U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-686
Drug Name:	Exanta (ximelagatran)
Indication(s):	• Prevention of VTE in patients undergoing knee replacement surgery • Long term secondary prevention of VTE after standard treatment for an episode of acute VTE
Applicant:	Astra Zeneca
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Astra Zeneca has proposed Exanta (ximelagatran) tablets for the prevention of venous thromboembolism (VTE) in patients undergoing knee replacement surgery and for the long term secondary prevention of VTE after standard treatment for an episode of acute VTE. The applicant claimed that ximelagatran reduced the incidence of total VTE and/or mortality in patients undergoing total knee replacement and that ximelagatran reduced the recurrence of VTE events among patients who previously received 6 months of anticoagulation therapy for an acute VTE. Based on my evaluation of NDA 21-686, I concluded that statistical evidence supported the efficacy of ximelagatran for the proposed indications. However, several additional issues required consideration to completely ascertain the strength of the efficacy results. The issues were beyond the scope of this review and included the adequacy of the period of follow-up for the short term indication, the appropriateness of warfarin as a comparator, and concerns regarding the safety profile of the drug. These concerns are addressed in the clinical review of Dr. Ruyi He.

1.2 Brief Overview of Clinical Studies

Support for the oral anticoagulant, ximelagatran, was primarily derived from three studies. Two studies, EXULT A and EXULT B, investigated the superiority of ximelagatran to warfarin in the prevention of VTE. A single study, THRIVE III, investigated the superiority of ximelagatran to placebo in the long term secondary prevention of VTE.

EXULT A and EXULT B were randomized, double-blind, multi-center studies conducted in patients undergoing total knee replacement. Eligible participants in the former study were randomized to ximelagatran 24 mg, ximelagatran 36 mg, or warfarin. Patients in the latter study were randomized to ximelagatran 36 mg or warfarin. Due to varying appearances and dosing schedules, the treatments were administered utilizing a double-dummy design. Patients received treatment twice daily for 7 to 12 days. The primary measure of efficacy was the incidence of total VTE and/or all-cause mortality where total VTE was defined as distal and/or proximal deep vein thrombosis and/or symptomatic pulmonary embolism. Treatment group differences were assessed using a Cochran-Mantel-Haenszel chi-square test stratified by type of surgery.

THRIVE III was a randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy of ximelagatran 24 mg given as a prolonged prophylaxis after a six-month anticoagulation treatment. The pool of eligible patients included individuals who had an objectively verified, symptomatic VTE and had received anticoagulation treatment for approximately six months. Two to seven days prior to randomization, patients were instructed to terminate their anticoagulation treatment. Study participants were randomized to ximelagatran 24 mg or placebo administered twice daily for 18 months. The primary measure of efficacy was

the time to the first VTE event. The analysis employed a log-rank test to assess the treatment differences.

1.3 Statistical Issues and Findings

One methodological issue arose during the course of my review. In THRIVE III, analyses of the outcomes utilized the statistical methodology of survival analysis. An underlying assumption of the methodology, as applied by the applicant, is that all study participants will experience a recurrence. However in THRIVE III, a substantial number of participants may never experience a recurrence; therefore, caution should be exercised when interpreting conclusions from the planned analysis. I subsequently dichotomized the response and performed an analysis similar to that of EXULT A and EXULT B. My analysis was post-hoc; however, the sole purpose was to validate the conclusions.

The evidence taken collectively from EXULT A and EXULT B indicated statistical support of the efficacy of the ximelagatran for short-term use. When comparing ximelagatran 36 mg to warfarin, a significant reduction in the incidence of VTE and/or all-cause mortality was demonstrated in both studies. The magnitude of the reduction was 7.3% and 9.3% (ximelagatran 36 mg versus warfarin) in the two studies, respectively. A 24 mg dose of ximelagatran was additionally included in EXULT A; however, the dose failed to demonstrate a significant difference in the reduction of total VTE and/or all-cause mortality as compared to warfarin. The evidence from THRIVE III indicated statistical support of ximelagatran for the long term secondary prevention of VTE. Specifically, ximelagatran 24 mg (administered twice daily for 18 months) significantly reduced the recurrence rate of VTE events compared to placebo. The estimated cumulative risk of a recurrent VTE was 2.8% for patients randomized to ximelagatran and 12.6% for patients randomized to placebo.

2. INTRODUCTION

2.1 Overview

Astra Zeneca has proposed Exanta (ximelagatran), an oral anticoagulant, for the following indications: prevention of venous thromboembolism (VTE) in patients undergoing total knee replacement, long term secondary prevention of VTE after standard treatment for an episode of acute VTE, and prevention of stroke and other thromboembolic complications associated with atrial fibrillation. According to the applicant, "The development program for ximelagatran has been designed to offer an oral alternative anticoagulant to VKAs for major indications." Exanta was introduced to the Division of Gastrointestinal and Coagulant Drug Products through IND 56, 611. The development plan was discussed via several meetings and correspondences. Discussion topics focused on the appropriateness of various clinically defined outcomes, the justification of the proposed non-inferiority margin for specified studies, and the number and type of studies required for the proposed indications. The current submission includes studies investigating the superiority of ximelagatran to warfarin in prevention of VTE in patients undergoing knee replacement, the superiority of ximelagatran to placebo in the secondary prevention of VTE, and the non-inferiority of ximelagatran to warfarin in the prevention of complications associated with atrial fibrillation. This review will focus on the former two indications only. The latter indication will be reviewed by the Division of Cardio-Renal Drugs.

2.2 Data Sources

Primary support for ximelagatran for the prevention of VTE was derived from two randomized, double-blind, multi-center studies, namely, EXULT A and EXULT B. Support for the long term secondary prevention indication was derived from THRIVE III, a randomized, double-blind, multi-center study. The drug application was electronic. The study reports and data were archived in the Food and Drug Administration internal document room under the network path location \\CDSEUB1\N21686\N_000\2003-12-23. A summary of the studies is provided in Table 1.

