-0010), EXULT B (SH-TPO-0012), and SH-TPO-0006 are pooled and presented here. Fewer than 8% of patients in any of the ximelagatran or warfarin groups had an investigator-reported bleeding AE during study treatment, and most events were non-serious. The incidence of any bleeding AE was numerically slightly higher in the ximelagatran 36-mg and 24-mg groups (6.7%, 7.2%) compared with warfarin (5.0%, 5.6%) (Table 15). The increase in the ximelagatran group was primarily due to postoperative complications (ximelagatran 36 mg 3.2% versus 2.3% warfarin and ximelagatran 24 mg 3.1% versus 2.2% warfarin). Reported serious bleeding AEs were few and indicated a similar profile for ximelagatran 36 mg bid compared with warfarin (0.8%, 0.6%) as well as for ximelagatran 24 mg bid compared with warfarin (0.4%, 0.7%). Two patients in the ximelagatran 36-mg group had fatal non-surgical bleeding events of GI hemorrhage. There was no apparent relationship between ximelagatran dose and bleeding risk, as indicated by similar proportions of patients with bleeding events in the ximelagatran 36-mg and 24-mg groups. Discontinuations due to bleeding AEs were slightly higher in the ximelagatran groups (36 mg, 1.1% and 24 mg, 1.0%) compared to the warfarin groups (0.5% in both comparator groups). The 10 most frequently reported bleeding AEs are presented in Table 15.

Table 15 Number (%) of patients with the 10 most frequently reported bleeding AEs, presented by investigator-reported term: Warfarin-comparison Pool (exposed safety population, during treatment)

	Warfarin-comparison Pool							
	Ximelagatran 36 mg bid		Warfarin[a]		Ximelagatran 24 mg bid		Warfarin[a]	
Investigator-reported term[b]	(n=1913)		(n=1897)		(n=1097)		(n=1081)	
Total number (%) of patients with AEs:	*129*	*(6.7)*	*95*	*(5.0)*	*79*	*(7.2)*	*61*	*(5.6)*
Post-operative complications	61	(3.2)	43	(2.3)	34	(3.1)	24	(2.2)
Hematuria	21	(1.1)	14	(0.7)	11	(1.0)	12	(1.1)
Purpura	11	(0.6)	14	(0.7)	6	(0.5)	10	(0.9)
Hemarthrosis	7	(0.4)	5	(0.3)	1	(0.1)	2	(0.2)
Hemoptysis	7	(0.4)	1	(0.1)	1	(0.1)	2	(0.2)
GI hemorrhage	6	(0.3)	5	(0.3)	2	(0.2)	4	(0.4)
Epistaxis	5	(0.3)	6	(0.3)	3	(0.3)	3	(0.3)
Hematemesis	5	(0.3)	4	(0.2)	7	(0.6)	2	(0.2)
Hemorrhage rectum	5	(0.3)	2	(0.1)	2	(0.2)	1	(0.1)
Melena	5	(0.3)	2	(0.1)	1	(0.1)	0	(0.0)

[a] 752 patients (from EXULT A, SH-TPO-0010) included in both the 36-mg Pool and the 24-mg Pool.
[b] Patients can appear in more than one category.
AE Adverse event; bid Twice daily; GI Gastrointestinal.

6.2.3.3 Bleeding adverse events by subgroup analysis

Event rate differences between ximelagatran and warfarin according to demographic subgroups are shown in Figure 30 for 36 mg ximelagatran and in Figure 31 for 24 mg ximelagatran. Patients who would be expected to have higher ximelagatran exposure by virtue of renal impairment, low BMI, and age >75 years did not demonstrate significant difference in risk for bleeding events compared to warfarin. In addition, there were no significant differences in the risk of bleeding with either 24 mg or 36 mg ximelagatran as compared to dose-adjusted warfarin.

Figure 30 **Ximelagatran versus comparators (difference in percent events with 95% CI) for bleeding AEs, according to demographic factors – Warfarin-comparison Pool (36 mg)**

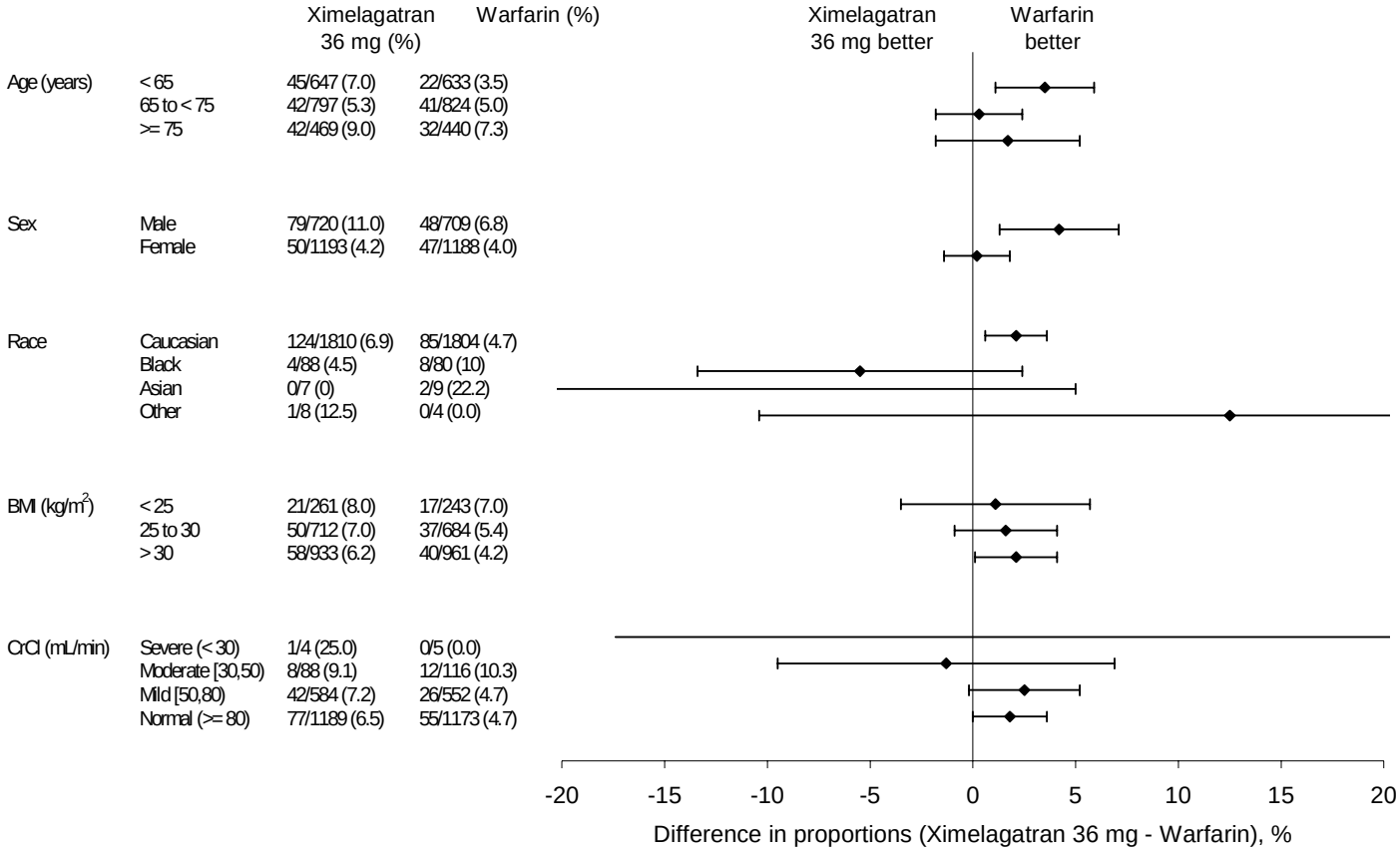
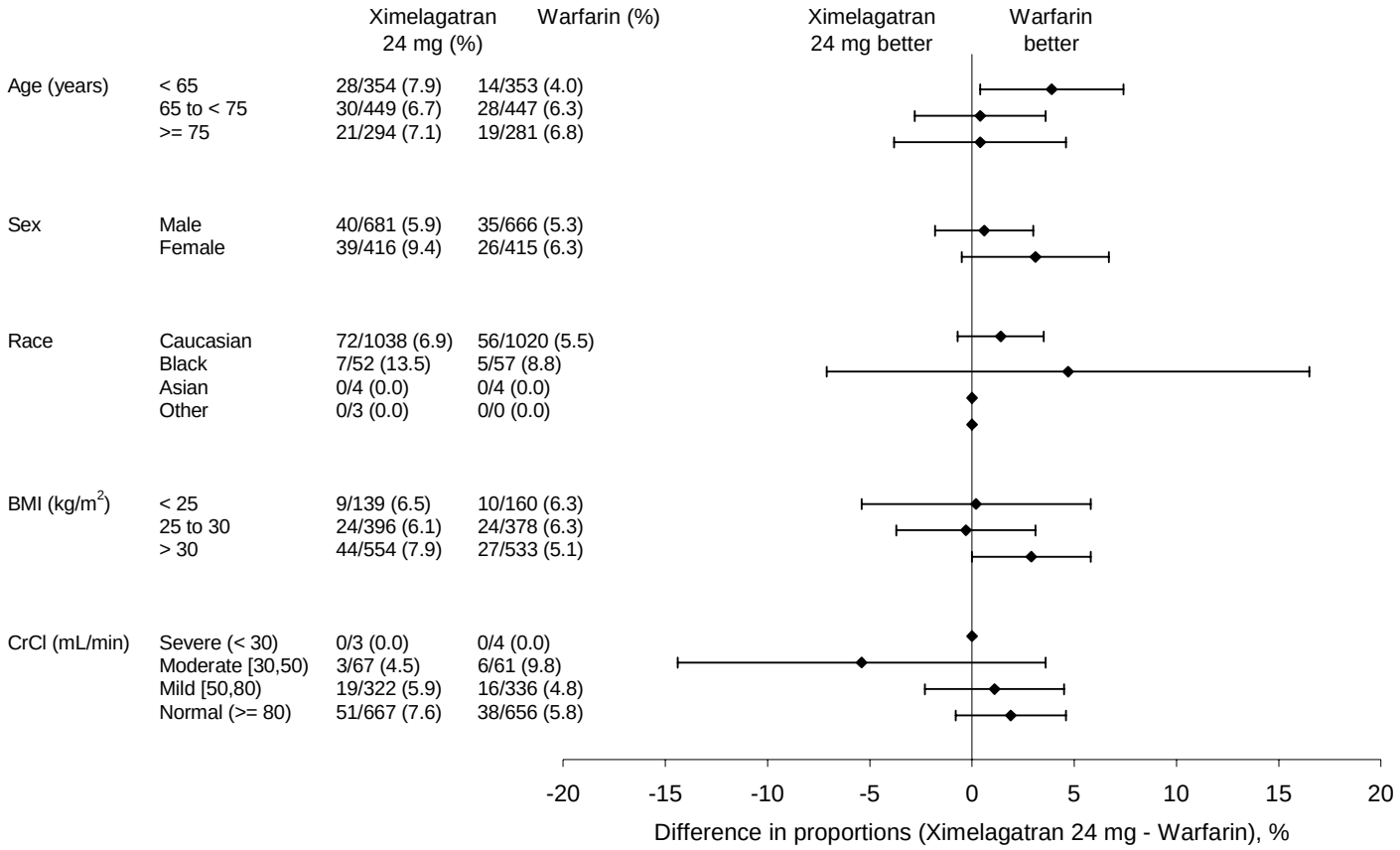


Figure 31 **Ximelagatran versus comparators (difference in percent events with 95% CI) for bleeding AEs, according to demographic factors – Warfarin-comparison Pool (24 mg)**



6.2.3.4 Bleeding indicators

In the 36-mg and 24-mg Pools, post-operative wound drainage volumes and the bleeding index were similar between the 2 treatment groups (Table 16). For both pools, the proportion of patients in each treatment group who received blood transfusions (one-third) was similar, as were the mean volumes transfused. In the 36-mg Pool, similar proportions received unplanned transfusion (~9%). The volume of the transfusions were similar between treatment groups, ximelagatran 36-mg compared to warfarin and ximelagatran 24-mg compared to warfarin.

Table 16 Bleeding indicators: Surgical safety - Warfarin-comparison Pool (N=5236), 36-mg and 24-mg Pools

	36-mg Pool			24-mg Pool		
Indicator by treatment	**N**	**Value**	**95% CI**	**N**	**Value**	**95% CI**
Post-op wound drainage, mean (mL)						
Ximelagatran	1504	696.7	(675.0, 718.4)	893	659.2	(632.1, 686.4)
Warfarin	1497	703.5	(681.8, 725.2)	849	653.9	(626.0, 681.7)
Bleeding index, mean						
Ximelagatran	1679	3.4	(3.3, 3.4)	919	3.2	(3.13, 3.3)
Warfarin	1662	3.3	(3.2, 3.4)	923	3.1	(3.02, 3.2)
Transfusions, unplanned, %						
Ximelagatran	1913	8.9	–		Not assessed	
Warfarin	1897	8.1	–		Not assessed	
Total patients receiving transfusion, %						
Ximelagatran	1913	33.5	–	1097	37.6	–
Warfarin	1897	33.6	–	1081	34.3	–
Volume transfused/Patient, mean (mL/units)						
Ximelagatran	640	630.2 mL	(601.8, 658.6)	412	1.7 units	(1.6, 1.8)
Warfarin	637	606.3 mL	(577.9, 634.7)	371	1.7 units	(1.6, 1.8)

Note: There were no statistically significant differences between groups for any parameter.

6.2.3.5 Overall wound appearance and characteristics

To capture the surgeon's subjective evaluation of effect on the surgical wound, a pre-specified subjective assessment was performed on post-operative Day 3, at the end of treatment, and again at follow-up. The wound was rated as "expected", "better than expected", or "worse than expected." If wound appearance was evaluated as "worse than expected" then wound swelling, drainage, erythema, and bleeding were assessed using the same rating criteria. In the 36-mg and 24-mg Pools the wound was assessed as "expected" or "better than expected"

for 90% of the patients in the ximelagatran and warfarin groups. For patients with "worse than expected" wounds, the proportions of swelling and erythema were comparable in the ximelagatran and warfarin groups at most time points examined. Numerically more patients in the ximelagatran 36-mg group than in the warfarin group had a rating of "worse than expected" for drainage at post-operative Day 3 and end of treatment, and at postoperative Day 3 only for the 24-mg Pool.

Bleeding complications of the surgical wound, including unusual bruising, hematomas, intra-articular bleeding, and bleeding requiring an intervention, were few and comparable between treatment groups (Table 17).

Table 17 Frequency (%) of unusual bruising and/or hematoma and intra-articular bleeding at surgical wound - Warfarin-comparison Pool (exposed safety population)

	Warfarin-comparison Pool			
	36-mg (EXULT) Pool		24-mg Pool	
Wound characteristic	**Ximelagatran (n=1913)**	**Warfarin[a] (n=1897)**	**Ximelagatran (n=1097)**	**Warfarin[a] (n-1081)**
Bruising and/or hematoma				
Postop Day 3	2.4	1.6	2.5	2.3
End of treatment	3.8	3.6	3.1	3.5
Follow-up	0.2	0.4	0.5	0.4
Overall	4.9	4.6	4.7	5.0
Intra-articular bleeding				
Postop Day 3	2.3	2.4	1.3	1.2
End of treatment	1.6	0.9	0.6	0.9
Follow-up	0.3	0	0.3	0
Overall	3.4	2.9	1.9	1.8

[a] 752 patients (from EXULT A, SH-TPO-0010) included in both the 36-mg Pool and the 24-mg Pool.

6.2.3.6 Summary of bleeding evaluation in the surgical population

Evaluation of bleeding in the surgical population demonstrates a numerically higher number of adjudicated major or minor bleeding events in the ximelagatran group compared to comparators, which was not statistically different. The incidence of major bleeding events was low in both groups. The results of investigator-reported adverse bleeding events or serious adverse bleeding events mirror the adjudicated bleeding incidences. There is no difference in objective measure of other bleeding indicators such as transfusion volume or percent of patients transfused or incidence of wound bleeding complications. Wound appearance was considered "as expected" or "better than expected" in 90% and similar

between groups at all time points with the exception of wound drainage at Day 3 and end of treatment for the 36-mg Pool. Overall, there does not appear to an important difference in bleeding between the use of ximelagatran 36- or 24-mg dose and dose adjusted warfarin.

6.2.4 Hepatic effect

Although the incidence of gamma glutamyl transferase (GGT) elevations reported as an AE (5.6% for ximelagatran 36 mg, 4.4% for ximelagatran 24 mg, and 4.2% for warfarin) (Table 14) were higher in the ximelagatran group, evaluation of laboratory data suggested no differences before treatment, during treatment, or after treatment. No hepatobiliary signal was observed for the surgical population. The frequency of ALT elevations in the short-term studies in the US is presented in Table 18. Ximelagatran patients demonstrated no difference versus the comparators for an increased incidence of ALT elevations. Appendix D presents additional data to support this conclusion in the surgical population.

Table 18 Frequency of ALT elevations in short-term studies

Study	Drug	Incidence of ALT >3x ULN
Studies in TKR: ximelagatran compared with warfarin		
EXULT A (SH-TPO-0010)	Ximelagatran (24 mg)	4/706 (0.57%)
	Ximelagatran (36 mg)	6/723 (0.83%)
	Comparator (warfarin)	12/704 (1.70%)
EXULT B (SH-TPO-0012)	Ximelagatran (36 mg)	7/1095 (0.64%)
	Comparator (warfarin)	6/1087 (0.55%)

ALT Alanine aminotransferase,; ULN Upper limit of normal; THR Total hip replacement; TKR Total knee replacement; LMWH Low molecular weight heparin.

6.2.5 Deaths

Overall, mortality rates were low. Eighteen fatal SAEs (0.3%) were reported among the 5236 patients in the Warfarin-comparison Pool, with more among patients who received ximelagatran (12/3010, 0.4%) than among those who received warfarin (6/2226, 0.3%). Seven of the 18 occurred during the treatment period (4 on ximelagatran, 3 on warfarin); 11 occurred after study medication discontinuation (8 on ximelagatran, 3 on warfarin). All 18 cases underwent independent central adjudication using the same classification for the entire oral-only postoperative dosing orthopedic surgery program. Two deaths were adjudicated as 'death due to fatal bleeding event', 8 were adjudicated as 'cannot exclude PE', and 8 were adjudicated as 'death not associated with VTE or bleeding.'

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): one event was associated with upper GI bleeding due to a duodenal ulcer after 8 days of therapy, and the other event involved upper GI bleeding after one day of therapy that may have lead to the patient's death 45 days later. Six out of the total 12 deaths were fatal events in which 'PE could not be

excluded'; one event occurred while the patient was on treatment. That patient had been bedridden for the 18 months immediately prior to his TKR procedure and died suddenly on his first day of mobilization out of bed (6 days postoperatively). The other 5 patients ('PE could not be excluded') had completed study medication but 2 patients were found to have bilateral calf vein thromboses at venography, and so were treated with standard anticoagulation. The patients went on to develop fatal PEs. For the other 3 patients with PE, the deaths occurred 4, 12 and 23 days after stopping study drug. The remaining 4 out of the 12 fatal SAEs in the ximelagatran group were adjudicated as 'death not associated with VTE or bleeding'.

Of the 6 fatal SAEs reported among the 2226 patients who received warfarin (0.3%), 2 events were fatal events in which 'PE could not be excluded'. One event occurred while the patient was on therapy. This patient developed shortness of breath on the third postoperative day, having received warfarin on the 2 prior evenings. Bilateral PE was diagnosed by pulmonary arteriogram and the patient died after embolectomy failed. In the other patient, study medication was discontinued after 4 days on treatment due an elevated INR. The event occurred on Day 17, the day of discharge. The remaining 4 out of the total 6 fatal SAEs in the warfarin-treated patients were adjudicated as 'death not associated with VTE or bleeding'.

6.2.6 Withdrawal and rebound

No indications of any withdrawal or rebound phenomena were seen for the short-term exposure to ximelagatran.

An analysis of the 16 patients in the efficacy ITT population who had symptomatic VTE events during the follow-up period in the 3 Phase III TKR studies showed that 7 of these patients had a normal venogram at the end of treatment (5/12 in the ximelagatran group and 2/4 in the warfarin group). In keeping with accepted practice, none of these 7 patients with a normal venogram at the end of treatment received routine extended prophylaxis (ie, did not receive anticoagulant therapy during the follow-up period prior to the occurrence of their symptomatic event).

6.2.7 Summary of safety for the surgical population

Following TKR surgery, ximelagatran demonstrated no important differences in AEs, SAEs, deaths on-treatment, adjudicated bleeding events, wound assessment, or bleeding AEs when compared to well-controlled warfarin. There was no apparent relationship between ximelagatran dose and safety. The subgroup analysis supports a fixed dose for this population. Overall, these studies support the safe use of oral ximelagatran 36 mg bid for 7 to 12 days after surgery (beginning the morning of the day after surgery) in the prevention of VTE, in patients undergoing TKR surgery.

6.3 Non-surgical population

Safety of ximelagatran in the non-surgical population is presented for the LTE Pool (13147 patients). The LTE Pool consists of 4 disease-based populations: prevention of stroke and SEE in patients with AF (7557 patients), treatment of VTE (VTE-T, 2484 patients), secondary prevention of VTE after treatment of acute VTE (VTE-P, 1223 patients) and

treatment post ACS (1883 patients). Although the safety data from the studies conducted for the treatment of VTE (THRIVE II&V, SH TPV-0002 and SH-TPV-0005) and post ACS (ESTEEM, SH-TPC-0001) are integrated into the LTE Pool, the efficacy data were not included in the efficacy section of this document because approval for these indications is not being sought at this time. Summaries of the Phase III studies THRIVE II&V (THRIVE Treatment, SH TPV-0002 and SH-TPV-0005) and ESTEEM (SH-TPC-0001) are provided in Appendix A. The safety populations included all randomized patients who received at least one dose of study medication (active or placebo); therefore, the population numbers are different than those presented in the efficacy section for the ITT populations.

