AstraZeneca

SH-TPO-0012

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Exanta™

ACTIVE INGREDIENT: Ximelagatran (H 376/95)

Trial title (number): EXULT KNEE: Optimization of Dose (Study A) and Confirmation of Safety and Efficacy (Study B) of H 376/95 (Oral Direct Thrombin Inhibitor ximelagatran) Compared to Warfarin (COUMADIN®) for the Prevention of Venous Thromboembolism Following Total Knee Arthroplasty

This Clinical Study Report describes the methods and results for the confirmation of safety and efficacy study (EXULT B). The methods and results of the dose refinement study (EXULT A) are described in a separate Clinical Study Report.

Developmental phase: Therapeutic confirmatory (3)
First subject recruited:24 June 2002
Last subject completed:04 April 2003
Approval date:08 September 2003

OBJECTIVES

The purpose of this study was to confirm the superior efficacy of ximelagatran 36 mg compared to warfarin for the prevention of venous thromboembolism (VTE) in patients after total knee replacement (TKR). The primary analysis was to focus on the primary composite endpoint of proximal and distal deep vein thrombosis (total DVT) and/or pulmonary embolism (PE) and/or all-cause mortality, according to independent central adjudication.

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

- The secondary composite endpoint of proximal DVT and/or PE and/or all-cause mortality
- The primary composite endpoint according to local on-site evaluations
- The incidence of major and any bleeding during the study drug treatment period.

A pharmacokinetic (PK) substudy was included to investigate the pharmacokinetic profile of melagatran after oral dosing with ximelagatran post-surgery in TKR patients. The primary objective of this substudy was to compare the early post-surgery (Day 1) pharmacokinetics of melagatran with the late post-surgery (Day 3 or later) pharmacokinetics in patients who received ximelagatran 36 mg after unilateral or bilateral TKR. The secondary objective of the substudy was to evaluate the effects of ximelagatran on activated partial thromboplastin time (APTT).

METHODS:

Study design

This (EXULT B) was a multicenter, randomized, double-blind, double-dummy, parallel-group active comparator study in patients who had undergone primary elective TKR. Patients were randomized to 1 of 2 treatment groups: ximelagatran 36 mg twice daily (bid) (initiated as early as possible on the morning after surgery) or warfarin once daily (od) (initiated the evening of surgery), administered for 7 to 12 days. The goal was to confirm the superior efficacy of ximelagatran compared with warfarin for the prevention of VTE. Independent Central Adjudication Committee (ICAC) evaluation of mandatory bilateral venography (performed at the End of Treatment Period Study Visit) in conjunction with objectively confirmed, symptomatic VTE events and/or all-cause mortality were used to determine the primary endpoint. Symptomatic events or deaths occurring within 2 days following mandatory

venography or up to Day 12, if no mandatory venography was done, were included in the primary analysis of efficacy.

Target patient population and sample size

Adult male or female patients whose body weight was between 88 and 300 pounds, inclusive, and who were scheduled for primary elective TKR were eligible for inclusion in the study. Patients who required concomitant therapy with agents known to affect coagulation or platelet function, who had any history of bleeding episodes, or who had thrombocytopenia or significant renal impairment were not eligible for entry. Assuming a 27% incidence of VTE in patients treated with warfarin and a 20% incidence of VTE in patients treated with ximelagatran, a total of 1720 evaluable patients undergoing TKR, derived from 2300 randomized patients, provided 90% power to detect a 25% risk reduction in the incidence of VTE at a 5% level of significance.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

The investigational product was ximelagatran (H 376/95) 36 mg orally (po) bid, and the comparator was warfarin sodium (COUMADIN®, Bristol-Myers Squibb) po given od to maintain a target international normalized ratio (INR) of 2.5 (range: 1.8 to 3.0). Warfarin (or matching placebo dummy) was started the evening of surgery and ximelagatran (or matching placebo dummy) was started the morning after surgery (minimum of 12 hours post-surgery). Batch numbers were: ximelagatran 36-mg tablet, H 1384-02-01-13 and H 1384-02-01-17; warfarin sodium capsule 2.5 mg, B02014; placebo to match ximelagatran 36 mg, H 1444-01-01-07; placebo to match warfarin 2.5 mg, A02014. Lot numbers for study drug were: AM-666, AM-667, AM-668, AM-669, AM-670, AM-748, AM-749, AM-750, and AM-751.

Duration of treatment

7 to 12 days.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary endpoint: The number of patients with verified distal and/or proximal DVT, and/or symptomatic PE with objective confirmation, and/or all-cause mortality during the treatment period according to central evaluations.
- Secondary endpoints:
  - The number of patients with proximal DVT/PE (venographic assessment of the proximal veins + symptomatic, objectively confirmed proximal DVT and/or PE during the treatment period) + all-cause mortality during the treatment period.
  - The number of patients with verified distal and/or proximal DVT, and/or symptomatic PE with objective confirmation, and/or all-cause mortality during the treatment period according to local on-site evaluations.
- Pharmacokinetic endpoints: Area under the curve (AUC), maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), and half-life ($t_{1/2}$).
- Pharmacodynamic variables: Level of APTT.