Table 1: Table of studies

Study Number **Number of centers (n)**	**Study Design**	**Treatment Arms and Number of randomized patients (n)**	**Primary measure of efficacy**
SH-TPO-0010 EXULT A Multi-center (114)	Phase 3, randomized, double-blind, active-controlled study in patients undergoing total knee replacement	•Exanta 24 mg (762) •Exanta 36 mg (775) •Warfarin (764)	Composite endpoint of DVT and/or PE and/or all-cause mortality
SH-TPO-0012 EXULT B Multi-center (113)	Phase 3, randomized, double-blind, active-controlled study in patients undergoing total knee replacement	•SKY0401 36 mg (1152) •Warfarin (1151)	Composite endpoint of DVT and/or PE and/or all-cause mortality
SH-TPO-0005 Multi-center (126)	Phase 3, randomized, double-blind, active-controlled, , non-inferiority study in patients undergoing total hip arthroplasty	•Exanta 24 mg (918) •Enoxaparin 30 mg (920)	Incidence of overall VTE
SH-TPO-0006 Multi-center (77)	Phase 3, randomized, double-blind, active-controlled study in patients undergoing total knee replacement	•Exanta 24 mg (348) •Warfarin (332)	Incidence of overall VTE
SH-TPO-0004 Multi-center (55)	Phase 2, randomized, dose-finding, safety, and pharmacokinetics study in patients undergoing total knee replacement	•Exanta 8 mg (85) •Exanta 12 mg (134) •Exanta 18 mg (126) •Exanta 24 mg (130) •Enoxaparin 30 mg (125)	Incidence of overall VTE
SH-TPV-0003 THRIVE III Multi-center (142)	Phase 3, randomized, double-blind, placebo-controlled study in patients having received six-month anticoagulation treatment for VTE	•Exanta 24 mg (617) •Placebo (616)	Time to first VTE event

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The main body of my evaluation of efficacy will discuss each study individually.

3.1.1 SH-TPO-0010(EXULT A)

Study Design and Endpoints

Due to the varying appearances and dosing schedules, treatments were administered utilizing a double-dummy design. After surgery, eligible patients were randomized to one of the following three treatment regimens:

- ximelagatran 24 mg tablet with a 36 mg placebo tablet and placebo capsule(s) matching warfarin,
- ximelagatran 36 mg with a 24 mg placebo tablet and placebo capsule(s) matching warfarin, or
- warfarin 2.5 mg capsule(s) and two placebo tablets matching ximelagatran 24 mg and 36 mg.

The first dose of warfarin (and matching placebo) was administered on the evening of the day of surgery, and subsequent doses were administered each evening. Ximelagatran (and matching placebo) was initially administered the morning after surgery. Subsequent doses of ximelagatran were administered twice daily, in the morning and evening with doses taken at 12 hour intervals. Of note, the dose of warfarin was adjusted to maintain a target international normalized ratio of 2.5 (range 1.8 to 3.0). The duration of treatment varied from 7 to 12 days.

The primary measure of efficacy was incidence of total venous thromboembolism (VTE) and/or all-cause mortality. Total VTE was defined as distal and/or proximal deep vein thrombosis and/or symptomatic pulmonary embolism (with objective Independent Central Adjudication Committee confirmation). Deep vein thrombosis (DVT) was assessed using a venographic procedure. The diagnosis of pulmonary embolism (PE) was established by a ventral perfusion lung scan, pulmonary angiography, or spiral computed tomography. Additional details regarding the methodology used for assessments and diagnoses of VTE are included in the appendix. Secondary measures of interest included the incidence of proximal DVT, PE, and/or all-cause mortality (via Independent Central Adjudication Committee assessment) and the incidence of total VTE and/or all-cause mortality (via local assessment).

Based on previous studies, a sample size of 1700 was determined to be sufficient to detect an approximate 7.5% difference in reduction in VTE between treatment groups and warfarin with 80% power. According to the applicant, the needed sample size was increased to 2250 to account for the percentage of patients (at most 25%) not having evaluable venograms. Of note, 116 international centers participated in the study; however, patients were only randomized at 114 centers.

Patient Disposition, Demographic and Baseline Characteristics

Descriptive demographic and baseline information was summarized using 2285 of the 2301 randomized patients. The excluded patients did not receive study medication. The ages of patients were between 32 and 89 with a mean age of 68. In the study, approximately 96% of the study participants were Caucasian, and 4% of the participants were African American. Females composed 62% of the patient population. Baseline characteristics included weight, body mass index, nicotine use, alcohol use, and creatinine clearance. Demographic and baseline characteristics did not differ between treatment arms. A detailed table outlining the composition of the study population is presented in the appendix.

Of the 2285 randomized patients, 1851 of the patients had surgery, received at least one dose of the study medication, and were included in the efficacy analyses. Approximately 98% of the patients in the analysis population completed the study. Four patients discontinued due to adverse events. Specifically, one patient in the warfarin group, one patient in the ximelagatran 24 mg group, and two patients in the ximelagatran 36 mg group discontinued due to an adverse event.

Statistical Methodologies

The primary analysis employed a Cochran-Mantel-Haenszel chi-square test stratified by type or surgery (i.e. bilateral or unilateral) to assess the treatment group differences. Pairwise comparisons between each dose of ximelagatran and warfarin were examined via a sequential testing procedure to control the type I error rate. The ximelagatran 36 mg treatment arm was initially compared to the warfarin arm. The ximelagatran 24 mg group was subsequently compared to the warfarin group if the previous comparison was significant at the 0.05 alpha level. The applicant additionally explored the heterogeneity of the treatment effect across centers. According to the applicant, "Event rates and non-evaluability rates were summarized by investigative site and the possibility of treatment by center interaction was examined for sites with large numbers of patients." The analysis of secondary endpoints was identical to the primary analysis; however, no adjustments for multiple comparisons were made. A blinded interim analysis was planned; however, the alpha inflation was considered negligible. Details of the interim analysis are included in the appendix.

Analyses were conducted on the intent-to-treat (ITT) population including all randomized patients who had elective total knee replacement and who received at least one dose of the study medication. The applicant further stated, "No attempt was made to impute data for those patients who did not have an evaluable venogram (as determined by central adjudication) and did not experience a symptomatic, objectively confirmed VTE or death. Thus, the efficacy ITT analysis population included all patients who had (1) an evaluable venogram or (2) symptomatic DVT/PE while being treated with study medication (objectively confirmed by central adjudication) or (3) a fatality while being treated with study medication."