6.3.1 Demographics and treatment exposure

The treatment groups in the non-surgical LTE Pool were well balanced regarding demographic characteristics (Table 19). Most patients were 65 years or over, although there was a wide range of ages in the program (18 to 97 years). Nearly all of the patients (>93%) were Caucasian and the majority (64%) were males. Thirty percent of the patients had a BMI of >30 kg/m^2 and 46% of the patients had a CrCL <80 mL/min (ie, some level of renal impairment). Melagatran depends on renal excretion as the primary route of elimination. For this reason, subjects with severe renal insufficiency (CrCL <30mL/min) were intended to be excluded from the Phase III clinical trials.

Table 19 Demographic description: Long-term exposure Pool

	Ximelagatran (n=6931)		Comparators (n=6216)	
Demographic characteristic	**n**	**%**	**n**	**%**
Age, years				
Mean	66.3		66.5	
Range	18 - 97		18 - 97	
Age in years				
<65	2487	35.9	2188	35.2
65-74	2417	34.9	2171	34.9
≥75	2027	29.2	1857	29.9
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
Gender				
Male	4462	64.4	3998	64.3
Female	2469	35.6	2218	35.7
BMI in 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
CrCL in mL/min				
<30	40	0.6	31	0.5
≥30 to <50	697	10.1	664	10.7
≥50 to <80	2417	34.9	2088	33.6
≥80	3665	52.9	3351	53.9
Missing	112	1.6	82	1.3

BMI Body mass index, CrCL Creatinine clearance.

Ximelagatran exposure in the LTE Pool consists of 6931 patients comprising 3838 patients with AF, 1236 patients for treatment of VTE (VTE-T), 612 patients for secondary prevention of VTE (VTE-P), and 1245 patients with recent acute coronary syndrome (post ACS). The patients in the LTE Pool received doses from 20 to 60 mg (75% received 36 mg bid), for a mean of 357 days, representing an overall exposure of 6768 patient-years (Table 20). 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 mean of 389 days, mainly to the reference anticoagulant warfarin (n=4967), but also to placebo in a smaller number of patients (n=1249).

Table 20 Ximelagatran exposure in the Long-term exposure Pool

Baseline Disease	n (%)	Mean Duration (days)	Total Patient Years
AF	3838 (55)	480	5039
VTE-P	612 (9)	445	745
VTE-T	1236 (18)	154	521
ACS	1245 (18)	136	463
Total	6931 (100)	357	6768

AF Nonvalvular atrial fibrillation; VTE-P Secondary prevention of venous thromboembolism; VTE-T Treatment of venous thromboembolism; ACS Acute coronary syndrome.

6.3.2 Adverse events

Oral administration of ximelagatran 24 mg and 36 mg bid was generally well tolerated. As expected, the number of patients who experienced at least one AE was high (85%) in both groups (Table 21) due to the severity of the underlying diseases in these populations and the long follow-up. Most AEs were mild or moderate in intensity, with 27.3% of the patients in the ximelagatran group reporting SAEs versus 28.2% in the comparators group.

There were more DAEs in patients treated with ximelagatran (17%) than with comparators (13%), primarily due to the protocol-mandated discontinuation of patients with pre-specified ALT elevations. Similar types and frequencies of AEs were noted in both groups with the exception of slightly higher incidence of purpura reported in the comparator group (Table 21).

Table 21 Number (%) of patients with the 10 most commonly reported AEs: LTE Pool

Investigator-reported term[a]	Ximelagatran (n=6931)	Comparators (n=6216)
Total number (%) 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)
Dyspnea/dyspnea (aggravated)	551 (7.9)	592 (9.5)
Diarrhea	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)

[a] Patients can appear in more than one category.
AE Adverse events, LTE Long term exposure.

Three categories of AEs have been identified to be of special interest in the safety profile of long-term ximelagatran: (1) coronary artery disease; (2) bleeding, as expected for an anticoagulant; and (3) an unanticipated increase in ALT elevations, which were mostly asymptomatic. Coronary artery disease is presented in Section 6.3.2.1. An evaluation of bleeding is presented in Section 6.3.3. Bleeding AEs were reported less frequently in the ximelagatran group (27%) than in the comparator group (32%) despite the fact that the comparator group included patients who received placebo. Although in the individual pools in which ximelagatran was compared to placebo (VTE-P and Post ACS), there were more bleeding-related AEs in the ximelagatran group; in the pools in which ximelagatran was compared to well-controlled warfarin (AF and VTE-T), there were fewer bleeding-related AEs in the ximelagatran group. Hepatobiliary AEs (see Section 6.3.4.3) were reported more frequently in the ximelagatran group (11.1%) than in the comparator group (4.5%). The difference is accounted for by enzyme elevations reported as AEs without any difference in clinical events noted. This effect was consistent across all populations.

6.3.2.1 Coronary artery disease

In all LTE populations, except the post ACS, the proportion of patients with coronary artery disease AEs was numerically higher in the ximelagatran groups than in the comparator groups. This trend was consistent across the pools for MI; however, the difference in event rates (%/patient year) was small. There were no consistent findings for other less severe expressions of coronary artery disease. Overall, there was no clear or consistent pattern that indicated a safety concern with respect to coronary artery disease.

In the AF, VTE-T and VTE-P pools, the proportion of patients with coronary artery disease AEs was slightly higher in the ximelagatran groups than in the comparator groups. This section presents the incidence of coronary artery disease AEs by indication pool, and, in order to investigate this effect further, the risk of AMI in the individual studies and pools.

Patients with coronary artery disease AEs

The safety evaluation in this section is based on the following preferred terms coding for the events reported by the investigator: Angina pectoris, Angina pectoris aggravated, Coronary artery disorder, Myocardial infarction, Myocardial ischemia, Thrombosis coronary.

The frequency of coronary artery disease AEs is summarized for the indication pools for the safety population in Table 22 to Table 25.

- In the AF, VTE-T and VTE-P Pools, the proportion of coronary artery disease AEs was numerically higher in the ximelagatran groups than in the comparator groups (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). This trend is consistent across the pools for MI, but not for the other preferred terms.

- In the post-ACS Pool, ximelagatran plus ASA was associated with fewer coronary artery AEs than placebo plus ASA. This is consistent with the results from this study showing a statistically significant dose-response in favor of ximelagatran on the composite clinical endpoint of all cause mortality, AMI, and severe recurrent ischemia. This supports the concept that long-term treatment with an oral thrombin inhibitor added to ASA reduces arterial events.

Table 22 Number (%) of patients with coronary artery disease adverse events[a] (safety population): AF Pool

Drug:	**Ximelagatran**		**Warfarin**	
Dosage:	**36 mg bid**		**Individual**	
No. of patients:	**(n=3838)**		**(n=3719)**	
Preferred term	**n**	**(%)**	**n**	**(%)**
Total no. of patients with AE:	***268***	***(7.0)***	***248***	***(6.7)***
Angina pectoris/angina pectoris aggravated	178	(4.6)	167	(4.5)
Myocardial infarction	62	(1.6)	52	(1.4)
Coronary artery disorder	42	(1.1)	37	(1.0)
Myocardial ischemia	5	(0.1)	4	(0.1)
Thrombosis coronary	3	(0.1)	2	(0.1)

[a] Coronary artery disease AEs with onset during treatment are presented. The events are sorted in decreasing frequency in the ximelagatran group.

AF (atrial fibrillation) Pool includes SPORTIF II/IV (SH-TPO-0002/0004), SPORTIF III (SH-TPA-0003), SPORTIF V (SH-TPA-0005).

bid Twice daily; AE Adverse event.

During SPORTIF III (SH-TPA-0003) and SPORTIF V (SH-TPA-0005), an efficacy comparison between ximelagatran and warfarin was made for the composite of the incidence of all-cause mortality, stroke, SEE, and AMI. The pooled event rate for ximelagatran was 4.21%/year and 4.62%/year for warfarin, a difference per year of –0.40%/year (95% CI: -1.23% to 0.42%/year). A prognostic factor analysis for this composite endpoint was conducted to identify risk factors for events. ASA use was studied in this analysis. Pooling of data from SPORTIF III (SH-TPA-0003) and SPORTIF V (SH-TPA-0005) for those patients not receiving concomitant ASA indicated a rate for this endpoint of 3.9%/year in the ximelagatran group and 4.3%/year for the warfarin group. For those patients taking concomitant ASA, the rates were 9.2%/year in both groups. Pooled adjudicated events in SPORTIF III (SH-TPA-0003) and SPORTIF V (SH-TPA-0005) revealed a total of 100 AMIs; 50 AMIs occurred in the ximelagatran group (8 were fatal) and 50 in the warfarin group (13 were fatal).

Table 23 Number (%) of patients with coronary artery disease adverse events[a] (safety population): VTE-T Pool

Drug:	**Ximelagatran**		**Warfarin**	
Dosage:	**36 mg bid**		**Individual**	
No. of patients:	**(n=1236)**		**(n=1248)**	
Preferred term	**n**	**(%)**	**n**	**(%)**
Total no. of patients with AE:	***16***	***(1.3)***	***1***	***(0.1)***
Angina pectoris	11	(0.9)	0	
Myocardial infarction	3	(0.2)	0	
Myocardial ischemia	3	(0.2)	0	
Coronary artery disorder	1	(0.1)	1	(0.1)
Thrombosis coronary	1	(0.1)	0	

[a] Coronary artery disease AEs with onset during treatment are presented. The events are sorted in decreasing frequency in the ximelagatran group.

VTE-T (Treatment of venous thromboembolism) Pool includes THRIVE II&V (SH TPV-0002 and SH-TPV-0005).

bid Twice daily; AE Adverse event.

Table 24 Number (%) of patients with coronary artery disease adverse events[a] (safety population): VTE-P Pool

Drug:	**Ximelagatran**		**Placebo**	
Dosage:	**24 mg bid**			
No. of patients:	**(n=612)**		**(n=611)**	
Preferred term	**n**	**(%)**	**n**	**(%)**
Total no. of patients with AE:	***16***	***(2.6)***	***12***	***(2.0)***
Myocardial infarction	10	(1.6)	3	(0.5)
Angina pectoris/angina pectoris aggravated	7	(1.1)	7	(1.1)
Coronary artery disorder	1	(0.2)	2	(0.3)
Myocardial ischemia	0		1	(0.2)

[a] Coronary artery disease AEs with onset during treatment are presented. The events are sorted in decreasing frequency in the ximelagatran group.

VTE-P (Secondary prevention of venous thromboembolism) Pool includes THRIVE III (SH-TPV-0003).

bid Twice daily; AE Adverse event.

Table 25 Number (%) of patients with coronary artery disease adverse events[a] (safety population): Post-ACS Pool

Drug:	Ximel + ASA		Ximel + ASA		Ximel + ASA		Ximel + ASA		Placebo + ASA	
Dosage:	**24 mg bid**		**36 mg bid**		**48 mg bid**		**60 mg bid**			
No. of patients:	**(n=307)**		**(n=303)**		**(n=311)**		**(n=324)**		**(n=638)**	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total no. of patients with AE:	***81***	***(26.4)***	***82***	***(27.1)***	***71***	***(22.8)***	***87***	***(26.9)***	***195***	***(30.6)***
Angina pectoris/angina pectoris aggravated	42	(13.7)	43	(14.2)	41	(13.2)	55	(17.0)	122	(19.1)
Myocardial infarction	16	(5.2)	17	(5.6)	13	(4.2)	14	(4.3)	51	(8.0)
Coronary artery disorder	14	(4.6)	22	(7.3)	11	(3.5)	13	(4.0)	21	(3.3)
Myocardial ischemia	17	(5.5)	16	(5.3)	12	(3.9)	14	(4.3)	37	(5.8)
Thrombosis coronary	0		0		1	(0.3)	0		1	(0.2)

[a] Coronary artery disease AEs with onset during treatment are presented. The events are sorted in decreasing frequency in the ximelagatran group.

Post ACS (Acute coronary syndrome) Pool includes ESTEEM (SH-TPC-0001).

Ximel Ximelagatran; ASA Acetylsalicylic acid; bid Twice daily; AE Adverse event.

6.3.3 Evaluation of bleeding in the non-surgical population

Bleeding was evaluated in the nonsurgical population with several different measures. In addition to the usual collection of bleeding AEs reported by investigators, a pre-specified objective assessment of bleeding was performed through the measurement adjudicated major bleeding events. Bleeding AEs and serious bleeding AEs are presented for the LTE population in Section 6.3.3.2. Adjudicated major bleeding is presented only for the pivotal trials for the 2 indications.

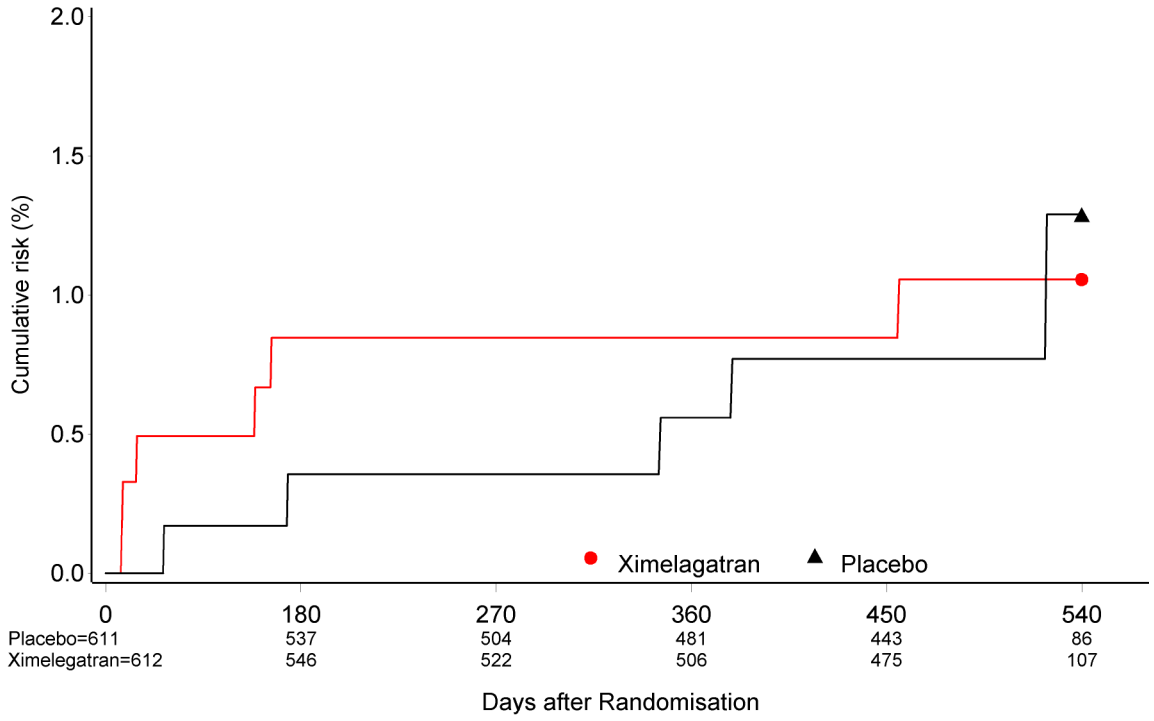
6.3.3.1 Adjudicated bleeding events

The long-term study protocols indicated major bleeding events as a secondary endpoint, with specific criteria and central adjudication. Minor bleeding events were not pre-specified in the long-term pivotal trials. Presented below are the adjudicated major bleeding events for the pivotal trials for the extended secondary prophylaxis of VTE and AF populations in support of the indications. The definitions of major and minor events for the LTE trials are presented in Appendix B.

Extended Secondary Prophylaxis of VTE population

The incidence of adjudicated major bleeding events during THRIVE III (SH-TPV-0003) was low and similar in the 2 groups (n=6 for ximelagatran and n=5 for placebo, hazard ratio 1.16 [95% CI: 0.29 to 4.81]; p=0.2) (Figure 32).

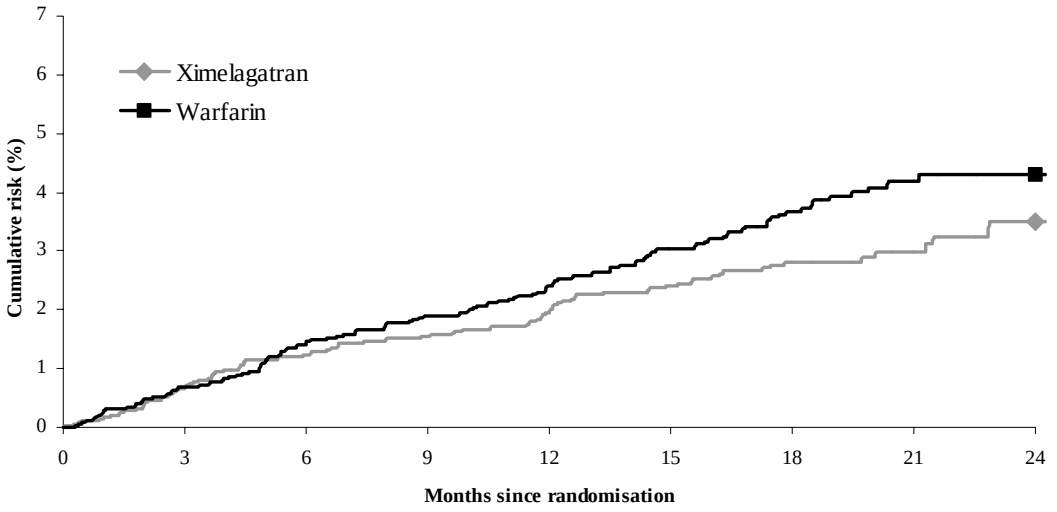
Figure 32 **Major bleeding events during THRIVE III (SH-TPV-0003), cumulative risk versus time after randomization (ITT approach)**



Atrial fibrillation population

In patients with AF, ximelagatran was associated with statistically significant fewer major bleeding events than warfarin (2.4% ximelagatran, 3.4% warfarin). The cumulative risk of a major bleeding event is summarized by treatment group over time in Figure 33.

Figure 33 **Major bleeding events during SPORTIF III and SPORTIF V (SH-TPA-0003 and SH-TPA-0005) combined, cumulative risk versus time after randomization (OT approach)**



ximelagatran=3664	3337	3109	2968	2817	2365	1485	711	230
warfarin=3665	3431	3272	3134	2963	2482	1554	700	223

6.3.3.2 Bleeding adverse events

The incidence of reported bleeding AEs with ximelagatran (27.0%) was less than that observed with the comparator groups (32.0%) (Table 26). The incidence of reported bleeding SAEs with ximelagatran was also numerically lower (2.9%) than observed with the comparators (3.6%). Similarly, the incidence of discontinuations due to bleeding AEs with ximelagatran was low (2.7%) and similar to that observed in the comparator groups (2.2%). The most commonly reported bleeding AEs were similar between the treatment groups with the exception of purpura and epistaxis, which were more commonly reported in the comparators group.

Table 26 Number (%) of patients with the most commonly reported bleeding AEs: LTE Pool

	Ximelagatran n=6931		Comparators n=6216	
Investigator-reported term[a]	**n**	**%**	**n**	**%**
Total patients	*1861*	*27.0*	*1988*	*32.0*
Purpura	558	8.1	742	12.0
Epistaxis	384	5.5	594	9.6
Hematuria	339	4.9	290	4.7
Melaena	183	2.6	149	2.4
Hemorrhage rectum	155	2.2	119	1.9
Gingival bleeding	126	1.8	121	1.9
Hemorrhage NOS	109	1.6	116	1.9
Hemorrhoids	93	1.3	72	1.2
Hemoptysis	80	1.2	78	1.3
GI hemorrhage	74	1.1	54	0.9
Scleral bleeding	67	1.0	111	1.8

[a] Patients can appear in more than one category.
AE Adverse events, LTE Long term exposure, NOS Not otherwise specified.

There were numerically fewer fatal bleeding events in the ximelagatran groups compared to standard anticoagulant treatment. During treatment, there were 5 fatal bleeding-related SAEs in the ximelagatran group compared to 8 in the comparator groups. After study drug discontinuation, there were 7 fatal bleeding-related SAEs in the ximelagatran group compared to 9 in the comparator groups. Almost all fatal bleeding events were intracranial or gastrointestinal.

During the ximelagatran program, the use of concomitant medication that could affect hemostasis was discouraged, ie, heparin, LMWH, or open-label warfarin, NSAIDs, fibrinolytic agents, or antiplatelets. Concomitant antiplatelet treatment with ASA ≤100 mg/day was allowed in the SPORTIF trials. A total of 1020 AF patients (28%) took concomitant ASA and ximelagatran. Concomitant ASA and warfarin was taken by 1058 AF patients (29%). There was a lower rate of bleeding in patients on both ximelagatran and ASA when compared to well controlled warfarin and ASA.