Safety

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

Statistical methods

The presence or absence of DVT, PE, and all-cause mortality was assessed locally at each investigative site and by the ICAC. The primary statistical analysis was performed using central evaluations. To address the primary objective of this study, ximelagatran 36 mg was compared to warfarin. As part of this comparison, the incidence of VTE was to be determined for each treatment group by the type of surgery performed (unilateral/bilateral). Treatment differences were tested using

the Cochran-Mantel-Haenszel (CMH) chi-square test, stratified by type of surgery (unilateral and bilateral). All objectives were assessed at a significance level of 0.05. Local and central venography assessments of total and proximal DVT were summarized and compared for consistency. A secondary analysis, in which the local venography assessments were substituted for the central venography assessments and analyzed, as described previously, was also performed. Sub-group analyses were also performed on the frequency of thromboembolic events (total VTE and proximal VTE). The main analysis of efficacy was performed on the efficacy intention-to-treat (ITT) population, ie, all randomized and treated patients with a venogram adequate for evaluation or objectively confirmed, symptomatic DVT/PE and/or all-cause mortality while on treatment.

The frequency of adjudicated bleeding events (major and/or minor) was determined for each treatment group by the type of surgery performed. Differences among treatment groups were tested using the CMH chi-square test, stratified by type of surgery (unilateral/bilateral). The overall appearance of the surgical wound and bleeding complications of the surgical wound were summarized for each treatment group by type of surgery. Fluid loss associated with surgery (including volume of blood loss, postoperative wound drainage, transfusion requirements, and bleeding index [pre- minus post-event hemoglobin in g/dL plus the number of units of red blood cells transfused]) was summarized by type of surgery. Sub-group analyses were also performed on the frequency of adjudicated bleeding events. Liver function test results (alanine aminotransferase [ALAT], aspartate aminotransferase [ASAT], alkaline phosphatase, total bilirubin) were summarized according to the proportion of patients with results greater than 2, 3, 5, and 7 times the upper limit of normal (ULN). Analyses of AEs, laboratory parameters (including hemoglobin and platelet count), and vital signs were summarized descriptively.

Descriptive statistics were provided for the pharmacokinetic variables: AUC, C_{max}, t_{max}, and $t_{1/2}$. APTT was summarized using descriptive statistics and depicted graphically. Graphic representation of the data consisted of a linear regression relationship of APTT ratios (relative to predose on Day 1) versus the plasma concentration of melagatran. The PK substudy samples from patients receiving ximelagatran 36 mg collected during EXULT A were combined with those collected in this study (EXULT B).

RESULTS:

Patient population

Of the 2813 patients who were enrolled into this study, 2303 were randomized to receive double-blind treatment with ximelagatran 36 mg (n=1152) or warfarin (n=1151) at 113 centers. Despite randomization, 4 patients were excluded from the safety analysis population because they did not receive study drug (1 ximelagatran and 3 warfarin). Of the 2299 patients included in the safety population, data from 982 and 967 patients in the ximelagatran and warfarin groups, respectively, were analyzed for efficacy in the ITT population while data from 941 and 883 patients, respectively, were included in the per protocol (PP) population. The discrepancy in the number of patients in each treatment group evaluable for the PP population was primarily due to a higher proportion of patients in the warfarin group compared with the ximelagatran group who were noncompliant (did not have minimum INR of 1.5) with study drug or who did not receive their first dose of study drug on schedule. Approximately 94% of patients in each treatment group completed the study and comparable proportions of patients in the ximelagatran (4.6%) and warfarin (4.5%) groups discontinued study drug early. The most common reason for early discontinuation of study drug in the ximelagatran and warfarin groups was AEs (29 and 34 patients, respectively).

Demographic and key baseline characteristics of patients in the ximelagatran and warfarin groups were well matched at baseline (Table S1). Approximately 95% of patients in each treatment group underwent unilateral knee surgery and most (>94%) had surgery performed for osteoarthrosis. Prostheses were cemented in place for approximately 90% of patients in either treatment group.

Table S1 Demographic and baseline characteristics (safety population)

Demographic or baseline characteristic		Ximelagatran 36 mg (n=1151)		Warfarin (n=1148)	
Gender, n (%)	Male	446	(38.7)	415	(36.1)

Demographic or		Ximelagatran 36 mg		Warfarin	
	Female	705	(61.3)	733	(63.9)
Age (years)	Mean (SD)	66.9	(9.4)	67.1	(9.4)
	Range	26.0 to 91.0		32.0 to 89.0	
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)
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)

SD standard deviation.