Results and Conclusions

Table 2 depicts results of the applicant's primary analysis. Patients in the ximelagatran 36 mg group had a significant reduction in the frequency of total VTE and/or all-cause mortality as compared to patients in the warfarin group. The reduction in the frequency of the composite endpoint in patients randomized to ximelagatran 36 mg was 7.3% relative to patients randomized to warfarin. Moreover, the relative risk reduction (i.e. risk difference expressed as a percent of the risk in warfarin) was 26.4%. A significant difference in the incidence of VTE and/or all-cause mortality was not demonstrated between ximelagatran 24 mg and warfarin. For completeness, the applicant performed a post-hoc analysis comparing the 24 mg and 36 mg doses of ximelagatran. There was no significant difference in the composite outcome between the ximelagatran doses. These findings based on assessments by the Independent Central Adjudication Committee (ICAC) were further supported by assessments conducted locally at study centers. Based on my independent evaluation of the data, I concur with the primary results and conclusions.

Table 2: Frequency of total venous thromboembolism and/or all-cause mortality-ITT population
(Source: Table 24, Clinical Study Report SH-TPO-0010)

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

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

I additionally explored the individual events that composed the primary endpoint to further elucidate the results in Table 2. My results are illustrated in Table 3 and are in agreement with the applicant's results. Of note, asymptomatic DVTs were detected during mandatory venography, and symptomatic DVTs were diagnosed by compression ultrasound and confirmed using venograms. As evident from the table, most events were asymptomatic, distal DVTs.

Table 3: Symptomatic and asymptomatic events over the treatment duration -ITT population

Event	Ximelagatran 24 mg	Ximelagatran 36 mg	Warfarin
Number of subjects	614	629	608
Asymptomatic DVT	151 (25%)	124 (20%)	166 (27%)
Proximal DVT	12 (2%)	13 (2%)	23 (4%)
Distal DVT	139 (23%)	111 (18%)	143 (24%)
Symptomatic DVT	5 (.8%)	7 (1%)	9 (2%)
Proximal DVT	1 (.2%)	2 (.3%)	4 (.7%)
Distal DVT	4 (.7%)	5 (.8%)	5 (.8%)
Pulmonary embolism	2 (.3%)	2 (.3%)	0 (0%)
Death	1 (.2%)	1 (.2%)	1 (.2%)

Per the clinical team's request, I also performed the primary analysis on the safety population including all randomized patients who received at least one dose of study drug. My results are shown in Table 4.

Table 4: Frequency of total venous thromboembolism and/or all-cause mortality-Safety population

			Ximelag vs warfarin		
Treatment group	**% (n/N)**	**Exact 95% CI**	**%**	**95% CI**	**CMH p-value***
Ximelag 24 mg	20.2 (153/757)	(17.4, 23.1)	-1.9	(-6.2, 2.3)	0.692
Ximelag 36 mg	16.6 (128/769)	(14.0, 19.3)	-5.5	(-9.6, -1.4)	0.010
Warfarin	22.1 (168/759)	(19.2, 25.1)			

* Treatment differences were tested using the Cochran-Mantel-Haenszel test, adjusted for the type of surgery performed.

The reduction in the frequency of the secondary composite outcome, incidence of proximal DVT, PE, and/or all-cause mortality, was not significantly different between the ximelagatran groups and the warfarin group. Specifically, incidence of the outcome was 2.5%, 2.7% and 4.1% for patients randomized to ximelagatran 24 mg, ximelagatran 36 mg, and warfarin, respectively. Of note, the incidence of proximal DVT, PE and/or all-cause mortality was computed utilizing the same methodology as used in the primary analyses; however, the denominator varied due to the exclusion of patients classified as "indeterminants". A table detailing the results of the analysis of this secondary endpoint is included in the appendix.

3.1.2 SH-TPO-0012(EXULT B)

Study Design and Endpoints

The design and endpoints of study SH-TPO-0012 or EXULT B were nearly identical to that of the previously described study (EXULT A) with variations in the tested doses and sample sizes. In EXULT B, 2303 patients scheduled to undergo total knee replacement were randomized to ximelagatran 36 mg or warfarin.

Based on event rates in EXULT A, a sample size of 1720 was determined to be sufficient to detect a 25% relative risk reduction in VTE with 90% power. According to the applicant, the

needed sample size was increased to 2300 to account for the percentage of patients (at most 25%) not having evaluable venograms. Of note, 115 international centers participated in the study; however, patients were only randomized at 113 centers.

Patient Disposition, Demographic and Baseline Characteristics

The ages of patients were between 26 and 91 with a mean age of 67. In the study, 94% of study participants were Caucasian, and 5% were African American. Females composed 63% of the patient population. Baseline characteristics included weight, body mass index, nicotine use, alcohol use, and creatinine clearance. Demographic and baseline characteristics were similar across treatment groups. Detailed tables outlining the composition of the study population with respect to demographic and baseline characteristics are presented in the appendix.

Of the 2303 randomized patients, 2299 received at least 1 dose of study medication. Moreover of these 2299 patients, 1949 patients had a venogram adequate for evaluation and were included in the analysis population. Approximately 99% of the patients in the analysis population completed the study. Three patients in the warfarin group and six patients in the ximelagatran group discontinued due to adverse events.

Statistical Methodologies

The primary analysis assessed treatment group differences using a Cochran-Mantel Haenszel test stratified by type or surgery (i.e. bilateral or unilateral). Secondary endpoints were analyzed using similar methodology.

Similar to EXULT A, analyses were conducted on the intent-to-treat (ITT) population consisting of all randomized patients who had elective total knee replacement and who received at least one dose of the study medication. The applicant again stated, "No attempt was made to impute data for those patients who did not have an evaluable venogram (as determined by central adjudication) and did not experience a symptomatic, objectively confirmed VTE or death. Thus, the efficacy ITT analysis population included all patients who had (1) an evaluable venogram or (2) symptomatic DVT/PE while being treated with study medication (objectively confirmed by central adjudication) or (3) a fatality while being treated with study medication."