The concomitant use of ximelagatran 24 to 60 mg with ASA 160 mg/day was evaluated in ESTEEM (SH-TPC-0001). This Phase II dose-finding study in post ACS, showed that the difference between the treatments was significant and the risk of bleeding with ximelagatran increased in a dose-related manner. The increased number of bleeding events for

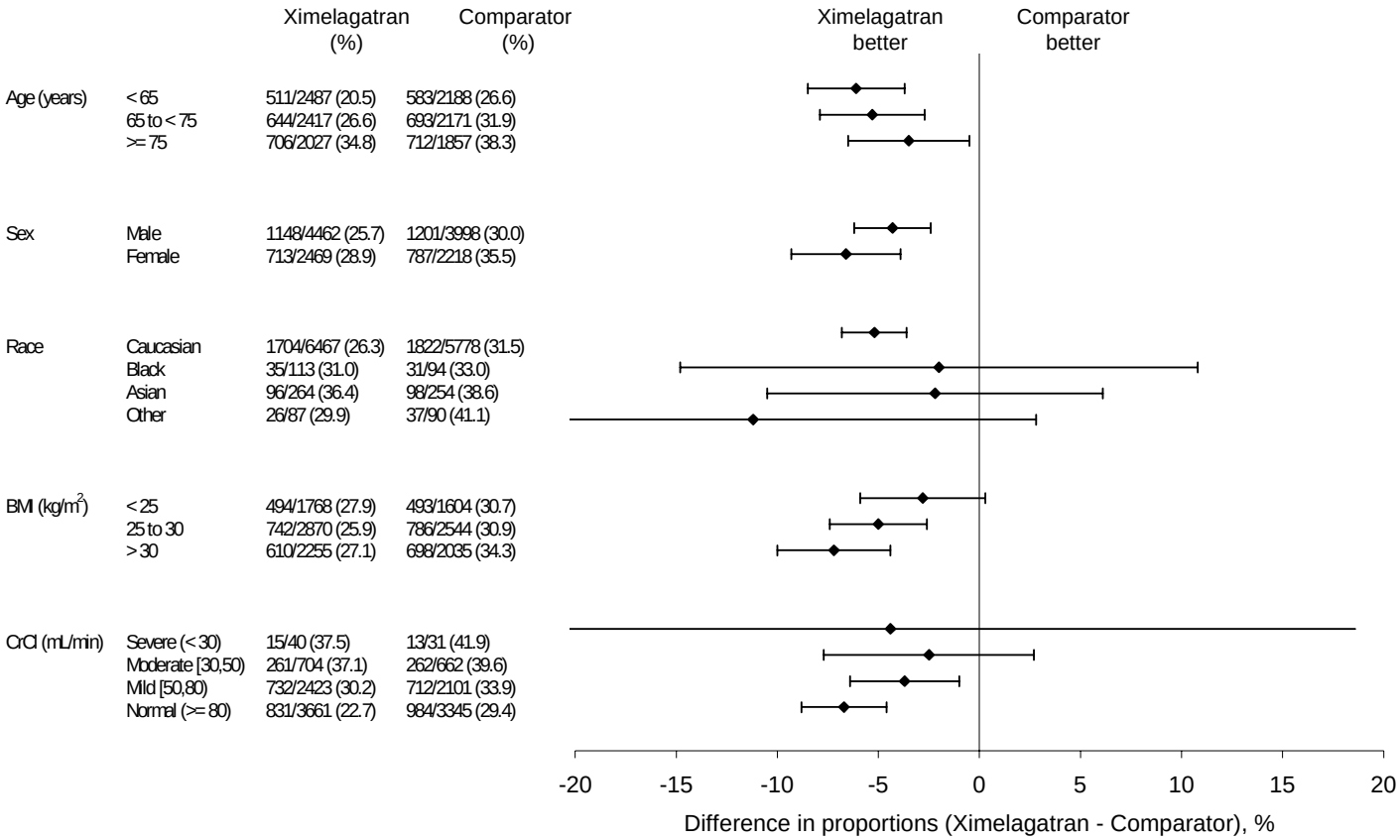
ximelagatran plus ASA compared to ASA plus placebo was expected because of the concomitant administration of an antiplatelet with an anticoagulant. The majority of the bleeding events were minor; with epistaxis and hematuria the most commonly reported events. Furthermore, critical site bleeding events occurred to a similar extent with placebo and ximelagatran. In relation to the total number of bleeding-related AEs in the ximelagatran groups, the number of SAEs and DAEs with corresponding terms was small.

Overall these results indicate that bleeding is increased with the concomitant use of an anticoagulant and antiplatelet agent and is not specific to the anticoagulant used.

6.3.3.3 Bleeding adverse events by subgroup analysis

Event rate differences between ximelagatran and warfarin according to demographic subgroups are shown in Figure 34. There were no consistent differences in the event rates for specific subgroups and, for most subgroups; there was a lower rate of bleeding events with ximelagatran than for comparator.

Figure 34 Ximelagatran versus comparators (difference in percent events with 95% CI) for bleeding AEs, according to demographic factors – LTE Pool



6.3.3.4 Summary of bleeding evaluation in the non-surgical population

Overall, bleeding, both adjudicated major and investigator-reported bleeding AEs, has been demonstrated to be less on ximelagatran as compared to dose adjusted warfarin. In addition, there are no subgroups that appear to be at increased risk for bleeding events as compared to warfarin.

6.3.4 Hepatic effects

No hepatic safety issue was detected in the non-clinical studies nor in the Phase I clinical trials. No safety issue regarding possible hepatobiliary effects was observed for the surgical population during, or following, short-term (<35 days) exposure to melagatran sc or oral ximelagatran bid. Appendix D presents additional data to support this conclusion in the surgical population. In the Phase II, 3-month dosing study in AF patients, an increased incidence of asymptomatic elevations in ALT >3x ULN was noted. The frequency of standard laboratory testing (ALT, aspartate aminotransferase [AST], alkaline phosphatase [ALP] and total bilirubin) that was being performed was increased in the subsequent Phase III studies as a result. In addition, the exclusion of patients with elevated liver enzymes (>2x ULN) from the Phase III studies acted to decrease factors leading to subsequent liver enzyme increases associated with ximelagatran exposure. From May 2000, Algorithm 1 was introduced in all clinical studies with ximelagatran. Liver enzymes were monitored at least monthly for the first 6 months and, if a liver function test (LFT) increased to >3x ULN, weekly monitoring was instituted. If any LFT reached >7x ULN, or clinical signs of hepatotoxicity were observed, study drug was to be discontinued. From 2 November 2001, this algorithm was changed after one patient had biopsy documented hepatic necrosis (see Section 6.3.4.5). Algorithm 2 required that the threshold for beginning weekly monitoring was reduced from >3x ULN to >2x ULN, and the threshold for discontinuation of study drug was revised from >7x ULN to >5x ULN (or persistent increase >3x ULN for up to 4 to 8 weeks). In the program, 40% of the ximelagatran-treated patients who had an ALT >3x ULN were monitored using the more conservative algorithm.

In the following subsections, the laboratory findings will be described first, then the clinical hepatobiliary AE data.

6.3.4.1 ALT testing

The database of ALT measurements is extensive and based on central and local laboratory data. Of the 6948 patients randomized to ximelagatran, 6948 contributed at least one ALT measurement and 5648 had an ALT measurement at the 6-month visit. The ximelagatran patient population contributing to the ALT measurement pool (6948 patients) differs from the 6931 ximelagatran-treated patients in the safety population of the LTE Pool because the ALT analyses were performed using the ITT populations. Table 27 presents the numbers of patients from the long-term studies that contributed to the ALT-testing databases.

Table 27 Number of patients randomized, and contributing ALT measurements over time in the long-term studies (ITT population) - Central and local laboratory data

			Number of patients contributing ALT measurements					
Population Study	**Total**	**Ximelagatran only**	**>0 months**	**>3 months**	**>6 months**	**>12 months**	**>18 months**	**>24 months**
AF	7583	3851	3796	3560	3320	3032	1859	396
VTE-T	2489	1240	1212	1084	951	23	9	3
VTE-P	1223	612	612	579	541	500	253	3
Post ACS	1883	1245	1221	998	836	14	6	2
Total	**13178**	**6948**	**6841**	**6221**	**5648**	**3569**	**2127**	**404**

ITT Intention-to-treat; ALT Alanine aminotransferase; VTE-T Treatment of venous thromboembolism; VTE-P Secondary prevention of venous thromboembolism; ACS Acute coronary syndrome; AF Nonvalvular atrial fibrillation.

The patient exposure during Algorithms 1 and 2 was large for both the total number of patient years as well as the 'at risk' number of patient years. ALT increases are noted between 1 month and 6 months after drug initiation; therefore, the first 6 months are termed the 'at risk' period. Total exposure during Algorithm 1 implementation was 3071 patient years and 'at risk' exposure was 1962 patient years. Total exposure during Algorithm 2 implementation was 3505 patient years and 'at risk' exposure was 875 patient years.

6.3.4.2 Clinical laboratory ALT data

The incidence of elevated ALT, AST, ALP, and total bilirubin, according to various multiples of ULN, is shown for the LTE Pool in Table 28 for the ITT population. The pooled data shows a similar pattern to that seen in the individual studies.

Ximelagatran patients demonstrated an increased incidence of ALT elevations versus the comparators. Based on central and local laboratory data, the incidence of ALT >3x ULN was 7.9% for the ximelagatran group compared with 1.2% for comparators. The incidence of ALT >5x ULN was 4.7% and 0.5% in the ximelagatran and comparators group, respectively, and the incidence of ALT >10x ULN was 1.9% and <0.1%, respectively. AST increased in conjunction with ALT. Only a few of these increases were symptomatic. There was no difference between the groups in isolated bilirubin and ALP elevations.

Table 28 Cumulative incidence of patients with elevated ALT, AST, ALP, and bilirubin (ITT population): LTE Pool - Central and local laboratory data

	Ximelagatran (N=6948)	Comparator (N=6230)
Liver function test	**n (%)**	**n(%)**
ALT >2x ULN	860 (12.4)	192 (3.1)
ALT >3x ULN	546 (7.9)	74 (1.2)
ALT >5x ULN	328 (4.7)	29 (0.5)
ALT >10x ULN	132 (1.9)	5 (<0.1)
AST >2x ULN	555 (8.0)	109 (1.7)
AST >3x ULN	354 (5.1)	50 (0.8)
AST >5x ULN	194 (2.8)	23 (0.4)
AST >10x ULN	72 (1.0)	5 (0.1)
ALP >2x ULN	138 (2.0)	66 (1.1)
ALP >3x ULN	47 (0.7)	22 (0.4)
ALP >5x ULN	16 (0.2)	4 (<0.1)
ALP >10x ULN	2 (<0.1)	1 (<0.1)
Bilirubin >2x ULN	86 (1.2)	66 (1.1)
Bilirubin >3x ULN	41 (0.6)	16 (0.3)
Bilirubin >5x ULN	20 (0.3)	7 (0.1)
Bilirubin >10x ULN	4 (<0.1)	3 (<0.1)

ALT Alanine aminotransferase; AST Aspartate aminotransferase; ALP Alkaline phosphatase; ULN Upper limit of normal; LTE Long-term exposure.

In patients who develop an ALT elevation, the subsequent development of clinical jaundice is considered to be a signal of more severe injury. The definition selected in this program was more conservative, ALT >3x ULN and bilirubin >2x ULN within 1 month of the ALT rise. A total of 36 patients in the ximelagatran group had an ALT >3x ULN and bilirubin >2x ULN within one month for an overall incidence of 0.5% in the ximelagatran population (36/6948). Five patients in the comparators group had concurrent elevations for an overall incidence of 0.1% (5/6230). Evaluation of the incidence of bilirubin rise in the subgroup of only those patients who had an ALT >3x ULN demonstrated no difference between the groups with 6.6% (36/546) in the ximelagatran group and 6.8% (5/74) in the comparators. In the patients whose

ALT was < 3x ULN the incidence of elevated bilirubin >2x ULN was 0.8% (50/6402) and 1.0% (61/6156), respectively. The incidence of bilirubin >2x ULN (regardless of ALT value) was 1.2% (86/6948) in the ximelagatran group and 1.1% (66/6230) in the comparator group.

An alternative associated diagnosis was determined in 25 of the 36 ximelagatran-treated patients including biliary disease (10), metastatic carcinoma (4), right-sided heart failure (5), bilirubin elevated throughout study (2), dengue fever/sepsis (1), viral hepatitis (1), ischemic hepatitis (1), and diffuse liver disease on ultrasound (1). In the other 11 patients without an alternative associated diagnosis, 10 patients discontinued drug (9 patients recovered and one patient died). The remaining patient continued treatment and recovered (Table 29).

In the comparator group, an alternative associated diagnosis was determined in 3 of the 5 patients: pancreatic cancer (2) and suspected common duct stone (1). The other 2 patients had no alternative explanation (Table 30). The two patients with pancreatic cancer discontinued drug and died, and the other 3 patients continued drug and recovered.

Table 29 List of ximelagatran-treated patients with concomitant elevations of ALT >3x ULN and bilirubin >2x ULN – Central and local laboratory data

Patient ID	Ximel dose (bid)	Age	Gender	Days to ALT >3x ULN	Max ALT (x ULN)	Max Bilirubin (x ULN)	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	Discontinued	Recovered	Hospitalized 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 normalization.
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.

Table 29 List of ximelagatran-treated patients with concomitant elevations of ALT >3x ULN and bilirubin >2x ULN – Central and local laboratory data

Patient ID	Ximel dose (bid)	Age	Gender	Days to ALT >3x ULN	Max ALT (x ULN)	Max Bilirubin (x ULN)	Action with study drug	Outcome	Alternative diagnosis/ comment
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 study
SH-TPA-0005-9390-6560	36 mg	74	M	92	6.98	2.09	Discontinued	Recovered	Bilirubin elevated throughout study
SH-TPA-0005-9570-8387	36 mg	80	F	63	15.19	10.82	Discontinued	Recovered	No alternative diagnosis. AST higher than ALT throughout 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.

Table 29 List of ximelagatran-treated patients with concomitant elevations of ALT >3x ULN and bilirubin >2x ULN – Central and local laboratory data

Patient ID	Ximel dose (bid)	Age	Gender	Days to ALT >3x ULN	Max ALT (x ULN)	Max Bilirubin (x ULN)	Action with study drug	Outcome	Alternative diagnosis/ comment
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-Feto-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.
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.

Table 29 List of ximelagatran-treated patients with concomitant elevations of ALT >3x ULN and bilirubin >2x ULN – Central and local laboratory data

Patient ID	Ximel dose (bid)	Age	Gender	Days to ALT >3x ULN	Max ALT (x ULN)	Max Bilirubin (x ULN)	Action with study drug	Outcome	Alternative diagnosis/ comment
SH-TPA-0003-309-2452	36 mg	72	M	232	11.86	4.70	Temporarily discontinued	Recovered	Gallstones. Endoscopic retrograde cholangiopancreatography 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 ALT 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	Hematuria and positive fecal hemoglobin 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.
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.

Table 29 List of ximelagatran-treated patients with concomitant elevations of ALT >3x ULN and bilirubin >2x ULN – Central and local laboratory data

Patient ID	Ximel dose (bid)	Age	Gender	Days to ALT >3x ULN	Max ALT (x ULN)	Max Bilirubin (x ULN)	Action with study drug	Outcome	Alternative diagnosis/ comment
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.

Ximel Ximelagatran, ALT Alanine aminotransferase; AST Aspartate aminotransferase; ULN Upper limit of normal; Max Maximum; LFT Liver function test; CT Computerized tomography.

Table 30 List of comparator-treated patients with concomitant elevations of ALT >3x ULN and bilirubin >2x ULN – Central and local laboratory data

Patient ID	Treatment	Age	Gender	Days to ALT > 3xULN	Max ALT (xULN)	Max Bilirubin (xULN)	Action with study drug	Outcome	Alternative diagnosis/ Comment
SH-TPA-0003-187-3983	Warfarin	80	M	232	5.77	3.41	Continued	Recovered	No alternative explanation.
SH-TPA-0003-239-1380	Warfarin	73	F	278	6.00	3.39	Continued	Recovered	Suspected stone in the common bile duct. Papillotomy.
SH-TPA-0005-1190-8675	Warfarin	78	M	128	3.71	6.77	Discontinued	Died	Pancreatic cancer. Palliative treatment.
SH-TPC-0001-306-1232	Placebo	59	M	6	16.13	7.95	Discontinued	Died	Icterus after 12 days on study drug. Inoperable pancreatic tumour. Died from the malignant disease 2 months later.
SH-TPV-0002-237-4155	Warfarin	37	F	14	3.25	2.14	Continued	Recovered	Bilirubin elevated throughout the study.

ALT Alanine aminotransferase; ULN Upper limit of normal; Max Maximum.

The time pattern of ALT elevations was consistent across the studies. The increase typically occurred between 1 and 6 months after the initiation of ximelagatran. Before and after this time frame, the incidence of ALT increase was similar to comparators. The divergence occurred largely within the first 6 months of treatment. Thereafter the incidence decreases to approach background rates.

Table 31 shows the number of new patients presenting for the first time with an increase in ALT >3x ULN during the months of treatment. In the initial 6 months of treatment, there was an obvious difference in the incidence of ALT >3x ULN between ximelagatran and comparator-treated patients. The difference became less apparent after 6 months.

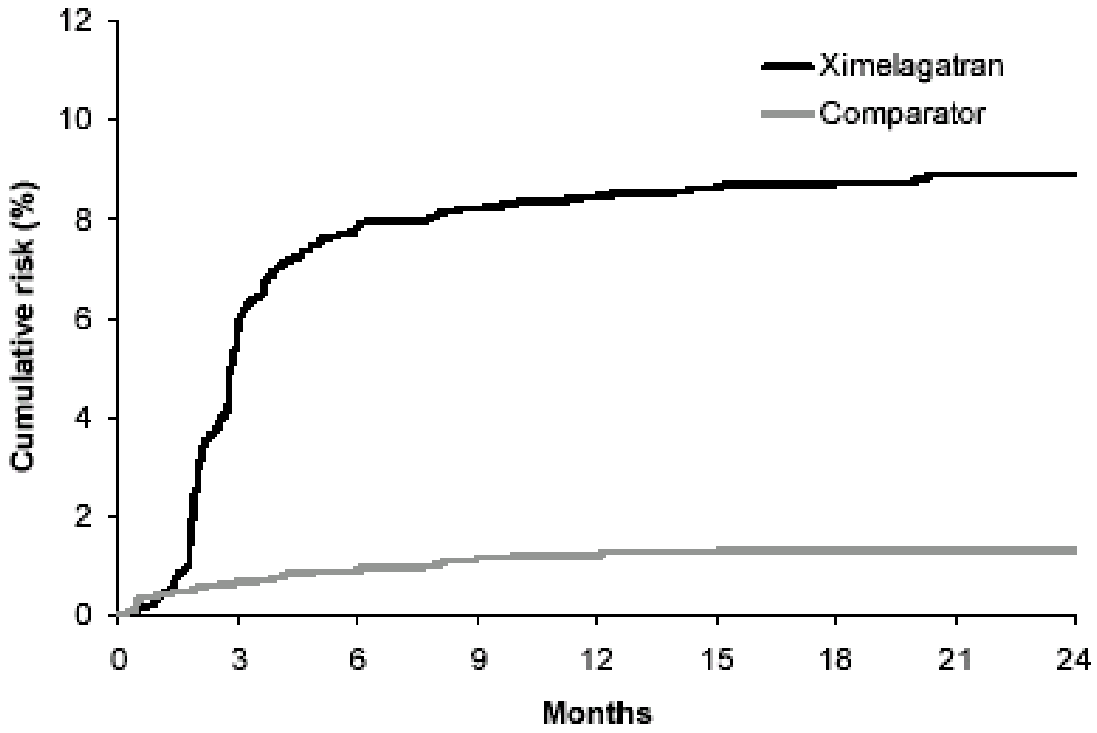
Table 31 Number (%) of new patients with ALT >3x ULN over time (central and local laboratory data): Non-surgical safety—LTE Pool (N=13178)

Time interval	Ximelagatran N=6948		Comparators N=6230	
(Months)	n	%[a]	n	%[a]
>0 to 3	373	(6.0)	42	(0.7)
>3 to 6	126	(2.2)	13	(0.2)
> 6 to 12	34	(1.0)	15	(0.4)
> 12 to 18	9	(0.4)	4	(0.2)
> 18 to 24	2	(0.5)	0	(0.0)

[a] Estimates are based on the denominator relevant for each time interval, which decreases over time.
ALT Alanine aminotransferase, ULN Upper limit of normal, LTE Long term exposure.

Figure 35 shows the cumulative risk over time for the ximelagatran-treated and comparator-treated patients who had ALT >3x ULN. The number of new elevations increased above background rates after 1 month and declined after 6 months. Of the 546 ximelagatran-treated patients who had ALT >3x ULN, 93.0% were detected during the first 6 months and 98% were detected within the first 12 months. Fifteen patients experienced their first ALT elevation >3x ULN 12 months (360 days) after their first dose of study drug (12 ximelagatran, 3 warfarin).

Figure 35 Cumulative risk of ALT >3x ULN versus time after randomization (central and local laboratory data) - LTE Pool (ITT Population)



Outcomes for patients with an ALT >3x ULN

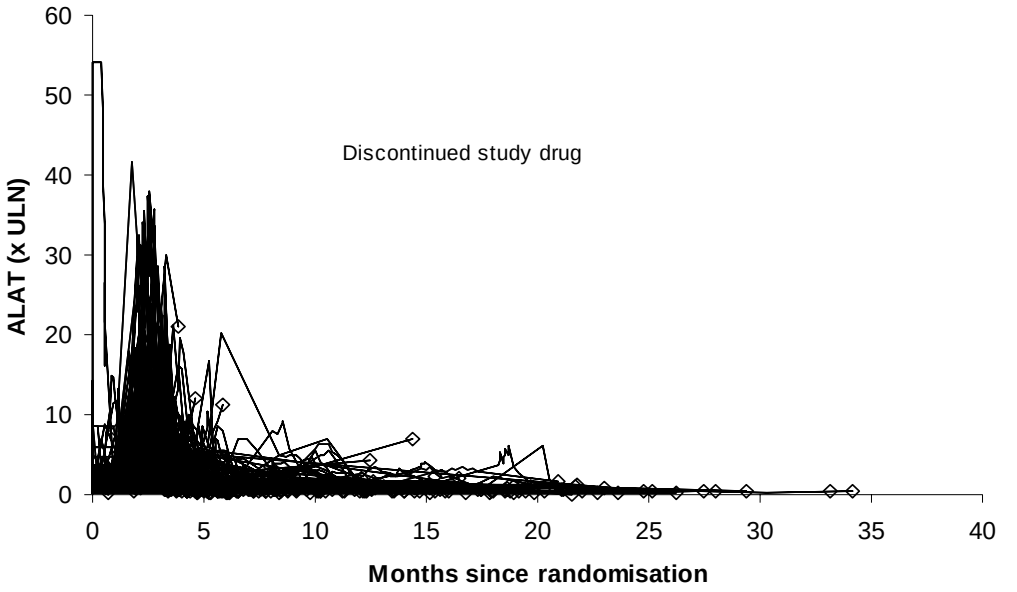
Among the 546 patients in the ximelagatran group who presented with an ALT >3x ULN, 296 (54%) discontinued study drug prematurely, although not necessarily at the time of the ALT elevation (Figure 36 – top panel). The remaining 250 (46%) continued treatment and completed the study (Figure 36 – bottom panel). Ninety-six percent (96%) of ximelagatran-treated patients returned to ALT ≤2x ULN by the end of the follow-up period. For the comparator groups, 93% returned to ALT ≤2x ULN. ALT returned to ≤2x ULN by a median of 40 days in patients who continued treatment and by a median of 28 days in patients who discontinued treatment. The time to recovery did not correspond to the height of the ALT rise. These data demonstrate the reversibility of the ALT increases.