Efficacy and pharmacokinetic results

Ximelagatran 36 mg was both clinically effective and superior to warfarin ($p<0.001$) in reducing total VTE and/or all-cause mortality among patients with TKR according to blinded ICAC assessment (Table S2). This analysis included patients with total DVT (proximal or distal) at the time of mandatory venography or symptomatic VTE and/or all-cause mortality that occurred within 2 days following mandatory venography or up to Day 12, if no mandatory venography was done.

According to blinded ICAC assessment, the absolute reduction in the frequency of total VTE and/or all-cause mortality in patients randomized to ximelagatran 36 mg was 9.3% in relation to patients randomized to warfarin (31.9% warfarin vs 22.5% ximelagatran 36 mg), providing a relative risk reduction of 29.3% (95% CI: 18.1 to 39.1) and a number needed to treat to obtain benefit (1/absolute risk reduction) of 11 (95% CI: 8 to 19). The incidence of proximal DVT, PE, and/or all-cause mortality was low in both treatment groups, 3.9% for ximelagatran and 4.1% for warfarin, and there was no statistically significant difference between treatment groups (p=0.802).

Table S2 Summary of efficacy analyses (efficacy ITT population)

Analysis					Ximelagatran vs Warfarin		
				Exact			CMH
	Treatment Group	%	(n/N)	95% CI	%	95% CI	p-value[a]
Frequency of total venous thromboembolism[b] and/or all-cause mortality – blinded ICAC assessment							
	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)			
Frequency of proximal deep vein thrombosis, pulmonary embolism, and/or all-cause mortality – blinded ICAC assessment							
	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)			
Frequency of total venous thromboembolism[b] and/or all-cause mortality – local assessments[c]							
	Ximelagatran 36 mg	30.1	(300/996)	(27.3, 33.1)	-5.7	(-9.8, -1.6)	0.007
	Warfarin	35.8	(363/1014)	(32.8, 38.8)			

[a] Treatment differences were tested using the Cochran-Mantel-Haenszel (CMH) chi-square test, adjusted for the type of surgery performed (unilateral/bilateral).
[b] Total venous thromboembolism includes distal DVT, proximal DVT, and PE.
[c] This analysis was performed on patients in the safety population according to local assessments.

CI confidence interval; DVT deep vein thrombosis; ITT intention-to-treat; PE pulmonary embolism.

The reduction in total VTE and/or all-cause mortality observed for the efficacy ITT population was confirmed by analyses of data from patients in the per protocol population ($p<0.001$) and using local assessments ($p=0.007$). A sensitivity analysis which excluded patients who did not have bilateral venograms adequate for evaluation performed also confirmed the results of the primary population, with a statistically significant reduction in total VTE and/or all-cause mortality in the ximelagatran group relative to the warfarin group ($p<0.001$).
In the treatment group randomized to ximelagatran, 221 patients had an endpoint event of total VTE or death of any cause detected during the efficacy treatment period, stipulated as the period either within 2 days following mandatory venography, or up to Day 12 if no mandatory venography was done. Of these 221 patients, 4 died. Of the 217 ximelagatran-treated patients with total VTE, 2 experienced a clinical (centrally adjudicated) non-fatal PE, 30 had an asymptomatic proximal DVT, 184 had an asymptomatic distal DVT, and 1 experienced an isolated, symptomatic proximal DVT. This latter event was detected via compression ultrasound (Post-op day 9). The mandatory venography, performed the same day and as part of the End of Treatment Period Study Visit (Post-op day 9), was normal by central adjudication.

Similarly, of the 308 warfarin-treated patients with total VTE and/or all-cause mortality during this same time period, 2 died. Of the remaining 306 patients with total VTE, 5 experienced a centrally adjudicated clinical non-fatal PE, 33 had an asymptomatic proximal DVT, and 268 had an asymptomatic distal DVT.

In the efficacy ITT population, 44 patients experienced a total of 45 symptomatic thromboembolic events (objectively confirmed clinical DVTs, PEs, death) over the entire study period. These included 20 (1.8%) patients in the ximelagatran group and 24 (2.0%) patients in the warfarin group. One patient in the ximelagatran group experienced both a symptomatic PE and a symptomatic proximal DVT. The majority of asymptomatic DVTs in both treatment groups occurred ipsilaterally and distal DVTs occurred more frequently than proximal DVTs.

Subgroup analyses based on prespecified demographic and other characteristics were generally consistent with the overall pattern of results seen for the total population in showing ximelagatran 36 mg was clinically effective and superior to warfarin in reducing total VTE and/or all-cause mortality. No statistically significant interactions were found between treatment and any of the subgroup factors ($p \geq 0.304$).