Results and Conclusions

The results of the applicant's analysis of the primary efficacy outcome as assessed by the ICAC are depicted in Table 5. Patients in the ximelagatran 36 mg group had a significant reduction in the frequency of total VTE and/or all-cause mortality as compared to patients in the warfarin group. The reduction in the frequency of the composite endpoint in patients randomized to ximelagatran 36 mg was 9.3% relative to patients randomized to warfarin. Moreover, the relative risk reduction (i.e. risk difference expressed as a percent of risk in warfarin) was 29.3%. Based on my independent evaluation of the data, I concur with the results.

Table 5: Frequency of total venous thromboembolism and/or all-cause mortality-ITT population
(Source: Table 15, Clinical Study Report SH-TPO-0012)

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

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

Table 6 further illustrates the individual components of the endpoint. Similar to EXULT A, most events were asymptomatic, distal DVTs.

Table 6: Symptomatic and asymptomatic events over the treatment duration -ITT population

Event	Ximelagatran 36 mg	Warfarin
Number of subjects	982	967
Asymptomatic DVT	214 (22 %)	301 (31 %)
Proximal DVT	30 (3 %)	33 (3 %)
Distal DVT	184 (19 %)	268 (28 %)
Symptomatic DVT	8 (1 %)	15 (2 %)
Proximal DVT	2 (.2 %)	1 (.1 %)
Distal DVT	6 (.6 %)	14 (1.4 %)
Pulmonary embolism	2 (.2 %)	5 (.5 %)
Death	4 (.4 %)	2 (.2 %)

Per the clinical team's request, I also performed the primary analysis on the safety population including all randomized patients who received at least one dose of study drug. My results are shown in Table 7.

Table 7: Frequency of total venous thromboembolism and/or all-cause mortality-Safety population

			Ximelag vs warfarin		
Treatment group	**% (n/N)**	**Exact 95% CI**	**%**	**95% CI**	**CMH p-value**
Ximelag 36 mg	19.2 (221/1151)	(17.0, 21.5)	-7.6	(-11.1, -4.1)	<0.001
Warfarin	26.8 (308/1148)	(24.3, 29.4)			

* Treatment differences were tested using the Cochran-Mantel-Haenszel test, adjusted for the type of surgery performed.

The reduction in the frequency of the secondary composite outcome, incidence of proximal DVT, PE, and/or all-cause mortality, was not significantly different between the ximelagatran group and the warfarin group. Specifically, the incidence of the outcome was 3.9% and 4.1% for

patients randomized to ximelagatran 36 mg and warfarin, respectively. Of note, the incidence of proximal DVT, PE and/or all-cause mortality was computed utilizing the same methodology as used in the primary analyses; however, the denominator varied due to the exclusion of patients classified as "indeterminants". A table detailing the results of the analysis of the secondary endpoint is included in the appendix.

3.1.3 ADDITIONAL STUDIES

Three additional controlled studies of the short-term use of ximelagatran were conducted but were not of primary focus due to the varying patient populations and/or doses. I will briefly describe those studies for completeness of review of the NDA submission. SH-TPO-0005 was a randomized, double-blind, active-controlled study of ximelagatran 24 mg and enoxaparin 30 mg for the prevention of VTE following total hip arthroplasty. Treatments were administered twice daily for 7-12 days utilizing a double-dummy design. Ximelagatran required oral administration while enoxaparin was administered subcutaneously. The primary measure of efficacy was the incidence of total VTE as confirmed by the ICAC. According to the applicant, "Statistical non-inferiority was established if the upper confidence bound around the between group difference in VTE frequency was less than 5%." The study failed to demonstrate the non-inferiority of ximelagatran to enoxaparin. In addition to statistical concerns regarding the non-inferiority margin, an indication in the hip arthroplasty population was not sought; therefore, the study was not of focus during the current review.

The applicant described SH-TPO-0004 as a "dose-finding, safety, and pharmacokinetic study of H 376/95 (ximelagatran) as a prophylaxis for thromboembolic complications after total knee replacement." Patients undergoing knee replacement were randomized to 8, 12, 18, or 24 mg of ximelagatran or enoxaparin 30 mg. Ximelagatran was administered orally twice daily under blinded conditions while enoxaparin was administered subcutaneously under open-label conditions. The study did not demonstrate a linear dose response among the four ximelagatran groups. Moreover, pairwise comparisons between each of the ximelagatran groups and the enoxaparin group failed to show significant differences in the incidence of VTE.

The design of SH-TPO-0006 mimicked that of EXULT A and EXULT B with variations in the treatment arms and the definition of the primary efficacy outcome. Patients were randomized to ximelagatran 24 mg or warfarin. The primary measure of efficacy was the incidence of VTE. The study failed to demonstrate a difference in the incidence of VTE between ximelagatran and warfarin.

3.1.4 SH-TPV-0003(THRIVE III)

Study Design and Endpoints

Study SH-TPV-0003 or THRIVE III was a double-blind, placebo-controlled, multi-center study to assess the efficacy of ximelagatran 24 mg given as a prolonged prophylaxis after a six-month anticoagulation treatment. The pool of eligible patients included individuals who had an

objectively verified, symptomatic VTE and had received anticoagulation treatment for approximately six months. Two to seven days prior to randomization, patients were instructed to terminate their anticoagulation treatment. Study participants were randomized to ximelagatran 24 mg or placebo administered twice daily for 18 months. "Study visits were scheduled at two weeks and four weeks and then every month (three to five weeks) during the first six months after randomization and thereafter every three months (10-14 weeks)."

Based on assumed event rates of 6% and 2% in the placebo and ximelagatran arms respectively, the applicant determined that a sample of size 1200 would be sufficient to detect a difference with 90% power. One hundred and forty-two centers from eighteen countries participated in the study.

Patient Disposition, Demographic and Baseline Characteristics

The ages of randomized patients ranged from 18 and 90 with a mean age of 57. In the study, 93% of study participants were Caucasian, and females composed 47% of the patient population. Baseline characteristics included weight, body mass index, nicotine use, alcohol use, and creatinine clearance. Demographic and baseline characteristics were similar across treatment groups according to the applicant. Detailed tables outlining the composition of the study population with respect to demographic and baseline characteristics are presented in the appendix.