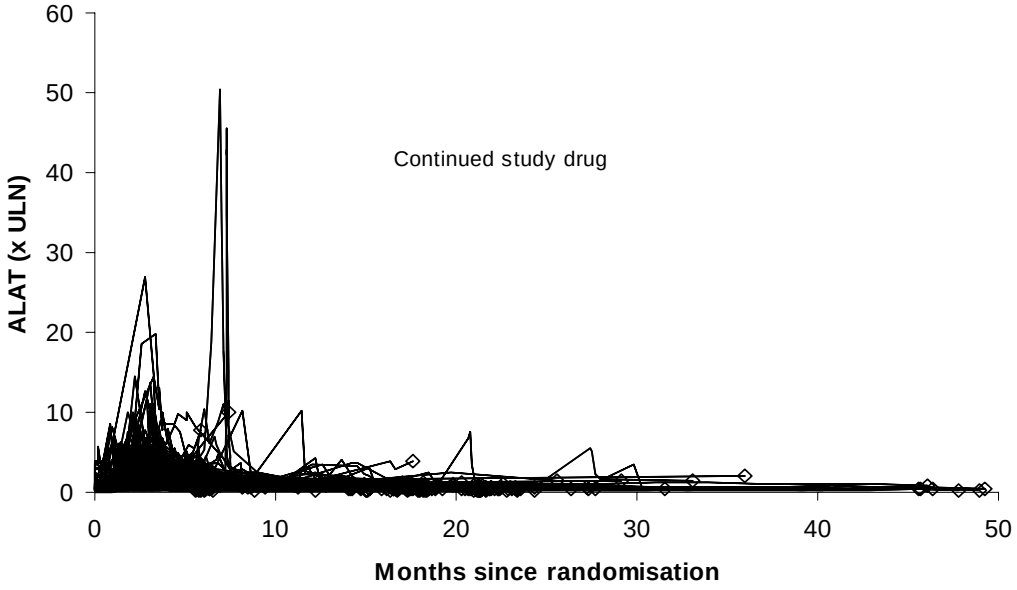
The pattern of changes in ALT in individual patients with ALT >3x ULN, according to whether or not the patient discontinued study drug, is shown in Figure 36 for all data (central and local laboratory data). Note that these curves are potentially influenced by the changes in the laboratory monitoring requirements and that the reason for discontinuing a patient due to an ALT increase was related to the height of the peak and the protocol-mandated withdrawal of patients when the ALT elevation was at the pre-specified level. Therefore, comparison

regarding the time pattern and recovery of the ALT elevation between patients who discontinue and those who did not should be done with caution, as patients with higher and steeper peaks were more likely to discontinue.

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

Figure 36 **Individual time courses for patients in the ximelagatran group with elevations of ALT >3x ULN identified by central and local laboratory data (ITT population)**





ALT did not return to ≤2x ULN by study end or last follow-up in 24 patients in the ximelagatran group and 5 patients in the comparator group. Of the ximelagatran-treated patients, 11 died (10 from non-hepatic cause and one from fulminant hepatitis B, see Section 6.3.4.4) and 13 were alive at last follow-up. Six non-fatal cases had an associated diagnosis resulting in increased ALT that included 3 attributed to alcohol, 2 to cardiac ischemia (MI or heart failure) and one with hepatitis C. The remaining 7 patients had no documented ALT value showing normalization to ALT <2x ULN after the elevation, however in all 7 patients clinical information was available showing that there was no severe hepatic condition developing after the peak ALT and discontinuation from ximelagatran.

In the comparator group, 2 patients died with pancreatic cancer and 3 were alive at follow-up. Of the 3 nonfatal cases, one patient had steatosis observed on ultrasound, one was diagnosed with right-sided heart failure, one with unexplained ALT rise.

Re-challenge cases

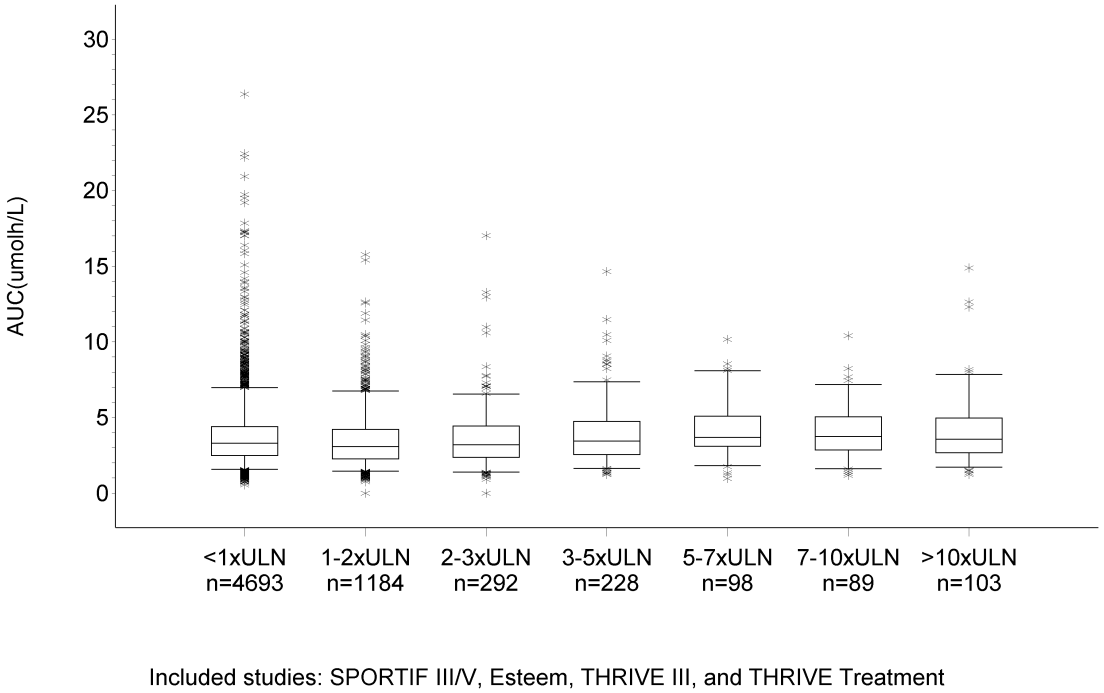
Eighteen patients were identified as re-challenge cases by investigators in the clinical studies as having an ALT elevation >3x ULN and a temporary stoppage of study drug considered to be related to the ALT rise. These re-challenge cases provide additional evidence of the lack of hypersensitivity and immunoallergic response following ximelagatran administration. Of the 18 patients, 16 had no further enzyme elevations. One patient (SPORTIF III, SH-TPA-0003) had a suspected recurrence of ALT elevation after re-challenge. Ximelagatran was first discontinued due to an ALT value of 10.3x ULN with no symptoms. Following re-challenge, after 65 days with no ximelagatran treatment, a second peak ALT value of 3.0x ULN was reached after 2 months and the decision was made to stop study drug permanently. There were no signs or symptoms of drug allergy (no fever, rash, or eosinophilia) and all hepatic enzyme levels in this patient normalized. The ALT profile over time of the last patient (SPORTIF V, SH-TPA-0005) does not represent true positive re-challenge, as this patient had several peaks above 3x ULN followed by decreases below this threshold. The patient had a treatment interruption of 9 days between 2 peaks but, overall, recovered while ximelagatran was continued.

Exposure response

An exposure-response analysis to investigate the relationship between melagatran AUC (exposure) and ALT elevations was performed. Melagatran exposure was predicted in individual patients using a population PK model (see Section 3.5.3). The exposure predictions represent the average melagatran exposure in an individual patient over time. As melagatran plasma concentrations are stable and reproducible, these exposure estimates are believed to be representative of an individual patient's plasma levels over time. However, the actual concentrations at the time of an ALT elevation may have differed from these predicted exposures. The population-model predicted melagatran exposure estimates in patients without any ALT rise overlapped with those who had an ALT rise (Figure 37). In addition, there is no relationship between melagatran exposure and the height of the ALT rise. Since there is no apparent separation in the distributions of melagatran concentration in patients who did or did not experience an elevated ALT, monitoring melagatran plasma concentrations or a surrogate

of melagatran concentrations (such as a coagulation time assay) would not help identify those at risk of an ALT elevation.

Figure 37 AUC by subject's maximum ALT elevation, LTE Pool



AUC Area under the curve; ALT Alanine aminotransferase; LTE Long-term exposure; ULN Upper limit of normal.
SPORTIF III/V SH-TPA-0003/0005; ESTEEM SH-TPC-0001; THRIVE III SH-TPV-0003; THRIVE Treatment SH-TPV-0002&0005.

6.3.4.3 Hepatic adverse events

The previous section presented the laboratory findings for ALT elevations. This section will focus exclusively on the clinical hepatic AEs. The clinical consequences of ALT rise were examined by evaluating the incidence of hepatobiliary AEs as well as the incidence of overall mortality. There was a greater number of hepatobiliary AEs in all categories (any AEs, SAEs, and DAEs) for the ximelagatran group compared to the comparator groups (Table 32). Overall, 11% of patients in the ximelagatran group were reported as having a hepatobiliary AE compared to 4.5% in the comparator group. This difference reflects laboratory abnormalities reported as AEs (Hepatic enzymes increased NOS, ALT increased, AST increased, hepatic function abnormal). The most commonly reported clinical hepatobiliary AEs for ximelagatran-treated patients were cholelithiasis (0.8%), bilirubinemia (0.6%), and cholecystitis (0.4%). There were few noticeable differences in the incidence of

clinical hepatobiliary AEs between the treatment groups, confirming that the transaminase elevation is primarily asymptomatic. Hepatobiliary AEs were considered to be serious for 172 patients (1.3%): 132 (1.9%) in the ximelagatran group and 40 (0.6%) in the comparators group and resulted in treatment discontinuation for 307 (2.3%) patients: 282 (4.1%) in the ximelagatran group and 25 (0.4%) in the comparators group. The difference between treatment groups in the number of DAEs was mainly due to discontinuations for elevated LFTs. The one case of investigator-reported biopsy documented hepatic necrosis was in the ximelagatran group and is described in Section 6.3.4.5.

Table 32 Number (%) of patients with the 10 most frequently reported clinical hepatobiliary AEs, presented by investigator-reported term by ALT >3x ULN: LTE Pool (safety population)

	Ximelagatran		Comparators	
Investigator-reported term[a]	**(n=6931)**		**(n=6216)**	
LIVER AND BILIARY SYSTEM DISORDERS	766	(11.1)	278	(4.5)
Cholelithiasis	52	(0.8)	53	(0.9)
Bilirubinemia	42	(0.6)	38	(0.6)
Cholecystitis	25	(0.4)	20	(0.3)
Hepatomegaly	18	(0.3)	12	(0.2)
Jaundice	9	(0.1)	5	(0.1)
Biliary pain	8	(0.1)	9	(0.1)
Hepatic cyst	7	(0.1)	5	(0.1)
Hepatitis	7	(0.1)	4	(0.1)
Hepatocellular damage	4	(0.1)	3	(<0.1)
Hepatitis cholestatic	3	(<0.1)	4	(0.1)

[a] Patients can appear in more than one category.
ALT Alanine aminotransferase, AE Adverse event, LTE Long-term exposure; ULN Upper limit of normal.

6.3.4.4 Analysis of deaths in ximelagatran-treated patients with and without ALT elevations

An assessment of the deaths in patients (ITT population) with ALT >3x ULN was also undertaken. Twenty-two ximelagatran-treated patients who had an ALT >3x ULN at some time subsequently died (22/546, 4.0%). In the comparator group, there were 4 deaths in 74 patients with an ALT >3x ULN at some time for an incidence of 5.4%. There was no apparent difference in the incidence of deaths between ximelagatran-treated patients with and without an ALT elevation, with values of 4.0% and 3.9%, respectively. Of the

22 ximelagatran-treated patients with an ALT >3x ULN at some time who subsequently died, 11 patients died while their ALT was still elevated (Table 33). The ALT had resolved in the other 11 patients prior to death and the causes of death were non-hepatic (Table 33). The investigator reported the causes of death for the 11 patients who died while their ALT was still elevated as: viral hepatitis (n=1), cardiac (n=4), PE (n=1), GI hemorrhage (n=1), multi-organ failure (n=1), neoplasm (n=1), stroke (n=1), and renal failure sepsis (n=1). Six of these 11 patients also had a concomitant increase in their bilirubin. Only one of these cases had an unexplained increase; however, the cause of death was GI hemorrhage. This case is discussed in Section 6.3.4.5. The investigator-reported cause of death in the other 10 patients whose ALT had resolved was associated with an alternative diagnosis.

Table 33 Summary of patients with ALT elevations >3x ULN at any time who died: patients with elevations still present at death, and patients with elevations that resolved before death (ITT population)

Treatment group Patient number	Cause of ALT elevation	Investigator-reported cause of death
Ximelagatran		
Patients with elevations still present at death		
SH-TPA-0005-0620-7259[a]	Unexplained	Gastrointestinal bleed
SH-TPA-0003-100-1793[a]	Metastases	Pulmonary embolism
SH-TPV-0002-265-5442[a]	Viral hepatitis	Hepatitis
SH-TPC-0001-120-0430[a]	Congestive heart failure	Congestive heart failure
SH-TPC-0001-348-2065[a]	Pancreatic cancer	Pancreatic cancer
SH-TPV-0002-504-4035[a]	Metastases	Multi-organ failure
SH-TPA-0003-258-3276	Unexplained	Stroke
SH-TPA-0005-0610-6082	Unexplained	Sudden death
SH-TPC-0001-150-0733	Unexplained	Sepsis
SH-TPC-0001-278-2524	Unexplained	Sudden death
SH-TPC-0001-310-2946	Unexplained	Myocardial infarction
Patients with elevations that resolved before death		
SH-TPA-0003-104-2978	Unexplained	Myocardial infarction
SH-TPA-0003-115-3963	Liver steatosis	Cardiogenic shock
SH-TPA-0003-118-1685	Unexplained	Sudden death
SH-TPA-0003-316-2826	Unexplained	Aortic rupture
SH-TPA-0005-0230-6977	Unexplained	Aneurysm
SH-TPA-0005-0760-7438	Unexplained	Cardiac arrest
SH-TPA-0005-1860-5022	Unexplained	Sepsis

Table 33 Summary of patients with ALT elevations >3x ULN at any time who died: patients with elevations still present at death, and patients with elevations that resolved before death (ITT population)

Treatment group Patient number	Cause of ALT elevation	Investigator-reported cause of death
SH-TPA-0005-2990-6603	Unexplained	Death
SH-TPA-0005-3030-7859	Unexplained	Gastrointestinal bleed
SH-TPA-0005-0050-8357	Pneumonia	Sepsis
SH-TPA-0003-217-2893	Cholecystitis	Cardiac arrest
Comparators		
Patients with elevations still present at death		
SH-TPA-0005-1190-8675	Pancreatic cancer	Pancreatic cancer
Patients with elevations that resolved before death		
SH-TPA-0003-183-2691	Unexplained	Cardiorespiratory failure
SH-TPA-0005-1290-7968	Unexplained	Congestive heart failure and coronary artery disease
SH-TPA-0005-3490-7158	Unexplained	Cardiac arrest

[a] Concomitant increased ALT >3x ULN and bilirubin >2x ULN.
ALT Alanine aminotransferase, ULN Upper limit of normal.

6.3.4.5 Case report

The one case of investigator-determined biopsy documented hepatic necrosis (Patient SH-TPA-0005-0620-7259) in the ximelagatran group is presented here. Patient SH-TPA-0005-0620-7259, an 80-year-old male, with a past medical history of hyperlipidemia treated in the past with simvastatin, AF, hydronephrosis, urinary retention, fibromyalgia treated with prednisone in the past, coronary artery disease treated with bypass grafting, and right colon cancer not in evolution, began ximelagatran 36-mg bid treatment on 11 June 2001. Concomitant medications included metoprolol, digoxin, and tamsulosin, all taken for months.

The patient's baseline and Month 1 LFTs were normal. At the Month 2 visit (Day 56), ALT was mildly elevated at 2x ULN, less than the threshold that required (at that time) weekly monitoring. At the next scheduled visit on Month 3 (Day 85), ALT was 20x ULN, leading to weekly LFT monitoring and study drug discontinuation 3 days later (Day 88). Despite cessation of study drug, transaminases continued to increase.

On Day 100, ALT was at 30x ULN, ALP just above normal; total bilirubin nearly twice the ULN (mainly unconjugated). At this point the patient entered hospital for observation overnight. Workup was negative for viral serology, immunologic markers, imaging of the liver and abdomen. A liver biopsy performed as outpatient on Day 108 demonstrated "severe

active hepatitis with hepatocyte necrosis, areas of collapse and marked bile ductular proliferation consistent with acute submassive necrosis." Transaminases peaked on Day 108 and then decreased on Day 115 when ALP peaked at 1.5x ULN. Total bilirubin was 8x ULN on Day 114 and remained around this level for a month. On Day 112, the patient's synthetic liver function started to deteriorate, as shown by an increase in PT/INR (16.3 sec and 1.7, respectively), in the absence of anticoagulant therapy, and decreased serum albumin. The investigator labeled the AE as life-threatening severe hepatic injury and readmitted the patient to hospital on Day 113, at which time the patient was jaundiced with no other symptoms and with a normal neurological examination. The patient began treatment with glucocorticoids, vitamin K and ranitidine. He developed thrombocytopenia that was initially attributed to therapy with ranitidine. INR remained elevated and serum albumin low.

The patient was discharged in stable condition after 7 days (Day 119), still with the same laboratory profile (low albumin, elevated INR, decrease in platelet count).

At a visit on Day 140, the patient complained of increasing fatigue over the previous 2 weeks, but otherwise was well. Liver enzymes and platelet count had continued to improve. Prednisone was decreased to 15 mg daily. Profound fatigue continued with no evidence of encephalopathy. However, the patient had developed ascites, significant lower extremity edema and oliguria. A paracentesis was planned for Day 145. However, on the morning of that day, the patient's wife found him unresponsive at home. Resuscitation failed and the patient was pronounced dead. An autopsy confirmed the presence of atherosclerotic disease, ischemic heart disease with triple coronary artery bypass graft 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:

1. 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.

2. 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 with areas of regeneration. Tissue architecture showed early resolution of the inflammation compared to the previous biopsy.

3. Serous ascites in the abdomen; the spleen was not enlarged.

4. 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 contributed to 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 severe hepatic injury as being related and the event of fatal bleed due to duodenal ulcer as not related to the study medication.

The testing algorithm was revised to be more conservative after the biopsy of the liver, and before the patient's death.

6.3.4.6 Hepatic events by subgroup analysis

To understand the factors contributing to an increased risk of ALT elevations, stepwise logistic regression analysis, where treatment was forced into the model, was performed looking at demographic factors, statin use, baseline disease, and ALT >3x ULN (the incidence of concomitant ALT and bilirubin was too low to undertake this analysis). An increased odds ratio for risk of ALT >3x ULN was found for the following factors: treatment (ximelagatran versus comparator), post-ACS patients, patients being treated for VTE, BMI <25 kg/m^2, and females (Table 34). However, the variable of ALT >3x ULN is generally asymptomatic and reversible; therefore, this analysis does not allow a prediction of those at risk for severe hepatic injury.

Table 34 Analysis of potential prognostic factors for ALT >3x ULN, stepwise model selection algorithm: Non-surgical safety - LTE Pool

		95% CI	
Factor	**Odds ratio**	**Lower**	**Upper**
Treatment	6.82	5.34	8.71
Post ACS	1.81	1.47	2.22
VTE-T	1.72	1.40	2.10
BMI <25 kg/m^2	1.42	1.18	1.69
Female gender	1.31	1.11	1.55
Asian	0.52	0.29	0.91

ALT Alanine aminotransferase, ULN Upper limit of normal, LTE Long-term exposure, ACS Acute coronary syndrome, VTE-T Patients being treated for venous thromboembolism, BMI Body mass index, CI Confidence interval.

6.3.4.7 Summary of hepatic effects

Across the studies in which patients received long-term administration of ximelagatran (>35 days), an increase in ALT >3x ULN occurred in 7.9% of the patients compared to 1.2% of patients receiving comparator treatments. The ALT increases were generally asymptomatic and reversible with no evidence of an immuno-allergic reaction. One patient developed biopsy-documented hepatic necrosis with coagulopathy with a fatal outcome from a perforated

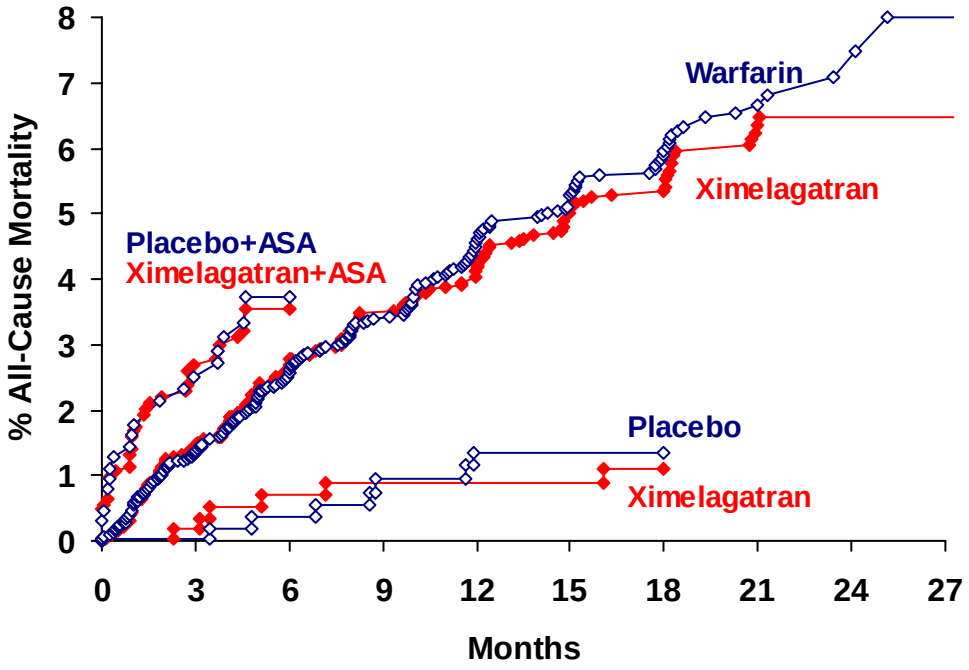
duodenal ulcer. The biopsy documented hepatic necrosis was preceded by an increase in ALT >2x ULN. This case was the reason for the algorithm being revised. After the revision no similar cases occurred.