Of the 1233 randomized patients, 10 patients did not have post-randomization data and were excluded from the efficacy analysis. Overall, 320 patients discontinued the study prematurely, and 129 of the discontinuations were caused by adverse events. Specifically, 144 patients within the ximelagatran group discontinued prematurely, and 62 (43%) were caused by adverse events. One hundred and seventy-six participants in the placebo group discontinued the study prematurely. Of the 176 participants, 38% discontinued due to an adverse event and 35% discontinued to the development of a study specific discontinuation criteria.

Statistical Methodologies

The primary measure of efficacy was the time to the first VTE event calculated as the number of days from randomization until the occurrence of the first relevant event. Secondary measures of efficacy included the time until death by any cause, the time to locally confirmed VTE events, and the time to the composite of VTE and/or death.

The analyses employed log-rank tests to compare recurrence rates between treatment and groups for the primary and secondary outcomes. Moreover, Kaplan-Meier estimates and hazard ratios were employed to gain additional insight.

An interim analysis was in the planned charter for the Safety Committee. The analysis employed a Peto-type boundary for monitoring a positive trend in VTE events. The alpha inflation was considered negligible ($\forall = 0.0476$).

Results and Conclusions

Study participants receiving ximelagatran 24 mg twice daily experienced a significant reduction in recurrent VTE events as compared to patients receiving placebo. The estimated cumulative risk of a recurrent VTE event at the end of 18 months was 2.8% for patients randomized to ximelagatran and 12.6% for patients randomized to placebo. The hazard or risk of a recurrent VTE event was smaller for participants in the ximelagatran group as evidenced by the hazard ratio of 0.16. The results were supported by the significant reduction in the secondary composite endpoint (VTE and/or death) among the treated group as compared to the placebo group. In addition, the risk of death from all causes was comparable among treatment arms. The estimated cumulative risk over time of the primary endpoint is displayed in Table 8. Figures 1 and 2 are

graphical depictions of the cumulative risk versus time for the primary endpoint and the secondary composite endpoint.

Table 8: Estimated cumulative risk (%) of a VTE event, ITT population

(Source: Table 23, Clinical study report SH-TPV-0003)

Treatment	Days	Effective sample size	Estimate	95% Confidence Interval	
				Lower limit	Upper limit
Ximelagatran	90	590.0	0.7	0.0	1.3
	180	546.5	1.0	0.2	1.8
	270	522.0	1.2	0.3	2.1
	360	506.0	1.6	0.6	2.6
	450	474.5	1.8	0.7	2.9
	540	107.0	2.8	0.9	4.7
Placebo	90	557.0	4.8	3.1	6.5
	180	532.0	6.4	4.4	8.3
	270	502.0	8.4	6.1	10.6
	360	474.0	10.8	8.2	13.3
	450	438.5	11.9	9.3	14.6
	540	86.0	12.6	9.9	15.4

Figure 1: Cumulative risk of recurrent VTE events versus time, ITT population

(Source: Figure 5, Clinical Study Report SH-TPV-0003)

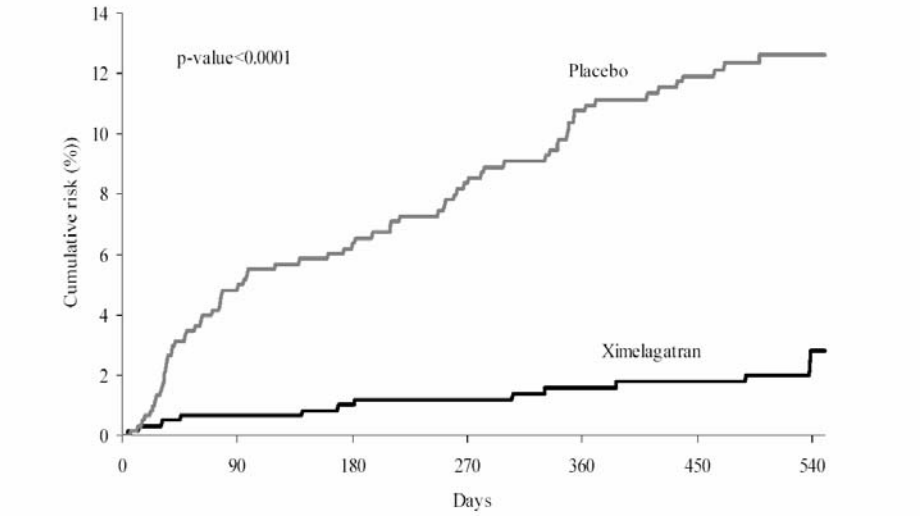
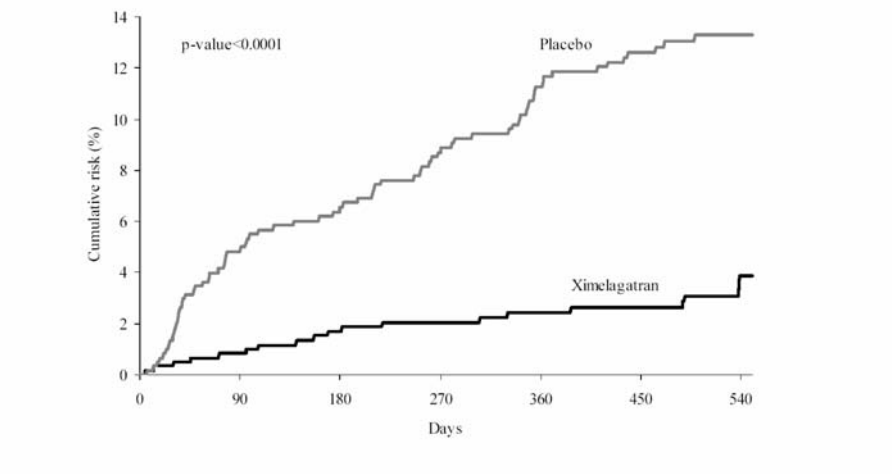


Figure 2: Cumulative risk of recurrent VTE events and/or all-cause mortality versus time, ITT population
(Source: Figure 7, Clinical Study Report SH-TPV-0003)



Upon exploration of the data, I found that 83 (71 in the placebo arm and 12 in the ximelagatran arm) of the 1223 study participants experienced a recurrent VTE event. Under this scenario, the analysis employed by the applicant may result in misleading conclusions; therefore, I performed a post-hoc categorical data analysis by dividing the population into two more stringent categories. One category included all patients having a VTE event and/or discontinuing the study prematurely. All remaining patients were classified as not having an event. My analysis demonstrated a significant reduction in recurrence rates for participants treated with ximelagatran as compared to participants randomized to placebo.