6.3.5 Deaths

The overall mortality in the ITT population was 3.9% in the ximelagatran group and 4.4% in the comparators group. 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 groups and 165 in the comparator groups). AEs that most frequently led to death were MI, sudden death, cardiac arrest and heart failure, events expected for the 2 populations at risk of cardiovascular events, AF, and post ACS.

In comparisons of ximelagatran with placebo (THRIVE III, SH-TPV-0003 and ESTEEM, SH-TPC-0001), the risk of death from any cause was numerically lower in the ximelagatran group (Figure 38). Analysis of the data from the long-term Phase III studies comparing ximelagatran with warfarin shows that mortality in the ximelagatran group was numerically lower than with the comparator (Figure 38). Overall, in the assessment of risk, mortality was similar to comparators, including placebo.

Figure 38 **All-cause mortality in the placebo-controlled, long-term studies (THRIVE III, SH-TPV-0003 and ESTEEM, SH-TPC-0001 [+ASA]) and the warfarin-controlled, long-term studies (SPORTIF III, SH-TPA-0003; SPORTIF V, SH-TPA-0005; SPORTIF II/IV, SH-TPA-0002/0004; and THRIVE Treatment, SH-TPV-0002/0005), ITT population**



Refer to Table 10 for details of the individual studies and indications; excluding SPORTIF II/IV (SH-TPV-0002/0004), which is the ongoing long-term study for the prevention of stroke and SEE in patients with AF.

6.3.6 Withdrawal and rebound

No indications of withdrawal or rebound phenomena were seen with long-term exposure to ximelagatran.

In SPORTIF V (SH-TPA-0005), a single stroke occurred in the ximelagatran group upon switching to open-label warfarin at the end of the study. The 1236 patients who entered the 2 week transition period accumulated 47.54 patient years at risk for stroke/SEE. The rate of 1.61%/year for patients taking ximelagatran predicts 0.77 patients with primary events in this period, consistent with the one stroke that occurred. Second, patients who discontinued ximelagatran treatment during the trial did not experience more frequent AEs in the 2 weeks following drug discontinuation compared with other time periods.

In SPORTIF III (SH-TPA-0003), 11 patients who had a stroke or SEE were censored from the OT analysis of this endpoint. Of these 11 patients, 2 had primary events within 30 days of stopping study drug; one was being treated with ASA 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: VKAs (3 patients), ASA (2), clopidogrel (2), LMWH (1) and no treatment (1).

During the 2 week follow-up period for THRIVE III (SH-TPV-0003), 3 VTE events occurred after cessation of study medication (2 patients in the ximelagatran group and 1 in the placebo group).

A follow-up visit was performed in study THRIVE II&V (SH-TPV-0002 and SH-TPV-0005) 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.

The total frequency of AMIs in ESTEEM (SH-TPC-0001) after stopping treatment was similar for ximelagatran (1.5%) and placebo (1.4%) and the total mortality was similar between the treatment groups.

6.3.7 Summary of safety in the non-surgical population

In the long-term studies, ximelagatran demonstrated a similar incidence of AEs, bleeding AEs, adjudicated bleeding events, and mortality when compared to well-controlled warfarin. ALT testing is recommended to minimize the potential risk of rare, severe hepatic injury.

Overall, these studies support the safe use of a fixed oral dose of ximelagatran 36 mg bid when ALT is monitored appropriately, in the absence of coagulation monitoring, for the life-long treatment of patients with AF. The data further support the safe use of a fixed oral dose of ximelagatran 24 mg bid, for the treatment of patients with VTE initiated after the completion of a standard treatment period, for the secondary prevention of VTE.

6.4 Practical management issues

6.4.1 Switching to and from ximelagatran

When switching from a VKA to ximelagatran, the recommendation based on the data is:

- Stop the VKA and initiate ximelagatran when the INR is <2.0.

When switching from LMWH to ximelagatran, the recommendation based on the PK of LMWH and ximelagatran is:

- Stop LMWH and initiate ximelagatran 8 to 12 hours after last dose.

When switching from UFH to ximelagatran, the recommendation based on the PK of UFH and ximelagatran is:

- Stop UFH and initiate ximelagatran 3 to 6 hours after stopping infusion.

Switching from ximelagatran to VKAs may result in a short period of decreased protection from VTE and stroke/SEE owing to the delay in onset of VKAs. Switching to heparins and LMWHs raises no concerns in this regard because their onset, like that of ximelagatran, is rapid. The following recommendations also take into account the half-life of ximelagatran.

When switching from ximelagatran to VKA:

- Stop ximelagatran and begin VKA (parallel treatment with heparin or LMWH as needed).

When switching from ximelagatran to LMWH/UFH:

- Initiate LMWH/UFH 12 hours after last dose of ximelagatran (can be started earlier based on judgment of physician).

6.4.2 Monitoring

The standard tests used to monitor the effect of other anticoagulants (VKAs or heparins) are relatively insensitive for monitoring the effect of ximelagatran (see Section 3.5.2).

6.4.3 Management of overdose

There is no known antidote for ximelagatran or melagatran and an overdose of ximelagatran could lead to hemorrhagic complications. The following recommendations are being proposed for the practical management of ximelagatran overdose. Patients in whom an overdose is suspected should discontinue the drug and acute overdose treatment should include supportive therapy. The effect of melagatran remains for approximately 12 to 24 hours following the last dose but, in patients with renal impairment, the effect may be longer. As melagatran depends on renal excretion as the primary route of elimination, satisfactory diuresis should be maintained. Melagatran can be dialyzed, and this method may be used to decrease drug levels in patients with renal impairment. Coagulation time assays (APTT, ACT, PT/INR, TT) may be prolonged and can be an indication of remaining anticoagulant effect.

6.5 Summary of ximelagatran safety

The safety of ximelagatran was evaluated in several large populations at risk of thrombotic disease. A large number of the patients were elderly with a variety of comorbidities. The number and type of AEs experienced by patients treated with ximelagatran, with the exception of hepatobiliary AEs, were similar to those of the comparator groups. DAEs were more frequent in the ximelagatran group due to the protocol-mandated discontinuation of patients with pre-specified ALT elevations. Bleeding events in the ximelagatran group were similar to or less than in the comparator groups. Mortality in the ximelagatran group was similar to or less than the comparator groups. Based on the ALT observations, ALT testing is specifically recommended in the proposed label and a comprehensive Risk Minimization Action Plan (RiskMAP) has been developed and proposed to support compliance with this recommendation and maximize the benefit-risk profile of ximelagatran in clinical practice.

7. XIMELAGATRAN RISK MINIMIZATION ACTION PLAN (RISKMAP)

As detailed in the safety section of this document (Section 6.3.4.2), ximelagatran was associated with reversible ALT elevations, which were rarely associated with severe hepatic injury. The characteristic time pattern of ALT elevations (predictable, occurring primarily between 1 month and 6 months after initiation of treatment) and reversibility suggest that regular ALT testing within the first year of administration will mitigate the rare risk of severe hepatic injury and, thereby, maximize the benefit-risk profile of ximelagatran.

Therefore, AstraZeneca has developed and proposed a comprehensive RiskMAP for ximelagatran that has been discussed with the FDA and was part of the original NDA submission. The ALT-testing and management algorithm proposed in the product labeling was shown to be effective during the Phase III clinical trials. AstraZeneca followed FDA guidance documents on Risk Management in the development and design of the RiskMAP (FDA Draft Guidance 2004a, 2004b, 2004c). The proposed RiskMAP is a voluntary, education-based system reinforced by a complementary, interconnected set of materials and programs that emphasize and support compliance with this ALT-testing and management algorithm. The RiskMAP was developed using a systematic approach to identify potential failures in the medication and use process and to create redundant interventions that were then field-tested with the 3 key groups (physicians and their hospital or office staff, pharmacists, and patients and their caregivers) and integrated into the marketing program as “Exanta ps” for Exanta patient support.

Beginning from the time of launch, AstraZeneca will actively measure compliance with the ALT-testing algorithm and the occurrence of hepatic events. Tested epidemiologic measures of compliance (using large automated healthcare databases) will be evaluated against pre-specified target compliance levels to be agreed with the FDA. Rapid and complete assessment of post-marketing hepatic events, including standardized data collection, enhanced follow-up, and epidemiology studies of large automated healthcare databases will be evaluated against known background rates. Both compliance and outcomes will be reviewed with the FDA on a periodic basis. Actions taken regarding the RiskMAP will be based on compliance with ALT-testing in the context of measures of hepatic outcomes.

7.1 What is the RiskMAP?

The RiskMAP is based on an ALT-testing and management algorithm, is implemented through active distribution of a set of educational materials and support programs directed to physicians, to pharmacists, and to patients, and is evaluated through extensive, standardized measures of compliance and hepatic outcomes using both epidemiologic and pharmacovigilance methods. The proposed RiskMAP is a voluntary, education-based system reinforced by a complementary, interconnected set of materials and programs that emphasize and support compliance with the ALT-testing and management algorithm.

7.2 Goals and objectives of the RiskMAP

The primary goal of the ximelagatran RiskMAP is to optimize the benefit-risk of ximelagatran by minimizing the potential risk of severe hepatic injury in patients who present with an elevation in hepatic transaminases.

The program objective of the RiskMAP is to facilitate compliance with the ALT testing recommendations by healthcare workers and patients

7.3 Rationale for ALT testing and management

The increases in ALT observed in the development program were primarily asymptomatic and reversible despite the continuation or discontinuation of the drug based on decisions directed by the algorithm (see Section 6.3.4.2). In addition, changes in AST, ALP, and bilirubin were smaller and less frequent than changes in ALT, and isolated increases in these tests occurred with similar frequencies in the comparator groups. While the incidence of increases in ALT did not predict the incidence of severe hepatic injury, any ximelagatran-induced hepatocellular injury will, by definition, be preceded by an increase in ALT. The underlying assumptions of basing this RiskMAP on the ALT-testing and management algorithm are that:

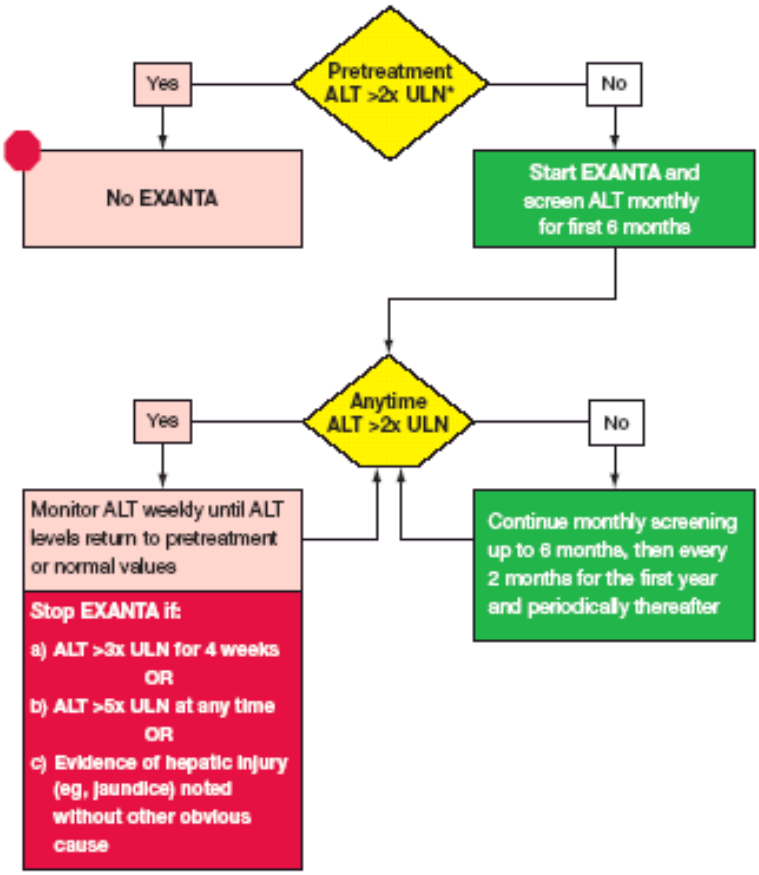
1. Severe hepatic injury will be preceded by an increase in ALT.

2. Appropriate ALT testing will identify individuals with elevated ALT levels, triggering the increased frequency of such testing for these individuals.

3. Cessation of ximelagatran therapy, in accordance with the proposed ALT-testing algorithm, will minimize the risk of developing severe hepatic injury.

The ALT-testing algorithm that is included in the proposed labeling is illustrated in Figure 39.

Figure 39 Proposed ALT-testing algorithm



7.4 The RiskMAP materials

The proposed program is termed “EXANTA ps” for EXANTA patient support. The various materials developed for “EXANTA ps” were developed with the consultation of physicians and pharmacists and then field tested for comprehension and usefulness.

7.4.1 RiskMAP materials development and testing design

The RiskMAP was developed in a systematic manner and is consistent with the guidelines presented in the FDA draft guidance on risk management (FDA Draft Guidance 2004a, 2004b, 2004c). AstraZeneca used a Failure Mode Effects Analysis (FMEA) to identify and select potential interventions throughout the *medication administration and use process* to reinforce compliance with ALT testing. The interventions proposed have been designed to address each step in the *medication administration and use process* where noncompliance could occur (ie, failure modes). The program was designed to ensure ease of use and to provide redundant interventions. In addition to the prescribing information, the primary tools of the RiskMAP

include educational material, practice management tools, and support systems. The tools are organized around specific target audiences and around specific failure modes.

Targeted audiences for the proposed RiskMAP include all those who prescribe, dispense, and receive ximelagatran. Specific materials have been developed for use by each of these groups with their input. After several hundred interviews and focus groups, each of the tools (eg, reminder sheets, box flaps on blister packaging) was extensively field tested with its respective group (514 physicians, 375 pharmacists, and 180 patients). AstraZeneca believes that the combination of these enhanced interventions, along with multiple outreach and distribution mechanisms, will increase the success of the program and; thereby, improve the benefit-risk of ximelagatran in clinical practice.

It is important to note that participants were blinded to the product name and manufacturer. Overall, more than 70% of the respondents in each of these quantitative comprehension studies indicated that the materials presented were easy to understand, useful, and likely to assist with patient counseling or managing the ALT-testing requirements.

7.4.2 RiskMAP materials implementation

Introduction

The overall success of the program will depend on effective dissemination of the "EXANTA ps" elements to the physicians, pharmacists, and patients. AstraZeneca will introduce and implement "EXANTA ps" using the following methods of communication.

All materials will be available online through a dedicated web site. Clinicians and office staff members, and pharmacists, patients and caregivers will be able to download and print all the materials. AstraZeneca will also provide a dedicated toll-free telephone number to call with questions about ximelagatran and/or "EXANTA ps", and from which they can request materials. Physicians, hospital staff, and pharmacists who are not personally contacted by sales representatives will receive the elements of the program via other means, including mail, educational programs, distribution by health plans, and distribution by hospital and professional organizations.

Physicians

AstraZeneca intends to reach all potential prescribers regarding the elements of the program. At launch, through sales and marketing efforts, AstraZeneca will disseminate the elements of "EXANTA ps" to physicians who are prescribers of oral anticoagulants. Continuing medical education credits for the physicians will be offered. AstraZeneca also plans to promote "EXANTA ps" in hospital settings. Institutions will receive specially packaged kits of tools and instructions to support the safe use of ximelagatran. Other institutions, such as long-term care facilities, will receive elements of the program via mail, using available mailing lists.

Pharmacists

AstraZeneca plans to distribute the elements directly to all pharmacists licensed to practice in retail pharmacy and hospital settings using commercially available mailing lists. AstraZeneca

will also solicit the support of pharmacy chains, hospitals, and pharmacist organizations to have similar communications sent to their members. Continuing education credits for pharmacists will be offered.

Patients

AstraZeneca plans to provide information and materials to healthcare providers and patients who receive ximelagatran. Patients will receive the elements of the program through their healthcare providers, including physicians, support staff, and pharmacists. The materials will include opt-in response forms to allow patients to register for ongoing risk management communications from AstraZeneca (a reminder system for patients who agree to participate).

7.5 RiskMAP evaluation plan

AstraZeneca believes the full benefit of ximelagatran can be realized in the intended patient population if patients are compliant with the ALT-testing and management algorithm. AstraZeneca also believes that compliance with the proposed ALT-testing algorithm is a process measure that reflects desirable safety behaviors and, therefore, serves as an objective, evidence-based measure of RiskMAP performance. An ongoing, quantitative evaluation of ALT-testing compliance will be obtained using large healthcare claims databases.

Enhanced post-marketing surveillance, as well as epidemiologic monitoring of large healthcare claims databases, for hepatic outcomes will address the RiskMAP objective of assessing outcomes in parallel with evaluation of testing compliance, and allow for ongoing assessment of the overall effectiveness of the RiskMAP.

7.5.1 Evaluation of compliance with ALT testing

For evaluation of compliance with ALT testing, the intended primary data source is the administrative claims database of a large Health Maintenance Organization (HMO). Comprising health plans distributed across the US, the database has linked prescription data, outpatient and inpatient data, laboratory claims and laboratory results data for over 16 million persons. This data source has several advantages over most other data sources, including national distribution, longitudinal data, and a large population base. In addition, AstraZeneca has tested and proven the ability to measure and evaluate compliance in this type of database.

The study sample will comprise the entire cohort of patients on ximelagatran therapy who have coverage in HMOs for laboratory claims. For all patients in the database, it can be determined if a laboratory test was performed. Compliance with the ALT-testing and management algorithm will be evaluated against a pre-specified target level of compliance to be agreed with the FDA.

7.5.2 Evaluation of hepatic outcomes

To address the second objective of the RiskMAP (minimize the risk of severe hepatic injury), both pharmacovigilance and pharmacoepidemiologic methods will be used to capture and measure hepatic outcomes in patients receiving ximelagatran after launch. A variety of outcomes in the database and other data sources will be evaluated using epidemiology

methods. However, pharmacovigilance will be the primary means of identifying and quantifying RiskMAP effectiveness with regards to outcomes. The observed rates of hepatic outcomes will be evaluated against: background rates of hepatic events and observed compliance with the ALT-testing and management algorithm.

7.5.2.1 Pharmacovigilance methods

The goal of the ximelagatran pharmacovigilance efforts will be the rapid and thorough assessment of all post-marketing hepatic events.

Post-marketing surveillance (worldwide)

Worldwide post-marketing surveillance is a standard AstraZeneca global process performed for every product marketed by the Company and is based on the standardized collection and evaluation of case reports coming from the following sources: spontaneous (unsolicited) AE reports, safety findings from ongoing and completed studies, literature reports, and reports on medication errors. When necessary, site visits will be conducted to investigate important events. AstraZeneca will comply with all routine, but also specific, spontaneous reporting procedures as requested by Regulatory Authorities, as these events will be labeled.

Solicited reports (US)

In addition to the special attention to the spontaneous reporting detailed above, AstraZeneca intends to obtain special agreements with institutions maintaining registries of acute severe hepatic injury, so that additional reports associated with the use of ximelagatran can be forwarded urgently to the Sponsor and investigated appropriately.

7.5.2.2 Pharmacoepidemiology methods (US)

The primary outcome of interest, severe hepatic injury, is a rare event. Therefore, hepatic outcomes and surrogate outcomes will be measured and their relationship to treatment and other factors assessed.

Pharmacoepidemiologic methods will be applied at 2 points in the post-marketing experience: (1) when sufficient data is available in HMO databases to conduct epidemiological analysis to assess rates of hepatic outcomes, and (2) in response to a signal generated by post-marketing safety surveillance.

7.6 Continuous Quality Improvement (CQI) of the RiskMAP

Compliance with the ALT-testing and management algorithm will be evaluated against a pre-specified target level of compliance to be agreed with the FDA. The observed rates of hepatic outcomes will be evaluated against: background rates of hepatic events and observed compliance with the ALT-testing and management algorithm. Both compliance and outcomes will be reviewed with the FDA on a periodic basis. Actions taken regarding the RiskMAP will be based on compliance with ALT-testing in the context of measures of hepatic outcomes and the benefits of ximelagatran.

8. BENEFIT-RISK EVALUATION

Thrombosis is a major cause of cardiovascular mortality. More than 60% of the 960000 cardiovascular deaths in the US in 1999 were caused by thrombotic disease (NHLBI 2002). VTE, a term that includes both DVT and PE, is the third most common cardiovascular disease after ischemic heart disease and stroke (US National Center for Health Statistics 2000), and is a major contributor to morbidity, mortality, and healthcare costs. The incidence in the total population is about 70 to 113 cases/100000 persons/year and increases with age, to as high as about 300 to 500 cases/100000 persons/year (age group 70 to 79 years) (White 2003). The population at greatest risk for VTE is those undergoing major lower extremity orthopedic surgery and those who experience major trauma or spinal cord injury. The risk for DVT after TKR surgery is greatest within the first 2 weeks after surgery. Without treatment, the prevalence of total DVT at 7 to 14 days after TKR surgery is between 40% and 84%, with proximal DVT rates between 9% and 20% (Geerts et al 2001). Atrial fibrillation, the most common sustained arrhythmia, affects 4% of those over 60 years of age and 10% of those aged over 80 years (Singer 1998) and is often associated with stroke. Atrial fibrillation, is one of the strongest independent risk factors for stroke, increasing stroke incidence 5-fold to rates of approximately 5% per year for initial stroke and 12% for recurrent stroke (Wolf 1998).

An extensive, primarily outcome-based clinical program has demonstrated ximelagatran to be an effective anticoagulant compared to placebo and to warfarin. Warfarin INR in these studies was well-managed and likely exceeded the rate of "in-range" levels achieved in clinical practice. Ximelagatran offers the advantages of an oral anticoagulant with consistent pharmacokinetics that allow fixed dosing without monitoring for dose adjustment. Efficacy was also attained without CYP450 drug interactions, food interactions, or alcohol interactions. Interactions have been noted with erythromycin and azithromycin but the degree of interaction was less than the inter-subject variability precluding the need for a dose modification. These interactions are not likely to be mediated via CYP450. Ximelagatran has a rapid onset of action precluding the need for bridging therapy with heparins when rapid anticoagulation is needed. The rapid offset of action allows for simple discontinuation of drug administration when anticoagulation needs to be stopped. Melagatran is effectively cleared by the kidneys, and if needed, can be dialyzed.