3.2 Evaluation of Safety

The evaluation of safety is deferred to the review of Dr. Ruyi He.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

For ease of exposition and completeness, I have included all the subgroup factors considered by the applicant in the following review of subpopulations. Although the applicant examined numerous prognostic factors, I focused primarily on the age, gender, and race factors.

4.1 Gender, Race and Age

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

The impact of various subgroup factors on the incidence of total VTE and/or all-cause mortality was investigated by the applicant via frequency tables and a logistic regression model. The logistic regression model employed in EXULT A included the following factors: treatment, gender, age, race, country, type of surgery, body mass index, creatinine clearance, history VTE, type of anesthesia, time to first dose, and time to ambulation. The logistic model employed in EXULT B included an additional factor for time to venography. In addition, the interaction of each subgroup factor with treatment was also investigated in both studies.

In EXULT A, the applicant concluded that females, older patients, and patients enrolled in Canada experienced a higher incidence of VTE. Of note in EXULT A, 67 patients (14 with VTE) were excluded from the logistic regression analysis due to missing values. In EXULT B, several factors were associated with an increased incidence of the event of interest. Specifically, female patients, older patients, patients enrolled in Canada, patients with bilateral surgery, patients with a history of VTE, and patients with earlier scheduled venograms demonstrated a higher incidence of the outcome. Eighty-six patients were excluded from the analysis due to missing data. Frequency tables illustrated a reduced incidence of the outcome of interest among patients randomized to ximelagatran 36 mg as compared to warfarin in both studies.

I additionally conducted separate analyses by gender, age, and race. I initially explored the effect of each subgroup factor on the primary endpoint using logistic regression models. In EXULT A, older patients (> 70) had slightly higher odds of experiencing a VTE and/or death as compared to younger patients (≤ 70). In EXULT B, older patients (> 70) and female patients had slightly higher odds of experiencing a VTE and/or death as compared to younger patients (≤ 70) and male patients, respectively. I also investigated the significance of the treatment effect after adjusting for covariates. The treatment effect was consistent across the subgroups.

The applicant did not propose any efficacy claims for any subgroup of patients. Overall, the results were consistent and lend support to the findings presented in the preceding sections.

4.1.2 SH-TPV-0003(THRIVE III)

The impact of several prognostic factors on the time to the first VTE event was investigated by the applicant via frequency tables and Cox regression models. Potential prognostic factors identified by the applicant included sex, age, creatinine clearance, weight, initial VTE event, previous VTE events, presence of malignancy, and prothrombotic state. Separate analyses for each prognostic factor were conducted via Cox regression models. The between treatment comparisons included treatment as a covariate in the models while the within treatment comparisons included the subgroup factors as covariates, respectively.

The applicant's analysis yielded a gender effect. Specifically, females experienced a lower risk of recurrent VTE events as compared to males. The treatment effect remained constant across age, race, and gender. I additionally conducted analyses on the dichotomized VTE outcome. The results of my analyses are in agreement with those of the applicant.

The applicant did not propose any efficacy claims for any subgroup of patients. Overall, the results were consistent and lend support to the findings presented in the preceding sections.

4.2 Other Special/Subgroup Populations

No additional analyses on other subgroup populations were warranted.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

One methodological issue arose during the course of my review. In THRIVE III, analyses of the outcomes utilized the statistical methodology of survival analysis. This methodology uniquely handles "time to event" data where observations may be censored due to discontinuation or to the limitation of the study's follow-up time. An underlying assumption of the methodology, as applied by the applicant, is that all study participants will experience a recurrence. However in THRIVE III, a reasonable assumption is that not all study participants will experience a recurrence. I subsequently dichotomized the response and performed an analysis similar to that of EXULT A and EXULT B. My analysis was post-hoc; however, the sole purpose was to validate the conclusions.

The evidence taken collectively from EXULT A and EXULT B indicated statistical support of the efficacy of the ximelagatran for short-term use. When comparing ximelagatran 36 mg to warfarin, a significant reduction in the incidence of VTE and/or all-cause mortality was demonstrated in both studies. A 24 mg dose of ximelagatran was additionally included in EXULT A; however, the dose failed to demonstrate a significant difference in the reduction of

total VTE and/or all-cause mortality as compared to warfarin. The evidence from THRIVE III indicated statistical support of ximelagatran for the long term secondary prevention of VTE. Specifically, ximelagatran 24 mg significantly reduced the recurrence rate of VTE events compared to placebo.

5.2 Conclusions and Recommendations

Astra Zeneca proposes ximelagatran for the prevention of VTE in patients undergoing knee replacement surgery and for the long term secondary prevention of VTE after standard treatment for an episode of acute VTE. The primary claims are that ximelagatran (36 mg) reduces the incidence of total VTE and/or mortality in patients undergoing total knee replacement and that ximelagatran (24 mg) reduces the recurrence of VTE events among patients who previously received 6 months of anticoagulation therapy for an acute VTE. My review of the collective evidence suggests statistical support of the efficacy of ximelagatran**;** however, statistical significance does not imply clinical meaningfulness. Issues warranting additional consideration include the adequacy of the period of follow-up for the short term indication, the appropriateness of warfarin as a comparator, and concerns regarding bleeding and liver toxicity. Discussion of these issues as they pertain to the clinical meaningfulness of the reduction in VTE events and the safety profile of the drug are deferred to the clinical review of Dr. Ruyi He.

6. APPENDIX

6.1 EXULT A

Additional details regarding the methodology used for assessments and diagnoses of VTE follow. The details are relevant to the statistical analyses as the variables were coded in the datasets according to the classifications described. The information is extracted from the clinical study report SH-TPO-0010 of NDA 21-686 (pages 47-49).