For each indication studied, consistent efficacy and safety of fixed-dose ximelagatran versus comparator was demonstrated across demographic subgroups including age, gender, race, body weight, BMI and renal function (calculated CrCL). Due to the dependence of melagatran on renal elimination, of particular importance is the consistent efficacy and safety of oral ximelagatran across the renal function subgroups, classified as normal or with mild or moderate renal impairment. Experience in patients with severe renal impairment is limited because patients with calculated CrCL <30 mL/min were excluded from the clinical trials. Together, these data indicate that the approximately 3 to 4-fold range of plasma melagatran concentrations are achieved in patients with a fixed dose of ximelagatran, and across the different renal functions. Despite this variation in plasma concentrations, the same fixed dose (either 24 or 36 mg bid depending on indication) result in consistent efficacy and safety. The use of a fixed dose of oral ximelagatran for the proposed indications is, therefore, supported

by the consistent safety and efficacy demonstrated across the diverse patient populations studied.

Oral ximelagatran (36 mg bid for 7 to 12 days) prevented significantly more VTE and/or all-cause mortality than warfarin in patients undergoing TKR surgery. The NNT for improved antithrombotic outcome was 12. Although slightly more bleeding adverse events were reported with ximelagatran than with warfarin this did not result in more transfusions nor did it affect surgical outcome or wound complications. The incidence of serious adverse bleeding events and of adjudicated major and minor bleeding events was similar between treatments.

Oral ximelagatran (24 mg bid for up to 18 months) demonstrated clear benefit over placebo (NNT of 10) in the long-term prevention of recurrent VTE events in patients with demonstrated risk for VTE. This included a clinically important reduction in PE, a condition that can result in serious morbidity and mortality. The incidence of major bleeding and major/minor bleeding events was comparable to that seen with placebo.

Oral ximelagatran (given as a fixed dose of 36 mg bid for up to 2.5 years) was effective when compared to well-controlled warfarin in reducing the risk of stroke and SEE in patients with AF, with a numerically lower risk of bleeding.

An increased incidence of ALT elevations to >3x ULN was seen in the patients treated long-term with ximelagatran. These elevations were mostly asymptomatic and reversible within the first 6 months of therapy. No hepatic signal was observed during short-term administration after orthopedic surgery. The observed incidence of ALT elevations with ximelagatran therapy was not accompanied by a predictable incidence of severe hepatic injury even when the medication was continued. The large clinical trial exposure helped to characterize rare cases of concomitant bilirubin increase as well as one case of biopsy-documented hepatic necrosis. These cases have resulted in a conservative algorithm of ALT testing and management that will be recommended in a comprehensive RiskMAP to be implemented at the time of introduction of ximelagatran into clinical practice. Although the RiskMAP will establish ALT testing as an integral part of ximelagatran long-term use, this testing is seen as less burdensome than the lifelong INR monitoring and dose-management required for warfarin.

Overall mortality can be regarded as an important benefit-risk measure. The overall mortality in the ITT population was 3.9% in the ximelagatran group and 4.4% in the comparators group. In comparisons of ximelagatran with placebo, the risk of death from any cause was similar between the groups. Analysis of the data from the long-term Phase III studies also indicated that mortality in the ximelagatran group was numerically lower than with warfarin.

Ximelagatran, an oral direct thrombin inhibitor, has been extensively investigated in the largest clinical trials ever conducted for the 3 clinical indications discussed in this briefing document. Ximelagatran has consistently shown effectiveness as a fixed-dose anticoagulant without dose adjustment or coagulation monitoring over time and has a favorable benefit-risk profile in each of the 3 proposed indications. Ximelagatran has demonstrated effectiveness as an oral anticoagulant in the prevention of thrombotic events in various patient populations

representing different spectrums of prothrombotic risk. As the first oral alternative to warfarin in 50 years, ximelagatran represents a true advance in medical therapy for the prevention of life-threatening thromboembolic disease.

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LIST OF APPENDICES

AstraZeneca

Advisory Committee Briefing Document
Appendix A

Drug Substance: Ximelagatran

Appendix A – THRIVE Treatment Study (SH-TPV-0002 & SH-TPV-0005) and ESTEEM Study (SH-TPC-0001)

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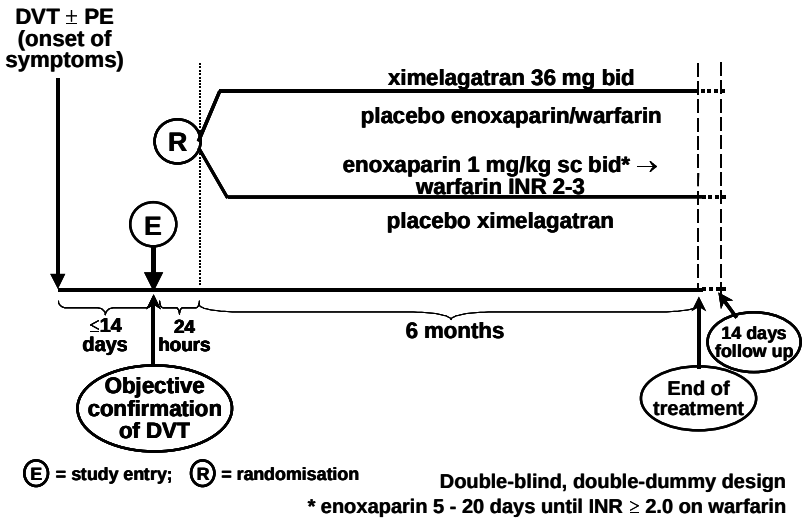
1. THRIVE TREATMENT (SH-TPV-0002 & SH-TPV-0005)

Objectives: Primary objective: assess whether ximelagatran 36 mg twice daily given as treatment for venous thromboembolism (VTE) is not clinically inferior to the standard treatment regimen (enoxaparin/warfarin) in the prevention of recurrent symptomatic, objectively confirmed VTE in patients who present with lower extremity DVT with or without PE. Secondary objective: assess all-cause mortality and safety with special regard to bleeding.

Design: An international double-blind, double-dummy, randomized, parallel-group multicenter study comparing the efficacy and safety of ximelagatran with standard treatment (see Figure 1). At baseline, bilateral ultrasound scanning of the legs and perfusion scanning of the lungs were performed. All recurrences of VTE (the primary endpoint), and all causes of death and major bleeding events, were objectively verified and centrally adjudicated by an independent committee. A non-inferiority margin (delta) of 4% was pre-specified.

Figure 1 Study design of THRIVE Treatment (SH-TPV-0002&SH-TPV-0005)



Open UFH/LMWH treatment was allowed for a maximum of 24 h prior to randomization. Baseline examinations (bilateral CUS, VQ scan, chest radiography) were to be performed within 72 hours after randomization.

Disposition and demographics: A total of 2489 patients were randomized and received study drug and 2363 completed the study. The treatment groups were comparable for demographic characteristics, baseline parameters, treatment compliance and use of concomitant medication.

Efficacy: Ximelagatran is not clinically inferior to the standard treatment regimen (enoxaparin/warfarin) in the prevention of recurrent symptomatic, objectively confirmed VTE in patients who present with lower extremity DVT with or without PE. The estimated cumulative risk of a recurrent symptomatic VTE event was 2.1% and 2.0% in the ximelagatran treatment arm and the enoxaparin/warfarin treatment arm, respectively. The estimated absolute treatment difference was 0.2% (95% CI: -1.0% to 1.3%). All-cause

mortality was numerically lower in the ximelagatran treatment group; the cumulative risk of death was 2.3% compared to 3.4% in the enoxaparin/warfarin treatment group, with an estimated absolute treatment difference of -1.1% (95% CI: -2.4% to 0.2%).

Pharmacokinetics: Plasma melagatran steady state levels (0.2 to 0.3 μM) were as predicted from the population pharmacokinetic model derived from study SH-TPV-0003 (THRIVE III).

Pharmacodynamics: Activated partial thromboplastin time (R^2=0.271) and ecarin clotting time (R^2=0.774) increased with increasing melagatran concentration.

Safety: The cumulative risks for a major bleeding event were 1.3% and 2.2% in the ximelagatran and enoxaparin/warfarin group, respectively, and for a major or minor bleeding event 6.1% and 7.5%, respectively. The differences between the treatment groups for major bleeding events and for major or minor bleeding events were not statistically significant. The cumulative risks for any bleeding event were 20.4% and 28.0% in the ximelagatran and enoxaparin/warfarin group, respectively, with a statistically significant treatment difference of –7.6% (95% CI: –11.1 to –4.1%) favoring ximelagatran treatment. There were 3 fatal PEs in each treatment group and 1 fatal bleeding event in the ximelagatran group compared to 4 such events in the enoxaparin/warfarin group (ITT analysis). According to OT analysis, there was 1 fatal PE in the ximelagatran group compared to none in the enoxaparin/warfarin group and 1 fatal bleeding event in the ximelagatran group compared to 2 in the enoxaparin/warfarin group.

The number of patients with AEs were almost identical between the ximelagatran (n=930) and enoxaparin/warfarin (n=934) treatment groups. There were 220 patients with SAEs in the ximelagatran treatment group and 191 in the enoxaparin/warfarin group, the overall difference being largely attributable to a difference within the System Organ Class (SOC) Liver and biliary system disorders. Patients with adverse events leading to discontinuation from study drug totaled 177 in the ximelagatran group and 126 in the enoxaparin/warfarin group, with 71 and 7 such discontinuations in the SOC Liver and biliary system disorders, respectively. Many of these discontinuations were required due to protocol stipulations regarding liver enzyme elevations.

The ALT elevation >3x ULN incidence was 9.6% in the ximelagatran group versus 2.0% in the enoxaparin/warfarin group. Bilirubin was elevated >2x ULN in 9 ximelagatran patients and 6 enoxaparin/warfarin patients The onset of the ALT elevations typically occurred during the second and third treatment months in the ximelagatran group and during the first 2 weeks in the enoxaparin/warfarin group. A resolution of the elevation was established for nearly all patients, both among those who discontinued study drug and those who continued. The ALT elevations were in most cases not associated with specific clinical symptoms. One case of suspected drug-induced hepatitis without known alternative explanation recovered after cessation of ximelagatran. No case of drug induced liver failure was identified in this study. It is unclear if the study drug contributed to the fatal course in one case of fulminant hepatitis B in the ximelagatran treatment group. There was no evidence from this study that the hepatic enzyme elevations associated with the ximelagatran-treatment causes persistent liver function

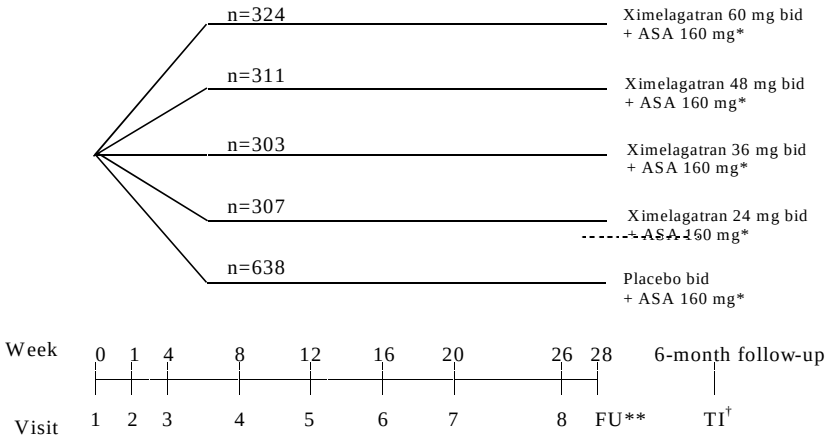
disorder. There were no other significant laboratory findings and no significant findings in the ECG, vital signs, or physical examination data.

Conclusion: Ximelagatran (36 mg twice daily) is non-inferior to a regimen of enoxaparin and well-controlled warfarin in prevention of recurrent symptomatic VTE in patients who present with DVT, with or without PE, over a 6-month treatment period. There were no significant differences for all-cause mortality or major and/or minor bleeding events between treatments. The clinical importance of ALT elevations >3x ULN, occurring more frequently in the ximelagatran group, is not clear.

2. ESTEEM (SH-TPC-0001)

Design and objectives: Multicenter, multinational, double-blind, placebo-controlled, parallel group, dose-guiding study comparing the efficacy and safety of 4 doses of ximelagatran versus placebo when given over a 6-month period to acetylsalicylic acid (ASA)-treated patients with elevated biochemical markers of myocardial damage following a recent acute coronary syndrome (ACS), (Figure 2). The primary objective was to investigate the relationship between the dose of ximelagatran and the frequency of the composite clinical endpoint of death (all cause mortality), myocardial infarction (MI) and severe recurrent ischemia. Suspected endpoint events including death, myocardial infarction, severe recurrent ischemia, stroke and major bleeding were adjudicated by an independent, blinded Clinical Event Adjudication Committee (CEAC).

Figure 2 Study design of ESTEEM (SH-TPC-0001)



* If a patient experiences side effects, which were judged by the investigator to be possibly related to the ASA treatment, the ASA does was to be reduced from 160mg od to 75mg od
** All patients were to attend this visit 2 weeks after discontinuing study medication and then continued to attend the remaining scheduled visits in accordance with the protocol
† Telephone interview

Disposition and Demographics: Of the 1900 patients randomized, 1883 patients (1245 ximelagatran, 638 placebo) took at least one dose of study drug. Mean duration of exposure from first to last intake of study drug was 143 days for the placebo group, compared with 143, 130, 13, and 132 days for the 24 mg, 36 mg, 48 mg, and 60 mg ximelagatran groups, respectively. Overall the demographic and baseline characteristics were balanced across the treatment groups.

Efficacy: The study fulfilled its primary objective, showing a statistically significant dose-response in the positive direction for ximelagatran (p=0.0357). This positive effect was driven by the efficacy of all ximelagatran dose groups combined, not by differences between dose levels of ximelagatran. The cumulative risk at 6 months for the primary endpoint comprising

death/MI/SRI was 12.7% for the combined ximelagatran groups (range 12.1% to 13.7%), compared with 16.3% in the placebo group, hazard ratio 0.76 (95% CI: 0.59, 0.98; p=0.0317). Consistent results were observed in the on-treatment analysis with a hazard ratio of 0.68 (95%CI: 0.51, 0.89; p=0.0052) for the primary endpoint.

Pharmacokinetics: The pharmacokinetics of melagatran was dose proportional and consistent during the 6-month treatment period. The total variability of melagatran exposure was about 50%, with renal function assessed as calculated creatinine clearance as the most important predictor of inter-individual variability. Concomitant drugs of various pharmacological classes that were used chronically by the studied patients were not found to have any clinically relevant influence on the pharmacokinetics of melagatran.

Pharmacodynamics: Not applicable.

Safety: The overall occurrence of AEs and SAEs (fatal and non-fatal) were similar in all treatment groups. DAEs (discontinuations of study drug due to AEs) were more common in the ximelagatran groups. This was partly explained by the protocol-specified criteria for discontinuation due to liver enzyme elevations. Discontinuation due to a bleeding event was also more frequent in patients receiving ximelagatran. The cumulative risk of major and/or minor bleeding events was increased upon administration of ximelagatran plus ASA compared to ASA alone (Table 1).

Table 1 Bleeding events: Number of patients with an event (OT analysis)

Endpoint	Placebo + ASA	Ximelagatran + ASA				
	(n=638)	24 mg (n=307)	36 mg (n=303)	48 mg (n=311)	60 mg (n=324)	Combined (n=1245)
Minor and/or major bleeding	72 (11.3%)	51 (16.6%)	50 (16.5%)	72 (23.2%)	74 (22.8%)	247 (19.8%)
Major bleeding[a]	3	4	1	7	3	15
Minor bleeding[b]	69	47	49	65	71	232
Major bleeding	3 (0.5%)	6 (2.0%)	1 (0.3%)	9 (2.9%)	5 (1.5%)	21 (1.7%)
Multiple bleeding and/or major bleeding	30 (4.7%)	20 (6.5%)	22 (7.3%)	33 (10.6%)	30 (9.3%)	105 (8.4%)
Major bleeding[a]	3	4	1	7	3	15
Multiple bleeding[c]	27	16	21	26	27	90
Bleeding leading to discontinuation of study treatment and/or major bleeding	10 (1.6%)	21 (6.8%)	9 (3.0%)	26 (8.4%)	24 (7.4%)	80 (6.4%)
Major bleeding[a]	3	6	1	9	5	21
Bleeding leading to discontinuation of study treatment	7	15	8	17	19	59

[a] Patients with major bleed occurring first.
[b] Patients with minor bleed occurring first in this category.
[c] Multiple bleeding is defined as 2 or more bleeding events. The same principle applies within each category ie, major bleeding, multiple/major, and discontinuation/major.

Epistaxis was the most commonly reported bleeding-related AE. There was an increased incidence of elevated liver enzymes in patients receiving ximelagatran. Typically the elevations occurred during the second and third treatment months. In most cases the ALT elevations were not associated with specific clinical symptoms. No case of drug-induced liver failure was identified. Both bleeding events and liver enzyme elevations showed a dose-relationship with ximelagatran. No other significant AEs were identified. There were no changes in vital signs or ECG causally related to ximelagatran.

Conclusions: Oral ximelagatran in combination with ASA was superior to ASA alone (placebo) in reducing the risk for the composite endpoint of death, non-fatal MI and SRI (p=0.0357). There was no evident difference in efficacy among the individual ximelagatran doses, suggesting a flat dose-response in the dose range studied.

Ximelagatran in doses 24 to 60 mg given with ASA was associated with a dose-related occurrence of bleeding events (minor and major bleeding events combined), as well as with a dose-related pattern of ALT elevations. In most cases the elevation of ALT was not associated with specific clinical symptoms.

Of the active dose range studied, the lower range may offer the greatest benefit/risk balance. Confirmatory studies are needed.

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Appendix B

Drug Substance: Ximelagatran

Appendix B – Definitions of Bleeding Events

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1. ADJUDICATED BLEEDING EVENTS

In all pivotal studies, bleeding events were prospectively collected using a specific questionnaire, and independently adjudicated. Additional data on number of transfusions and confirmation of bleeding (eg, CT scans) were required to allow this adjudication. In the surgical population, all bleeding events identified by the investigators were adjudicated. The definition of bleeding was consistent across the Phase III studies for the surgical population (Hull et al 1979). In the non-surgical population, the definitions of bleeding assessments were consistent across the major studies and were based on the same "Hamilton criteria" (Hull et al 1979). All major bleeding events were centrally adjudicated in all studies.

1.1 THRIVE III (SH-TPV-0003)

From Visit 2 and onwards the patients were asked if they had had any bleeding events since the previous visit. All bleeding events were recorded in the CRF and classified as major or minor. All major bleeding events were recorded in the Endpoint/SAE Report. A bleeding event fulfilling any of the following criteria was to be defined as major:

- Fatal bleeding
- Clinically overt bleeding associated with a fall in hemoglobin of 20 g/L (2.0 g/dL) or more
- Clinically overt bleeding leading to transfusion of 2 or more units of blood (whole blood or packed red cells)
- Retroperitoneal or intracranial bleeding
- Bleeding warranting permanent treatment cessation.

All other bleedings were to be classified as minor.

1.2 EXULT A and EXULT B (SH-TPO-0010 and SH-TPO-0012)

Special attention was to be given to bleeding complications. Any AE, as identified by the investigator, was to be recorded on the AE page of the CRF. With the exception of bleeding events that resolved prior to a patient's first dose of study drug, any AE that was reported as a bleeding event was categorized by the Adjudication Committee as major, minor, or criteria for **bleeding event not satisfied** according to the following criteria:

1. Clinically overt, defined as clinically apparent bleeding or signs and/or symptoms suggestive of bleeding with confirmatory imaging studies (eg, ultrasound, CT scan)
2. Critical site involvement (ie, intracranial, retroperitoneal, intraocular, intraspinal, or pericardial)

3. Bleeding index ≥2.0 (bleeding index defined as pre-event hemoglobin in g/dL minus post-event hemoglobin in g/dL plus the number of units of red blood cells [RBCs] transfused)

4. Medical intervention or surgical intervention for the reported bleed

5. Fatal bleeding event.

A patient was classified as having a:

1. **Major bleeding event** if the event satisfied criterion 1 and any of 2, 3, 4, or 5

2. **Minor bleeding event** if the event satisfied criterion 1, and none of 2, 3, 4, or 5

3. **Criteria for bleeding event not satisfied** if the reported bleeding event did not meet the criteria outlined in the Central Adjudication Manual and was not clinically overt.

In the adjudication of reported bleeding events, the following clinical situations were further described to aid in the clarification of major or minor bleeding events:

1. **Retroperitoneal bleeding, intracranial bleeding, or intraspinal bleeding:** Confirmatory objective testing was required for retroperitoneal bleeding (eg, ultrasound, CT scan), intracranial bleeding (eg, CT scan, magnetic resonance imaging [MRI]), and intraspinal bleeding (eg, CT scan or MRI) or autopsy. These were major bleeding events.

2. **Intraocular bleeding event:** An intraocular bleeding event was considered a major bleeding event if it was documented by ophthalmological examination.

3. **Intra-articular bleeding event**: An intra-articular bleeding event was considered a major bleeding event if it was documented by aspiration of blood from the joint.

4. **Epistaxis:** A nose bleed was considered a bleeding event if any of the following were fulfilled: a) the patient sought medical attention from a physician or visited the Emergency Room, b) the bleed required an intervention, ie, nasal pack, or c) it was a single bleeding episode persisting for longer than 5 minutes.

5. **Gastrointestinal bleeding event:** A gastrointestinal bleed was considered a bleeding event if any of the following were fulfilled: a) vomit containing frank blood, or coffee ground material which tested positive for blood; b) frank blood per rectum or melena stools; c) endoscopically-confirmed bleeding. Insignificant hemorrhoidal bleeding characterized by blood on toilet paper was not considered a bleeding event.

6. **Hematuria:** Hematuria was considered a bleeding event if there was overt spontaneous bleeding or if the bleeding persisted for more than 24 hours after instrumentation.

7. **Bruising:** Bruising was considered a bleeding event if the bruise was assessed as "unusual" (eg, greater than expected following surgery).

8. **Hematoma (including surgical site):** A hematoma was considered a bleeding event if either of the following were fulfilled: a) there was an overt blood collection associated with the wound, or b) there was a drop in hemoglobin with no external evidence of bleeding, but the presence of a hematoma was demonstrated radiographically (eg, ultrasound, CT scan, MRI).