The following assessments were assigned based on the review:

1. **Intraluminal filling defect (ILFD)**: An area of reduced or absent filling at least partially surrounded by contrast medium that is constant in two or more projections, or lack of filling in a vessel in which there was a cut-off which had the configuration of a thrombus

2. **Normal**: All deep veins visualized with no evidence of ILFD

3. **Indeterminate**: Lack of filling of a region of the deep vein system (proximal or distal) without the presence of an ILFD elsewhere in the same region. Failure to visualize the deep femoral veins of the thigh where the muscular veins of the calf or the anterior tibial veins of the calf did not classify a venogram as indeterminate.

   If the deep femoral, anterior tibial, or muscular veins were non-filling or judged to be indeterminate and all other veins in the proximal and distal regions were judged to be normal, then the classification was "having no DVT."

4. **Not done**: Venogram not performed

As a result of the independent, central evaluation, the assessed leg would be classified as:

1. **Having no DVT** if the proximal and distal veins were normal

2. **Having any DVT** if any of the proximal or distal veins had an ILFD

3. **Non-evaluable for any DVT** if neither (1) nor (2) above were satisfied

4. **Having no proximal DVT** if the proximal veins were normal irrespective of findings involving the distal veins

5. **Having proximal DVT** if any of the proximal veins had an ILFD irrespective of findings involving the distal veins

6. **Non-evaluable for proximal DVT** if neither (4) nor (5) above was satisfied

(b) Pulmonary embolism

Clinical symptoms suggestive of PE were to be objectively verified by a ventral perfusion (V/Q) lung scan. The results of the V/Q lung scan were classified using the following criteria:

1. **Normal**: No perfusion defects

2. **High probability of PE**: Segmental perfusion defect (≥1), seen in at least two views, with normal ventilation at that spot

3. **Non-high probability of PE**: Perfusion defect that does not qualify as high probability

4. **Not done**: V/Q lung scan not performed

The diagnosis of PE could also be established by pulmonary angiography or spiral computed tomography (CT). Intraluminal filling defects on pulmonary angiography or spiral CT within the pulmonary arteries and/or its branches were considered confirmation of PE. Pulmonary

embolic events were also centrally adjudicated by 2 independent reviewers from the Clinical Trials Methodology Group who were blinded to the identity of the study medication administered. As a result of the independent, central evaluation, a patient would be classified as:

1. **Having PE** if one of the following criteria were fulfilled: a) the V/Q lung scan was assessed as high probability; b) the V/Q lung scan was assessed as non-high probability and a venogram or compression ultrasound of the proximal region was assessed as diagnostic for acute DVT; c) the spiral CT was positive for an ILFD; d) the pulmonary angiogram was positive for ILFD or a sudden contrast cut-off of 1 or more vessels (> 2.5 mm in diameter); e) embolectomy confirmed the presence of a PE; or f) an autopsy confirmed the presence of a PE.

2. **Having no PE** if none of the criteria in (1) was satisfied.

Confirmed PE necessitated discontinuation of study medication and the start of conventional therapy. Additional details regarding the criteria used for adjudication are provided in Appendix 5 of the protocol (Appendix 12.1.1).

(c) All-cause mortality

All deaths were to be forwarded to the Independent Central Adjudication Committee for adjudication. The overall objective of the Independent Central Adjudication Committee was to classify the cause of death as:

1. Fatal PE

2. Fatal bleeding event

3. Death not associated with VTE or bleeding

A death would be classified as:

1. **Fatal PE** if the autopsy revealed major PE (occlusion of at least 2 segmental pulmonary arteries, or their equivalent) or if the clinical course was compatible with PE and there was not a more compelling alternative diagnosis to account for death.

2. **Fatal bleed** if there was overt bleeding (including autopsy evidence) and there was not a more compelling alternative diagnosis to account for death.
   Note: Death associated with pulmonary hemorrhage would usually be attributed to underlying PE.

3. **Death not associated with VTE or bleeding** – if neither (1) nor (2) were satisfied.

Demographic and baseline characteristics
(Source: Table 16, Clinical Study report SH-TPO-0010)

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

Demographic and baseline characteristics continued
(Source: Table 16, Clinical Study report SH-TPO-0010)

Demographic or baseline characteristic[a]		Ximelag 24 mg N=757	Ximelag 36 mg N=769	Warfarin N=759
	Range	18.5 to 57.0	18.6 to 49.2	14.5 to 61.8
Estimated	<30	0.1 (1/757)	0 (0/769)	0.5 (4/759)
creatinine	30 to 50	4.5 (34/757)	5.1 (39/769)	5.3 (40/759)
clearance	>50 to 80	30.3 (229/757)	33.0 (254/769)	30.4 (231/759)
(mL/min),	>80	61.6 (466/757)	58.5 (450/769)	61.3 (465/759)
% (n/N)	Mean (SD)	99.1 (37.8)	96.1 (36.5)	97.8 (39.2)
	Range	18.9 to 369.4	31.6 to 305.5	16.3 to 289.6
Nicotine use,	Nonsmoker	59.2 (448/757)	59.7 (459/769)	60.2 (457/759)
% (n/N)	Previous smoker	30.9 (234/757)	30.8 (237/769)	29.5 (224/759)
	Occasional smoker	1.2 (9/757)	2.7 (21/769)	2.6 (20/759)
	Daily smoker	8.7 (66/757)	6.8 (52/769)	7.6 (58/759)
Alcohol use	None	62.0 (469/757)	64.6 (497/769)	65.5 (497/759)
(drinks per week)	1 to 7	28.4 (215/757)	26.8 (206/769)	25.2 (191/759)
% (n/N)	8 to 14	3.2 (24/757)	4.0 (31/769)	4.5 (34/759)
	>14	2.9 (22/757)	1.6 (12/769)	1.3 (10/759)
	Mean (SD)	5.6 (7.0)	5.0 (7.5)	5.1 (6.2)
	Range	1.0 to 49.0	1.0 to 84.0	0.0 to 56.0

The following information extracted from page 66 of the clinical study report SH-TPO-0010 outlines the interim analysis.

5.7.7 Data safety monitoring committee

As indicated in Section 2.3.2.2, the responsibilities of the Safety Committee outlined in the Operations Manual (a copy of the manual is available in the Clinical Study File) included:

1. Reviewing interim safety and venogram data on a periodic basis. Initial review was to occur when 50 patients were enrolled and subsequent reviews were to occur on a monthly basis. Data to be reviewed on a periodic basis included: enrollment, demographics, operation characteristics, dosing errors, concomitant medications, SAEs, deaths, nonserious adverse events, centrally-adjudicated events, central laboratory tests (complete blood count, LFTs only), end-of-study status, venogram performance, evaluability rates, and warfarin therapy performance.

2. Making recommendations for any changes to the protocol. Any recommendations were reviewed by the study Executive Committee.

3. Performing a blinded interim analysis of the data after 25%, 50%, and 75% of the total anticipated enrollment to determine whether the study should be stopped in the event that the lower limit of the 95% confidence interval for the risk ratio of PE and/or central proximal venographic DVT or the risk ratio of major bleeding events was greater than 1.5. In addition, the study could be stopped in the event there was overwhelming evidence of benefit in the prevention of VTE (any DVT or PE). This latter rule would be met if the upper limit for the risk ratio was less than 0.3. The cumulative probability of stopping the study for beneficial efficacy is <0.0001, assuming VTE rates of 20% for ximelagatran 36 mg and 30% for warfarin. Since the probability of stopping under the null hypothesis of equal treatment groups would be even less, the alpha inflation in this study is considered negligible.

The Safety Committee did not unblind the data with respect to treatment group and all data summaries and reviews were conducted with treatment groups labeled A, B, and C. The complete Operations Manual can be found in Appendix 12.1.1

Secondary endpoint: Frequency of proximal DVT, PE, and/or all-cause mortality

(Source: Table 25, Clinical Study Report SH-TPO-0010)

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

Data derived from Table 11.2.1.1, Section 11.2.

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

CI Confidence interval.

6.2 EXULT B

Demographic and baseline Characteristics
(Source: Table 15, Clinical Study Report SH-TPO-0012)

Demographic or baseline characteristic		Ximelagatran 36 mg (n=1151)	Warfarin (n=1148)
Gender, n (%)	Male	446 (38.7)	415 (36.1)
	Female	705 (61.3)	733 (63.9)
Age in years, n (%)	<65	427 (37.1)	395 (34.4)
	65 to 74	469 (40.7)	500 (43.6)
	≥75	255 (22.2)	253 (22.0)
Age, years	Mean (SD)	66.9 (9.4)	67.1 (9.4)
	Range	26 to 91	32 to 89
Race, n (%)	Caucasian	1081 (93.9)	1087 (94.7)
	Black	62 (5.4)	50 (4.4)
	Oriental	3 (0.3)	6 (0.5)
	Other	5 (0.4)	5 (0.4)

Demographic and baseline characteristics continued

(Source: Table 15, Clinical Study Report SH-TPO-0012)

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

Secondary endpoint: Frequency of proximal DVT, PE, and/or all-cause mortality
(Source: Table 26, Clinical Study Report SH-TPO-0012)

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

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

6.3 THRIVE III

Demographic and baseline characteristics
(Source: Table 12, Clinical Study Report SH-TPV-0003)

		Ximelagatran	Placebo	Total
Age (years)	N	612 (100%)	611 (100%)	1223 (100%)
	Missing	0 (0%)	0 (0%)	0 (0%)
	Mean	56	58	57
	SD	15	15	15
	Min	18	19	18
	Median	57	60	59
	Max	87	90	90
	60+	274 (45%)	319 (52%)	593 (48%)

Demographic and baseline characteristics continued

(Source: Table 12, Clinical Study Report SH-TPV-0003)

		Ximelagatran	Placebo	Total
	70+	125 (20%)	146 (24%)	271 (22%)
	80+	15 (2%)	24 (4%)	39 (3%)
Sex	Male	331 (54%)	313 (51%)	644 (53%)
	Female	281 (46%)	298 (49%)	579 (47%)
Race	Caucasian	571 (93%)	569 (93%)	1140 (93%)
	Black	1 (0%)	4 (1%)	5 (0%)
	Oriental	1 (0%)	0	1 (0%)
	Other	34 (6%)	34 (6%)	68 (6%)
	Hispanic	5 (1%)	4 (1%)	9 (1%)
Smoking	None	343 (56%)	325 (53%)	668 (55%)
	Previous	143 (23%)	163 (27%)	306 (25%)
	Occasional	24 (4%)	28 (5%)	52 (4%)
	Habitual	102 (17%)	95 (16%)	197 (16%)
Malignancy (a)	No	578 (94%)	579 (95%)	1157 (95%)
	Yes	34 (6%)	32 (5%)	66 (5%)
Weight (kg)	N	612 (100%)	610 (100%)	1222 (100%)
	Missing	0 (0%)	1 (0%)	1 (0%)
	Mean	82	82	82
	SD	16	16	16
	Min	45	47	45
	Median	82	80	81
	Max	145	150	150
	80+	346 (57%)	332 (54%)	678 (55%)
	100+	86 (14%)	85 (14%)	171 (14%)
	120+	8 (1%)	10 (2%)	18 (1%)
Height (cm)	N	610 (100%)	607 (99%)	1217 (100%)
	Missing	2 (0%)	4 (1%)	6 (0%)
	Mean	170	170	170
	SD	10	10	10
	Min	144	142	142
	Median	170	170	170
	Max	200	200	200
BMI (kg/m^2)	N	610 (100%)	607 (99%)	1217 (100%)
	Missing	2 (0%)	4 (1%)	6 (0%)
	Mean	28	28	28
	SD	5	5	5
	Min	18	18	18
	Median	28	28	28
	Max	53	53	53
	25+	475 (78%)	486 (80%)	961 (79%)
	30+	213 (35%)	201 (33%)	414 (34%)
CrCl (ml/min)	N	597 (98%)	593 (97%)	1190 (97%)
	Missing	15 (2%)	18 (3%)	33 (3%)
	Mean	114	110	112

Demographic and baseline characteristics continued

(Source: Table 12, Clinical Study Report SH-TPV-0003)

	Ximelagatran	Placebo	Total
SD	42	41	42
Min	33	33	33
Median	109	106	107
Max	320	286	320
<50	20 (3%)	17 (3%)	37 (3%)
110+	292 (48%)	267 (44%)	559 (46%)

(a) According to baseline stratification