In addition, definitions for recording bleeding events in the other orthopedic surgery studies, including the European OS program (sc + oral regimen), are detailed in Section 2.

1.3 SPORTIF III and SPORTIF V (SH-TPA-0003 and SH-TPA-0005)

Bleeding assessments were performed from Visit 2 and then at every visit using the standard question "Have you had any bleeding events since your last visit (excluding normal menstrual bleeding, if applicable)?"

Bleeding events were categorized in the CRF as "Major," "Minor," or "Occult" bleeding, according to the following criteria:

Major bleeding was defined as one or more of the following criteria:

- Fatal bleeding
- Clinically overt bleeding associated with a fall in hemoglobin of 20 g/L (2 g/dL) or more
- Clinically overt bleeding leading to transfusion of 2 or more units of whole blood or erythrocytes
- Bleeding in areas of special concern, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or traumatic intra-articular bleeding.

All other bleeding was classified as **minor bleeding**, and these were further classified as:

- Minor bleeding events causing permanent treatment cessation
- Other minor bleeding.

If possible, **occult bleeding** was determined by laboratory testing and classified as a sign or symptom; the etiology of the bleeding was determined and reported as an AE depending on the patient's medical history and at the discretion of the investigator.

2. DEFINITION OF BLEEDING EVENTS IN THE OTHER OS STUDIES

Bleeding events in the Phase III total hip replacement surgery study (PLATINUM HIP [SH-TPO-0005]) conducted in North America with the oral only regimen, were evaluated using the same definitions used in the pivotal TKR studies (see Section 1.2). The criteria used in the Phase II TKR study (SH-TPO-0004) differed in only one respect—fatal bleeding was not explicitly listed as a criterion for adjudication (ie, Criterion 5 shown in Section 1.2 was not listed).

Bleeding events were evaluated in the European OS program (sc + oral regimen) as detailed in Table 1.

Table 1 Criteria for severe bleeding and the use of independent adjudication in the studies using a preoperative or early postoperative start

Study (year of first inclusion)	Pool	Criteria for severe bleeding	Independent adjudication[a]
SH-TR2-0002 (1996)	None	• Intracerebral, intraocular, intraspinal, or retroperitoneal bleeding • Peri-operative transfusion requirement exceeding 5 units of RBC or autotransfusion units • Total transfusion requirement exceeding 7 units of RBC or autotransfusion units	No
SH-TR2-0005 (1997)	None	• Intracerebral, intraocular, intraspinal, or retroperitoneal bleeding • "Excessive bleeding" as judged by the investigator	No
METHRO I SH-TPO-0001 (1998)	Dose levels	Same as in SH-TR2-0005	No
METHRO II SH-TPO-0002 (1998)	Dose levels	Same as in SH-TR2-0005	Yes
METHRO III SH-TPO-0003 (1999)	Dose levels	Same as in SH-TPO-0002, and in addition: • All bleeding related AEs as judged as "clinically overt bleeding" by the adjudicator and associated with transfusion of ≥2 units[b] of blood (except transfusion related to bleeding from the operation wound) • Fatal bleeding	Yes
EXPRESS SH-TPO-0007 (2001)	Dose levels	Same as in SH-TPO-0003	Yes

[a] Use of an independent, blinded-to-treatment, adjudicator.

[b] 1 unit equals 250 mL of transfused RBCs or 450 mL of whole blood.

AE adverse event; RBC red blood cell.

3. REFERENCE

Hull R, Delmore T, Genton E, Hirsh J, Gent M, Sackett D, et al. Warfarin sodium versus low-dose heparin in the long-term treatment of venous thrombosis. N Engl J Med 1979;301(16):855-8.

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Appendix C

Drug Substance: Ximelagatran

Appendix C – The Orthopedic Surgery Program

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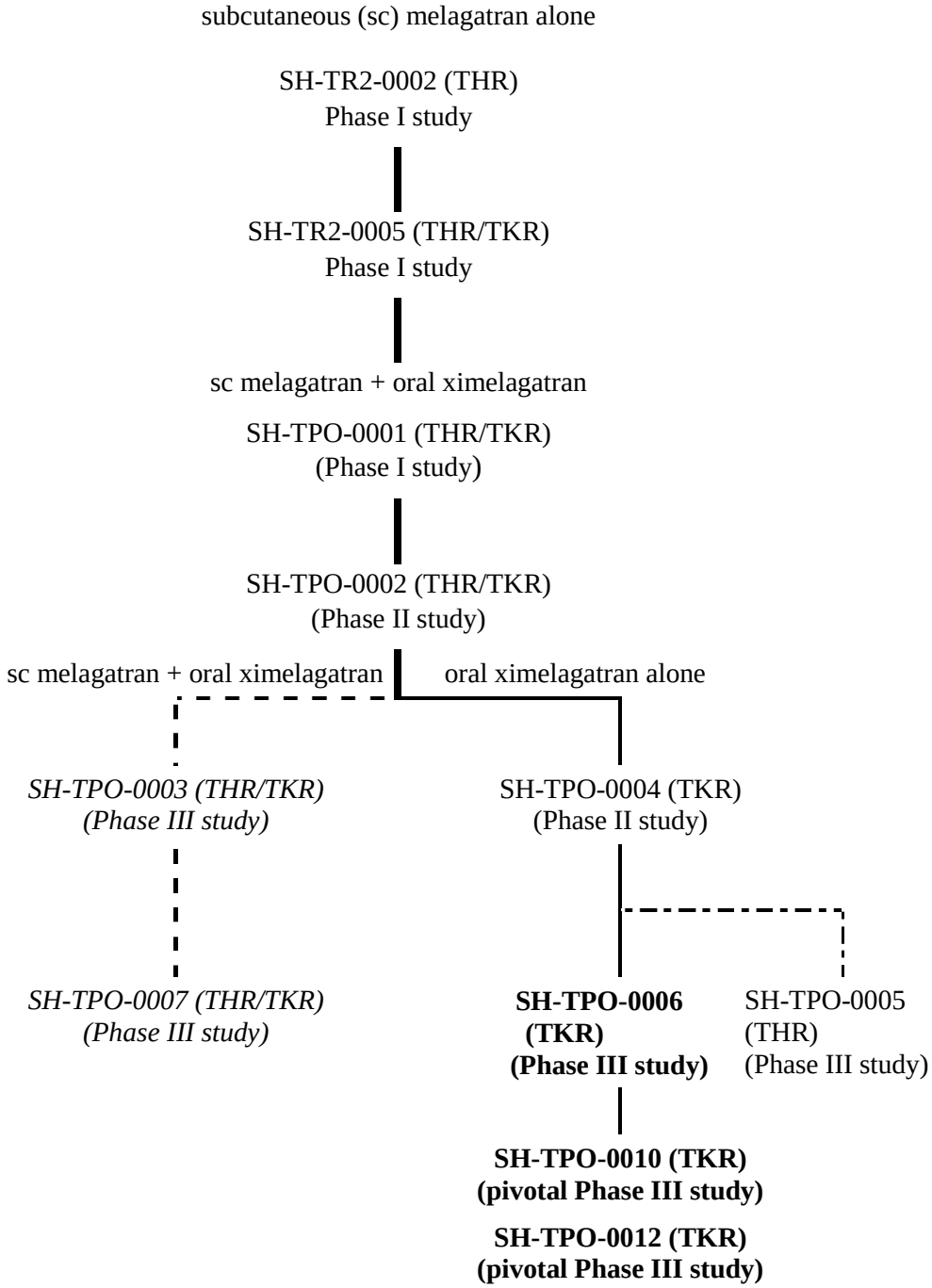
1. OVERVIEW OF THE ORTHOPEDIC SURGERY CLINICAL PROGRAM

The focus of NDA 21-686 is the 3 multicenter, double-blind, parallel-group, Phase III studies in patients undergoing primary, elective TKR surgery (PLATINUM KNEE [SH-TPO-0006], EXULT A [SH-TPO-0010] and EXULT B [SH-TPO-0012]). 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 the day of 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. These 3 studies are presented in the body of this briefing document and represent the entire Phase III study population in total knee replacement (TKR) surgery patients in which oral ximelagatran administration, without sc melagatran administration, was compared to warfarin.

Overall, AstraZeneca has conducted 11 studies in orthopedic surgery including more than 15000 patients. However, the majority of these studies were conducted with a dose regimen including subcutaneous (sc) administration of melagatran and included patients undergoing total hip replacement (THR) surgery. Figure 1 illustrates the clinical development program in orthopedic surgery.

Figure 1 **Flow diagram of the development of the program for the prevention of VTE in orthopedic surgery**



VTE venous thromboembolism; TKR total knee replacement; THR total hip replacement.
The 3 studies highlighted in bold text are the Phase III TKR studies detailed in the body of this briefing document.

As illustrated in Figure 1, the clinical program for ximelagatran began with sc melagatran. Melagatran was administered by sc injection alone in the first 2 pilot studies (SH-TR2-0002 and SH-TR2-0005) because of low and variable bioavailability following oral melagatran administration. In parallel with these first 2 pilot studies, the oral prodrug ximelagatran was being developed. When sufficient tolerability and pharmacokinetic information was available, a third pilot study was initiated in patients using oral ximelagatran (METHRO I, SH-TPO-0001). Study METHRO I (SH-TPO-0001) was the first study in orthopedic surgery patients in which the treatment regimen of sc melagatran followed by oral ximelagatran was tested. METHRO II (SH-TPO-0002), a dose-finding study, demonstrated a statistically significant dose-response relationship between risk of VTE and the amount of ximelagatran given, indicating that the highest dose of pre-operatively initiated sc melagatran, followed by oral ximelagatran, had superior efficacy over dalteparin.

The terms “oral only program” and the “sc + oral program” refer to the ximelagatran and melagatran treatment regimens used in the studies. The differences between the 2 programs are summarized here. The oral only program and the sc + oral program developed separately after METHRO II (SH-TPO-0002) was completed (Figure 1), as FDA considered sc melagatran and oral ximelagatran to be different chemical entities.

While the overall purpose of the oral only and sc + oral programs were similar, the designs were substantially different in key respects, reflecting different medical practices in the 2 regions in which these regimens were pursued (North America and Europe, respectively).

- Treatment regimen: The regimen used in the oral only studies was ximelagatran given orally bid the morning after the day of surgery, while in the sc + oral studies, sc melagatran was given, beginning pre-operatively or 4 to 12 hours post-operatively, for 1 to 3 days, followed by ximelagatran given orally bid thereafter.

- Time to dose: In North America, VTE prophylaxis is generally initiated post-operatively. The risk of increased bleeding with anticoagulation during surgery is considered sufficiently great that the benefit-risk ratio is considered better with a post-operative start. In Europe, VTE prophylaxis is generally initiated pre-operatively or within 12 hours post-operatively.

- Comparator: In the Phase III studies in the oral only program, the vitamin K antagonist (VKA), warfarin, was used while low molecular weight heparins (LMWHs) were used in the sc + oral program and the first oral only study in North America. Warfarin is commonly used as VTE prophylaxis in North America, and is the only oral anticoagulant recommended in the US for the prevention of VTE after orthopedic surgery (Geerts 2001).

- Indications: The oral only clinical development program in North America is being submitted to support a TKR indication, while in Europe, the sc + oral program was submitted for the prevention of venous thromboembolism after THR or TKR.

- Venography: Central adjudications of venograms were not comparable. The adjudications were completed by a different adjudication committee for the sc + oral studies (Östra, Sweden) than the one used for all oral only studies (Hamilton, Ontario).

Because of these differences, no attempt was made to compare efficacy data from the oral only program with efficacy data from the sc + oral studies. Thus, the clinical assessment of efficacy in NDA 21-686 is based on the oral only studies, specifically those in patients undergoing primary elective TKR surgery. The remainder of this section briefly presents the key design features and results for other orthopedic surgery studies that are not critical to the assessment of oral ximelagatran in patients undergoing TKR surgery.

2. SUMMARY OF ORTHOPEDIC SURGERY STUDIES NOT INCLUDED IN THE BODY OF THIS BRIEFING DOCUMENT

2.1 Orthopedic surgery: Oral only studies

Studies SH-TPO-0004 (TKR only) and SH-TPO-0005 (THR only) used only oral ximelagatran; however, both studies used enoxaparin as the comparator, and Study SH-TPO-0004 was a Phase II study and SH-TPO-0005 included only THR patients. The key study design features of these 2 studies are presented in Table 1 and the key efficacy and safety results in Table 2. The criteria used to define major and minor bleeding in these studies, and the extent of adjudication of the bleeding events are provided in Section 1.2 of Appendix B.

Table 1 Key design features of Phase II oral only TKR surgery study and Phase III oral only THR surgery study

Study No. Countries No. of centers	Design	Duration Diagnosis	Primary endpoints	Study dates Planned/randomized Randomized by treatment	Dose, route & regimen	Randomized/ completed
SH-TPO-0004 US & Canada 69	Phase II R, DB[a], CC, PG, MC	6 to 12 days TKR	Asymptomatic distal and/or proximal DVT confirmed by unilateral venography and/or objectively confirmed symptomatic DVT and/or PE. Incidence of bleeding events.	Oct 1998 to Jan 2000 T: 500/600 X: 475 E: 125	X: po bid 8 mg 12 mg 18 mg 24 mg E: sc bid 30 mg	X: 475/432 85/79 134/124 126/111 130/118 E: 125/113
SH-TPO-0005 (PLATINUM HIP) Israel, Mexico, South Africa, Argentina, Canada, & US 129	Phase III R, DB, DD, CC, PG, MC	7 to 12 days THR	Asymptomatic distal and/or proximal DVT confirmed by unilateral venography and/or objectively confirmed symptomatic DVT and/or PE. Incidence of bleeding events.	Mar 2000 to Apr 2001 T: 2075/1838 X: 918 E: 920	X: po bid 24 mg E: sc bid 30 mg	X: 918/855 E: 920/854

[a] Dose of ximelagatran blinded, dose of enoxaparin was open.

X ximelagatran; E enoxaparin; DB double-blind; DD double-dummy; R randomized; CC comparator-controlled; PG parallel-group; MC multicenter; bid twice daily; sc subcutaneous; po oral; DVT deep vein thrombosis; THR total hip replacement; TKR total knee replacement; PE pulmonary embolism.

Table 2 Results of Phase II oral only TKR surgery study and Phase III oral only THR surgery study

Study	Treatment Arm	Randomized/ Completed	VTE % (n/N)	Proximal DVT and/or PE % (n/N)	Major bleeding events % (n/N)	Minor bleeding events % (n/N)	Wound characteristics
SH-TPO-0004	Ximel						The volumes of postoperative blood loss and wound drainage were lower following treatment with ximelagatran 24 mg bid compared with enoxaparin 30 mg bid. There was no increase in blood loss or wound drainage with ximelagatran dose.
	8 mg po bid	85/79	27.0 (17/63)	6.6 (4/61)	0 (0/84)	8.3 (7/84)	
	12 mg po bid	134/124	19.8 (20/101)	2.0 (2/101)	1.5 (2/134)	14.2 (19/134)	
		126/111	28.7 (25/87)	5.8 (5/86)	2.4 (3/124)	12.9 (16/124)	
	18 mg po bid	130/118	15.8 (15/95)	3.2 (3/95)	0 (0/127)	10.2 (13/127)	
	24 mg po bid	125/113	22.7 (22/97)	3.1 (3/97)	1.6 (2/125)	8.8 (11/125)	
	Enox						
	30 mg sc bid						
SH-TPO-0005 (PLATINUM HIP)	Ximel						The volumes of postoperative blood loss and wound drainage were comparable across the treatment groups. Overall wound appearance was rated as "worse than expected" at 1 or more points following surgery by a small percentage of patients in the ximelagatran (9.5%) and enoxaparin (6.1%) groups (p=0.019).
	24 mg po bid	918/855	7.9 (62/782)	3.6 (28/782)	0.8 (7/906)	5.4 (49/906)	
		920/854	4.6 (36/755)		0.9 (8/910)	4.3 (39/910)	
	Enox			1.2 (9/774)			
	30 mg sc bid						

Ximel ximelagatran; Enox enoxaparin; po oral; bid twice daily; sc subcutaneous; VTE venous thromboembolism; DVT deep vein thrombosis; PE pulmonary embolism.

2.2 Orthopedic surgery: sc + oral studies

Studies METHRO I (SH-TPO-0001), METHRO II (SH-TPO-0002), METHRO III (SH-TPO-0003), and (EXPRESS) SH-TPO-0007 were conducted outside North America and included both TKR and THR patients, with comparison to LMWHs. The key study design features of these 4 studies are presented in Table 3 and the key efficacy and safety results in Table 4.

Table 3 All studies in the sc + oral clinical development program for VTE prophylaxis in orthopedic surgery: studies used either a preoperative or a postoperative treatment start

Study No. Countries No. of centers	Design	Duration Diagnosis	Primary endpoints	Study dates Planned/randomized Randomized by treatment	Dose, route & regimen	Randomized/ completed
SH-TPO-0001 (METHRO I) Sweden 8	Phase II M/X: DB vs open D R, CC, PG, MC	8 to 11 days THR and TKR	Incidence of deep vein thrombosis and pulmonary embolism. Plasma concentration of melagatran. APTT and ECT, which were correlated to plasma concentrations of melagatran. Volume of blood loss and general safety.	Feb 1998 to Jun 1998 T: 137/128 M/X: 104 D: 33	M/X: bid, sc/oral 1 mg / 6 mg 2 mg / 12 mg 4 mg / 24 mg D: od, sc 5000 IU	M/X: 34/31 34/32 36/31 D: 33/32
SH-TPO-0002 (METHRO II) Sweden, Norway, Denmark, Finland, Germany, Belgium, UK, France, Spain, Austria, Switzerland, Poland & Hungary 59	Phase II Dose finding R, DB, CC, PG, MC	8 to 11 days THR and TKR	Incidence of deep vein thrombosis and pulmonary embolism. Volume of blood loss and general safety.	Sep 1998 to Jun 1999 T: 1876/1900 M/X: 1495 D: 381	M/X: bid, sc/oral 1 mg / 8 mg 1.5 mg / 12 mg 2.25 mg / 18 mg 3 mg / 24 mg D: od, sc 5000 IU	M/X: 364/293 377/289 375/299 379/285 D: 381/307

M/X melagatran sc bid followed by ximelagatran po bid; M melagatran; X ximelagatran; D dalteparin; E enoxaparin; DB double-blind; R randomized; CC comparator controlled; PG parallel-group; MC multicenter; bid twice daily; od once daily; sc subcutaneous; TKR total knee replacement; THR total hip replacement; APTT activated partial thromboplastin time; ECT ecarin clotting time; T total; UK United Kingdom.

Table 3 All studies in the sc + oral clinical development program for VTE prophylaxis in orthopedic surgery: studies used either a preoperative or a postoperative treatment start

Study No. Countries No. of centers	Design	Duration Diagnosis	Primary endpoints	Study dates Planned/randomized Randomized by treatment	Dose, route & regimen	Randomized/ completed
SH-TPO-0003 (METHRO III) Italy, South Africa, Sweden, Norway, Denmark, Finland, Germany, Belgium, UK, France, Spain, Austria, Poland & Hungary 80	Phase III R, DB, CC, PG, MC	8 to 11 days THR and TKR	Incidence of deep vein thrombosis and pulmonary embolism. Volume of blood loss and general safety.	Nov 1999 to Jul 2000 2600/2874 M/X: 1439 E: 1435	M/X: bid, sc/oral 3 mg / 24 mg E: od, sc 40 mg	M/X: 1439/1395 E: 1435/1398
SH-TPO-0007 (EXPRESS) Italy, South Africa, Sweden, Norway, Denmark, Finland, Germany, Belgium, UK, France, Austria, Poland & Hungary 77	Phase III R, DB, CC, PG, MC	8 to 11 days THR and TKR	Incidence of deep vein thrombosis and pulmonary embolism. Volume of blood loss and general safety.	Apr 2001 to Feb 2002 2600/2821 M/X: 1403 E: 1418	M/X: bid, sc/oral 2 mg to 3 mg / 24 mg E: od, sc 40 mg	M/X: 1403/1301 E: 1418/1325

M/X melagatran sc bid followed by ximelagatran po bid; M melagatran; X ximelagatran; D dalteparin; E enoxaparin; DB double-blind; R randomized; CC comparator controlled; PG parallel-group; MC multicenter; bid twice daily; od once daily; sc subcutaneous; TKR total knee replacement; THR total hip replacement; APTT activated partial thromboplastin time; ECT ecarin clotting time; T total; UK United Kingdom.

Table 4 Key results in the sc + oral Phase II & III studies: combined THR and TKR

Study	Treatment arm	Enrolled/ completed	Total DVT and/or PE and/or death % (n/N)	Proximal DVT and/or PE and/or death % (n/N)	Severe bleeding events % (n/N)	Any bleeding events % (n/N)
SH-TPO-0001 (METHRO I)	M/X 1/6	34/31	21.0 (6/29)	10.3 (3/29)	2.9 (1/34)	29.4 (10/34)
	M/X 2/12	34/32	25.0 (6/24)	0 (0/24)	5.9 (2/34)	20.6 (7/34)
	M/X 4/24	36/31	16.0 (4/25)	0 (0/25)	0	20.0 (7/34)
	Dalteparin	33/32	19.0 (5/27)	7.4 (2/27)	0	11.8 (4/33)
SH-TPO-0002 (METHRO II)	M/X 1/8	364/293	37.8 (111/294)	9.2 (27/294)	1.1 (4/364)	8.2 (30/364)
	M/X 1.5/12	377/289	24.1 (70/290)	6.6 (19/290)	2.1 (8/377)	10.6 (40/377)
	M/X 2.25/18	375/299	23.7 (71/300)	4.7 (14/300)	2.9 (11/375)	10.7 (40/375)
	M/X 3/24	379/285	15.1 (43/285)	2.5 (7/285)	4.7 (18/379)	11.3 (43/379)
	Dalteparin	381/307	28.2 (87/308)	6.5 (20/308)	2.4 (9/381)	10.8 (41/381)
SH-TPO-0003 (METHRO III)	M/X 3/24	1439/1146	31.0 (355/1146)	5.7 (65/1146)	1.4 (20/1406)	10.0 (141/1406)
	Enoxaparin	1435/1122	27.3 (306/1122)	6.2 (69/1122)	1.6 (23/1394)	10.9 (152/1394)
SH-TPO-0007 (EXPRESS)	M/X 2/3/24	1403/1301	20.2 (231/1141)	2.3 (26/1141)	3.3 (46/1379)	11.8 (162/1379)
	Enoxaparin	1418/1325	26.6 (315/1184)	6.3 (75/1184)	1.2 (16/1388)	7.9 (110/1388)

M/X melagatran sc bid followed by ximelagatran po bid; M melagatran; X Ximelagatran; DVT deep vein thrombosis; PE pulmonary embolism; THR total hip replacement; TKR total knee replacement.

2.3 Orthopedic surgery - uncontrolled studies with sc alone

Studies SH-TR2-0002 and SH-TR2-0005 (each of which included both TKR and THR patients) included only sc administration of melagatran and examined primarily pharmacokinetic and pharmacodynamic endpoints.

3. REFERENCE

Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA, et al. Prevention of venous thromboembolism. Chest 2001;119(Suppl 1):132S-75S.

AstraZeneca

Advisory Committee Briefing Document
Appendix D

Drug Substance: Ximelagatran

Appendix D – No Hepatic Effect in the Surgical Population

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1. NO HEPATOBILIARY EFFECT IN THE SURGICAL POPULATION

1.1 Analysis of clinical laboratory data in the Surgical population

Since a signal of raised liver function tests (LFT) was observed in ximelagatran studies of prolonged exposure (>35 days), the same method that was used in the long-term studies was applied to the short-term treated Surgical population. Namely, ALT is a more specific marker of liver cell damage than AST, and because there was no pattern for an increase in alkaline phosphatase (ALP) or bilirubin in isolation, ALT forms the basis of the analysis. A threshold of ALT >3x ULN was used to indicate a signal of potential clinical relevance.

No safety signal regarding possible hepatobiliary effects was observed for the Surgical population during, or following short-term (<35 days) exposure to melagatran sc or oral ximelagatran bid. There were no differences in the on-treatment incidences of ALT elevation between ximelagatran and warfarin. When compared to LMWH, the incidences of ALT elevation were consistently lower in the ximelagatran groups. Confounding factors such as surgical trauma, perioperative exposure to LMWHs and other drugs including anesthesia medications, and previous illnesses may cause ALT elevations observed in patients within the first 4 to 6 weeks.

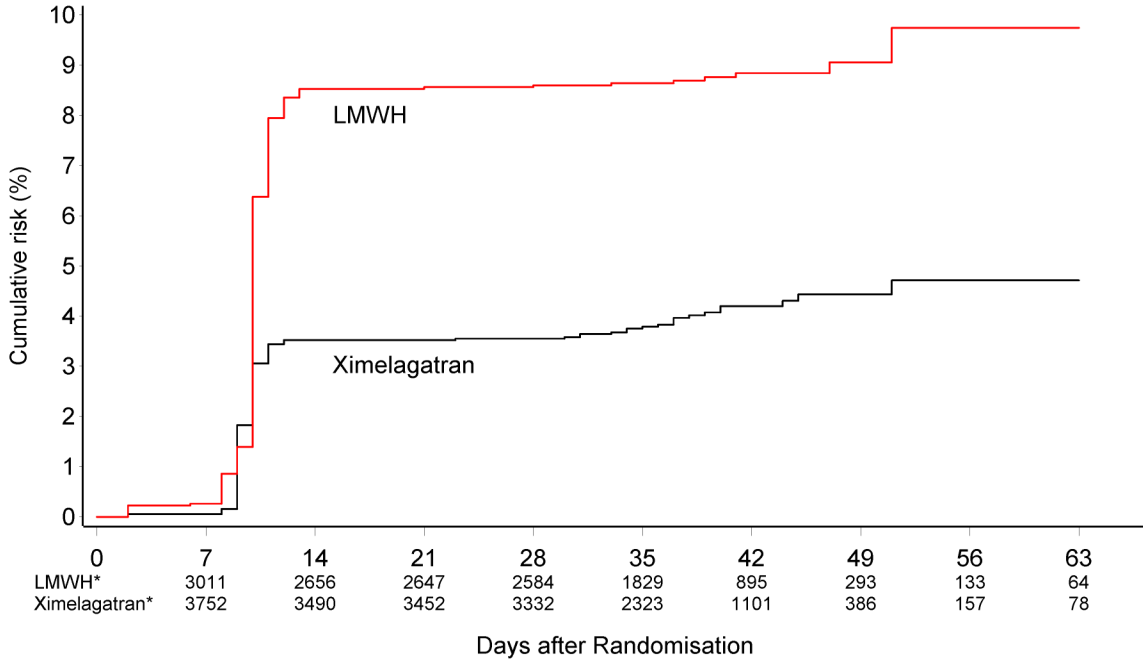
The number of patients with ALT >3x ULN in the ximelagatran and comparator groups are presented in Table 1, by type of surgery. The Kaplan-Meier plots shown below are divided by type of surgery: hip (Figure 1) and knee (Figure 2). These figures show the difference in effect related to the type of surgery.

Table 1 Number of patients with ALT >3x ULN, ximelagatran and comparator, by type of surgery: Surgical pool

Type of Surgery	Ximelagatran (n=8639)		LMWH (n=4233)		Warfarin (n=2194)		Total (n=15066)	
Hip	149/3788	(3.9%)	262/3055	(8.6%)	0	0	411/6843	(6.0%)
Knee	78/4826	(1.6%)	74/1128	(6.6%)	22/2194	(1.0%)	174/8148	(2.1%)
Total	**227/8614**	**(2.6%)**	**336/4183**	**(8.0%)**	**22/2194**	**(1.0%)**	**585/14991**	**(3.9%)**

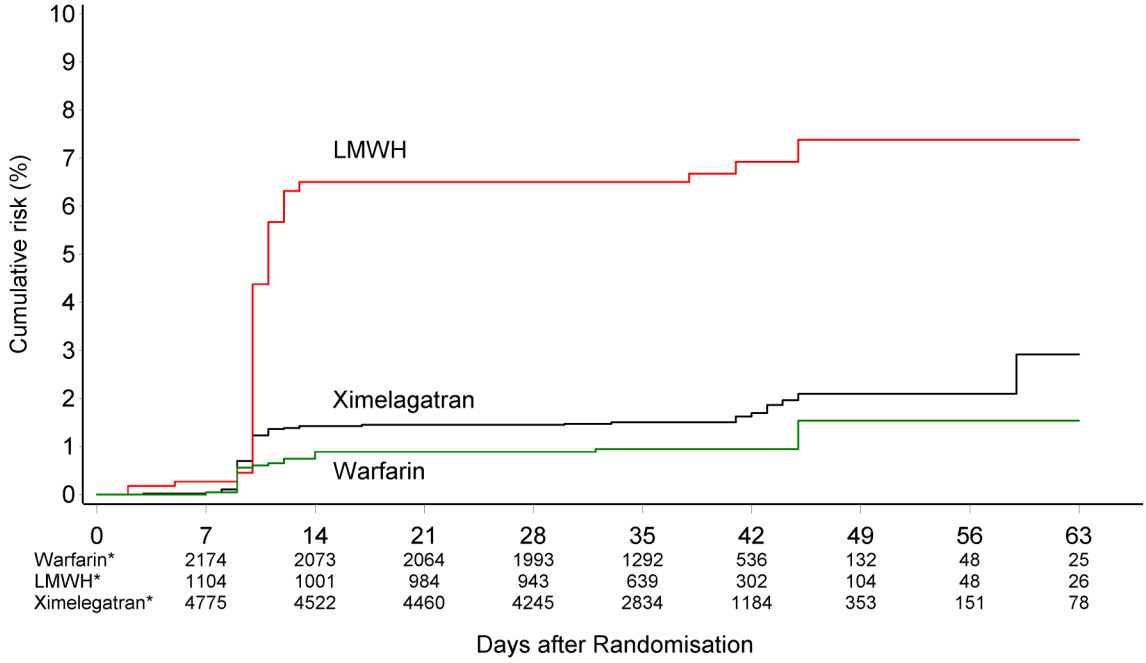
LMWH Low molecular weight heparins.

Figure 1 **Cumulative risk (%) of ALT >3x ULN versus time after randomization: Surgical pool, hip surgery patients**



*Patients at risk.

Figure 2 **Cumulative risk (%) of ALT >3x ULN versus time after randomization: Surgical pool, knee surgery patients**



*Patients at risk.

The incidence of elevated ALT, AST, ALP, and total bilirubin, according to various multiples of ULN, is shown for the surgical population pool in Table 2.

Ximelagatran patients demonstrated no difference versus the comparators for an increased incidence of ALT elevations. Based on central and local laboratory data, the incidence of ALT >3x ULN was 2.7% for the ximelagatran group compared with 5.6% for comparators. The incidence of ALT >5x ULN was 0.7% and 1.8% in the ximelagatran and comparators group, respectively. The incidence of ALT >10x ULN was 0.1% and 0.1%, respectively.

Table 2 Cumulative incidence of patients with elevated ALT, AST, ALP, and bilirubin (Surgical pool)

	Ximelagatran (N=8797)		Comparator (N=6530)	
Liver function test	**n**	**(%)**	**n**	**(%)**
ALT >2x ULN	668	(7.6)	806	(12.5)
ALT >3x ULN	236	(2.7)	366	(5.7)
ALT >5x ULN	59	(0.7)	117	(1.8)
ALT >10x ULN	8	(0.1)	8	(0.1)
AST >2x ULN	230	(2.6)	367	(5.7)
AST >3x ULN	63	(0.7)	150	(2.3)
AST >5x ULN	13	(0.2)	36	(0.6)
AST >10x ULN	3	(0.0)	3	(0.1)
ALP >2x ULN	317	(3.6)	252	(3.9)
ALP >3x ULN	126	(1.4)	71	(1.1)
ALP >5x ULN	51	(0.6)	21	(0.3)
ALP >10x ULN	41	(0.5)	15	(0.2)
Bilirubin >1.5x ULN	98	(1.1)	69	(1.1)
Bilirubin >2x ULN	22	(0.3)	21	(0.3)
Bilirubin >3x ULN	4	(0.1)	3	(0.1)

ALT Alanine aminotransferase, AST Aspartate aminotransferase; ALP Alkaline phosphatase; ULN Upper limit of normal.

PLATINUM KNEE (SH-TPO-0006), EXULT A (SH-TPO-0010), and EXULT B (SH-TPO-0012)

Changes from baseline in clinical chemistry parameters, including elevations in ALT, 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.

An examination of the first occurrence of elevation of ALT >3x ULN was done to evaluate the correlation of ALT elevation to exposure to ximelagatran for studies PLATINUM KNEE

(SH-TPO-0006), EXULT A (SH-TPO-0010), and EXULT B (SH-TPO-0012). The LFTs were measured at baseline (Screening Visit), venography (End-of-treatment Visit), and follow-up. The number of patients who had their first elevated ALT levels at each of these visits is displayed in Table 3. Overall, these data show that the number of patients who had elevations of ALT >3x ULN at venography in the ximelagatran and warfarin groups were small, did not differ significantly, and were not indicative of a safety issue.

Table 3 Number (%) of patients with the first occurrence of elevations of ALT > 3x ULN: PLATINUM KNEE (SH-TPO-0006), EXULT A (SH-TPO-0010), and EXULT B (SH-TPO-0012)

		Ximelagatran 36 mg		Warfarin		Ximelagatran 24 mg	
Study	**Visit**	**Ratio**	**%**	**Ratio**	**%**	**Ratio**	**%**
PLATINUM KNEE	Baseline	-	-	0/325	0.0	0/340	0.0
(SH-TPO-0006)	Venography	-	-	1/306	0.3	3/325	0.9
	Follow-up	-	-	2/295	0.7	0/323	0.0
EXULT A	Baseline	0/744	0.0	0/735	0.0	1/728	0.1
(SH-TPO-0010)	Venography	6/723	0.8	12/704	1.7	4/706	0.6
	Follow-up	4/698	0.6	0/697	0.0	1/693	0.1
EXULT B	Baseline	0/1125	0.0	0/1117	0.0	-	-
(SH-TPO-0012)	Venography	7/1095	0.6	6/1087	0.6	-	-
	Follow-up	3/1086	0.3	1/1079	0.1	-	-

Baseline = Screening Visit. Venography = End-of-treatment Visit.

In EXULT A (SH-TPO-0010), there were no differences between the ximelagatran groups and the warfarin group for patients who had ALT 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 ALT elevation >3x ULN. However, 3 of the 4 patients in the ximelagatran 36-mg group had their first ALT elevation >30 days after receiving their last ximelagatran dose while the fourth patient had their first ALT elevation 28 days after receiving their last ximelagatran dose. These results do not suggest a causal relationship with study drug. Also, one of these patients had a history of Hepatitis A and LFT elevations in the past. The one patient in the ximelagatran 24-mg group received a heparin beginning on Day 19, treatment for a bleeding duodenal ulcer on Day 25, and then had one ALT value just over 3x ULN on Day 28.

In EXULT B (SH-TPO-0012), there were no differences between the ximelagatran and warfarin groups for patients who had ALT 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 ALT elevation >3x ULN: 3 in the ximelagatran 36-mg group and one in the warfarin group. For all 3 ximelagatran 36-mg patients, the elevations were resolved within 30 days of elevation, including one patient who began a low molecular weight heparin (LMWH) on postoperative Day 11 as treatment for DVT.

Other studies in orthopedic surgery

In the completed short-term (12 days) clinical studies with LMWHs as comparator, the prevalence of ALT >3x ULN on the last study day with melagatran and ximelagatran was 3.0% (122/4019). The corresponding figure for LMWH was 7.3% (193/2660). The increase in ALT was transient and may be related to the surgical trauma (higher in patients with total hip than with total knee replacement) (Table 4 to Table 9). Comparing the 2 treatment regimens, ximelagatran treatment appeared to result in fewer transaminase elevations than did treatment with LMWH.

Table 4 Number and percentage of patients with the first occurrence of elevation of ALT >3x ULN by treatment visit: METHRO I (SH-TPO-0001)

		Ximelagatran 6 mg		Ximelagatran 12 mg		Ximelagatran 24 mg		Fragmin	
Study	**Period**	**Ratio**	**Percent**	**Ratio**	**Percent**	**Ratio**	**Percent**	**Ratio**	**Percent**
SH-TPO-0001	Baseline	0/34	0	0/34	0	0/34	0	0/33	0
SH-TPO-0001	Treatment	1/31	3.2	3/31	9.7	2/32	6.3	3/31	9.7
SH-TPO-0001	Follow-up	0/30	0	0/31	0	0/32	0	1/32	3.1

Table 5 Number and percentage of patients with the first occurrence of elevation of ALT >3x ULN by treatment visit: METHRO II (SH-TPO-0002)

		Ximelagatran 8 mg		Ximelagatran 12 mg		Ximelagatran 18 mg		Ximelagatran 24 mg		Dalteparin 5000 IU	
Study	**Period**	**Ratio**	**Percent**	**Ratio**	**Percent**	**Ratio**	**Percent**	**Ratio**	**Percent**	**Ratio**	**Percent**
SH-TPO-0002	Baseline	0/363	0	1/374	0.3	0/374	0	0/378	0	0/381	0
SH-TPO-0002	Treatment	10/352	2.8	16/351	4.6	12/360	3.3	11/352	3.1	38/362	10.5
SH-TPO-0002	Follow-up	1/341	0.3	5/351	1.4	0/357	0	1/349	0.3	3/357	0.8

Table 6 Number and percentage of patients with the first occurrence of elevation of ALT >3x ULN by treatment visit: METHRO III (SH-TPO-0003)

		Ximelagatran 24 mg		Enoxaparin 40 mg IU	
Study	**Period**	**Ratio**	**Percent**	**Ratio**	**Percent**
SH-TPO-0003	Baseline	3/1379	0.2	10/1391	0.7
SH-TPO-0003	Treatment	54/1329	4.1	107/1332	8
SH-TPO-0003	Follow-up	5/1321	0.4	4/1329	0.3

Table 7 Number and percentage of patients with the first occurrence of elevation of ALT >3x ULN by treatment visit: Study SH-TPO-0004

		Ximelagatran 8 mg		Ximelagatran 12 mg		Ximelagatran 18 mg		Ximelagatran 24 mg		Enoxaparin 30 mg	
Study	**Period**	**Ratio**	**Percent**	**Ratio**	**Percent**	**Ratio**	**Percent**	**Ratio**	**Percent**	**Ratio**	**Percent**
SH-TPO-0004	Baseline	0/83	0	0/132	0	0/121	0	0/126	0	1/122	0.8
SH-TPO-0004	Treatment	0/75	0	3/123	2.4	1/109	0.9	1/121	0.8	4/113	3.5
SH-TPO-0004	Follow-up	0/76	0	0/122	0	0/109	0	0/112	0	0/108	0

Table 8 Number and percentage of patients with the first occurrence of elevation of ALT >3x ULN by treatment visit: PLATINUM HIP (SH-TPO-0005)

		Ximelagatran 24 mg		Enoxaparin 30 mg	
Study	**Period**	**Ratio**	**Percent**	**Ratio**	**Percent**
SH-TPO-0005	Baseline	0/892	0	0/892	0
SH-TPO-0005	Treatment	6/851	0.7	42/858	4.9
SH-TPO-0005	Follow-up	3/826	0.4	2/816	0.2

Table 9 Number and percentage of patients with the first occurrence of elevation of ALT >3x ULN by treatment visit: EXPRESS (SH-TPO-0007)

		Ximelagatran 24 mg		Enoxaparin 40 mg	
Study	**Period**	**Ratio**	**Percent**	**Ratio**	**Percent**
SH-TPO-0007	Baseline	7/1370	0.5	6/1381	0.4
SH-TPO-0007	Treatment	55/1327	4.1	120/1336	9
SH-TPO-0007	Follow-up	6/1310	0.5	3/1321	0.2

1.2 Hepatobiliary adverse events in the Surgical population

Warfarin-comparison Pool

Overall frequency of hepatobiliary AEs 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% versus 5.1% with warfarin. This was due to a higher rate of reported GGT increase (ximelagatran: 5.6% in the 36-mg group, 4.4% in the 24-mg group, versus 4.2% in both warfarin groups). Incidences of ALT increase 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.

Dose-levels Pool

The Dose-levels Pool includes patients from all 9 orthopedic surgery studies using the oral formulation in the North American and European regimens, but further subdivides these patients into 5 groups based on the dose levels of study drug that they used. The 5 dose levels have been defined based on the dose of the oral form ximelagatran used in the post-operative period for 10 to 12 days, and range from 6 mg to 36 mg.

The dose levels evaluated in the individual studies included in the Dose-levels Pool are summarized in Table 10.

Table 10 Dose levels used for pooling safety data from orthopedic surgery studies

Dose level	Study No.	Doses included[a]	Exposed safety population[b] (N)	Total (N=8745)
1 (6 to 8 mg)	METHRO I (SH-TPO-0001)	Melagatran 1 mg bid sc and ximelagatran 6 mg bid po	34	
	METHRO II (SH-TPO-0002)	Melagatran 1 mg bid sc and ximelagatran 8 mg bid po	364	
	SH-TPO-0004	Ximelagatran 8 mg bid po	84	482
2 (12 mg)	METHRO II (SH-TPO-0002)	Melagatran 1.5 mg bid sc and ximelagatran 12 mg bid po	376	
	METHRO I (SH-TPO-0001)	Melagatran 2 mg bid sc and ximelagatran 12 mg bid po	34	
	SH-TPO-0004	Ximelagatran 12 mg bid po	134	544
3 (18 mg)	METHRO II (SH-TPO-0002)	Melagatran 2.25 mg bid sc and ximelagatran 18 mg bid po	375	
	SH-TPO-0004	Ximelagatran 18 mg bid po	124	499

Table 10 Dose levels used for pooling safety data from orthopedic surgery studies

Dose level	Study No.	Doses included[a]	Exposed safety population[b] (N)	Total (N=8745)
4 (24 mg)	EXPRESS (SH-TPO-0007)	Melagatran 2 mg sc, followed by 3 mg bid sc, then ximelagatran 24 mg bid po	1378	
	METHRO II (SH-TPO-0002)	Melagatran 3 mg bid sc, followed by ximelagatran 24 mg bid po	378	
	METHRO III (SH-TPO-0003)		1386	
	METHRO I (SH-TPO-0001)	Melagatran 4 mg bid sc, followed by ximelagatran 24 mg bid po	35	
	SH-TPO-0004	Ximelagatran 24 mg bid po	127	
	PLATINUM HIP (SH-TPO-0005)		906	
	PLATINUM KNEE (SH-TPO-0006)		343	
	EXULT A (SH-TPO-0010)		754	5307
5 (36 mg)	EXULT A (SH-TPO-0010)	Ximelagatran 36 mg bid po	767	
	EXULT B (SH-TPO-0012)		1146	1913

Data derived from individual CSRs.
Note that the Dose-levels Pool includes only those patients treated with ximelagation.
[a] Based on the main dosage used for ximelagatran po.
[b] Took active drug (ie, exposed to at least 1 dose of ximelagatran or comparator) irrespective of surgery and had at least 1 post-baseline measurement.
bid twice daily; sc subcutaneous; po orally.

Adverse events associated with liver and biliary disorders including ALT increased were slightly higher for Dose Levels 1 to 3 (melagatran sc and oral ximelagatran; 7.1%, 6.6%, and 6.4%, respectively) and 5 (oral ximelagatran only; 6.7%) compared to Dose Level 4 (melagatran sc and oral melagatran; 4.1%). There were no fatal SAEs reported that were attributed to liver and biliary disorders in any of the dose levels. There was one DAE due to cholelithiasis reported in Dose Level 3. In Dose levels 1 to 3, there was 1 (0.2%) non-fatal SAE reported for each level and, in Dose Level 4, there were 6 (<0.1%) non-fatal SAEs reported that were attributed to liver and biliary disorders. There were no reports of non-fatal SAEs that were attributed to liver and biliary disorders in Dose Level 5.

1.3 Conclusions of hepatobiliary effects in the Surgical population

- There were no differences in the on-treatment incidences of ALT elevation between ximelagatran and warfarin. When compared to LMWH, the incidences of ALT elevation were consistently lower in the ximelagatran groups.
- Confounding factors such as surgical trauma, perioperative exposure to LMWHs and other drugs including anesthesia medications, and previous illnesses may cause ALT elevations observed in patients within the first 4 to 6 weeks.
- No clinical signs or symptoms have been attributed to the ALT elevations that have occurred with short-term use.