A delay in peak plasma melagatran concentrations of approximately 2.5 hours on postoperative Day 1 relative to steady state was observed in the PK substudy. This post-surgical delay in absorption resulted in a mean systemic exposure to melagatran that was approximately 50% of the level at steady state. The absorption of melagatran, however, was essentially complete after the first dose of ximelagatran post-surgery as the melagatran $AUC0_{0-\infty}$ on postoperative Day 1 was similar to the melagatran AUC_{0-12} at steady state. The APTT was prolonged at 2 hours following the first dose of oral ximelagatran post-surgery and melagatran induced a concentration-dependent prolongation of the APTT on both postoperative Day 1 and at steady state.

Safety results

Overall, oral administration of ximelagatran 36 mg bid for up to 12 days was well tolerated among patients undergoing unilateral or bilateral TKR. The incidence of AEs in the ximelagatran group was comparable to those observed in the warfarin group (Table S3). Approximately 61% of patients in both treatment groups experienced at least 1 AE and fewer than 15% of patients in either treatment group had a drug-related AE. The most common AE was postoperative complications (preferred term coding for events such as anemia, pain, wound infection, and bleeding), reported by similar proportions of

patients in the 2 treatment groups (Table S4). Postoperative anemia was reported by approximately 5.5% of patients in both treatment groups. The most frequently reported drug-related AEs in the ximelagatran and warfarin groups were increased serum levels of gamma glutamyl transaminase (GGT; 4.8% and 3.6% for ximelagatran and warfarin, respectively), postoperative complications (3.7% and 2.9%, respectively), increased SGPT (2.6% and 2.3%, respectively), and increased alkaline phosphatase (2.6% and 2.5%, respectively).

Table S3 Summary of adverse events (safety population)

	Ximelagatran 36 mg (n=1151)		Warfarin (n=1148)	
Category	**n**	**(%)**	**n**	**(%)**
At least 1 adverse event	699	(60.7)	707	(61.6)
Bleeding-related adverse event	102	(8.9)	94	(8.2)
Non-bleeding related adverse event	670	(58.2)	673	(58.6)
Drug-related adverse event	156	(13.6)	169	(14.7)
Serious adverse event[a]	79	(6.9)	79	(6.9)
Discontinued due to adverse event[b]	28	(2.4)	34	(3.0)
Death	7	(0.6)	3	(0.3)

[a] One additional patient in the ximelagatran group (237/12706) and 2 additional patients in the warfarin group (201/12340 and 201/12350) had serious adverse events that resolved prior to the first dose of study drug. In addition, 1 warfarin patient (201/12136) who did not receive study drug experienced a serious adverse event.

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

AE adverse event.

Table S4 Number (%) of patients with adverse events occurring with a minimum incidence of 5% in either treatment group (safety population)

	Ximelagatran 36 mg (n=1151)		Warfarin (n=1148)	
Adverse event Preferred term	**n**	**(%)**	**n**	**(%)**
At least 1 adverse event	699	(60.7)	707	(61.6)
Postoperative complications	214	(18.6)	195	(17.0)
Fever	92	(8.0)	88	(7.7)
Nausea	69	(6.0)	60	(5.2)
GGT increased	71	(6.2)	57	(5.0)

GGT gamma glutamyl transferase.

Fewer than 10% of the patients in either treatment group had AEs that were considered bleeding-related, the most common of which was postoperative complications (5.5% and 4.1% of patients in the

ximelagatran and warfarin groups, respectively). Few of the bleeding-related AEs were adjudicated by the ICAC as major bleeding events in either treatment group. Although the incidence of major bleeding events was numerically higher in the ximelagatran group (1.0%) compared with the warfarin group (0.4%), this difference was not statistically significant (p=0.087) (Table S5). One additional patient in each treatment group had an adjudicated major bleeding event during the follow-up period. There were no statistically significant differences between the ximelagatran and warfarin groups in the frequency of minor or combined major or minor bleeding events during treatment ($p \geq 0.158$) or in the frequency of major, minor, or combined bleeding events during the entire study (treatment and follow-up) ($p \geq 0.105$).

Subgroup analyses performed on the frequency of adjudicated bleeding events based on prespecified demographic and other characteristics were consistent with that of the overall population. The interaction of each subgroup factor with treatment showed a significant interaction of treatment with age and body mass index ($p \leq 0.048$). In the warfarin group, the rate of on-treatment adjudicated bleeding events was highest in patients ≥ 75 years of age and those with a body mass index of ≤ 30 kg/m2. In the ximelagatran group, rates were similar across all 3 age and body mass index subgroup categories.

Table S5 Frequency of centrally adjudicated on-treatment bleeding events by event type (safety population)

				Ximelagatran vs warfarin		
Event type			**Exact**			**CMH**
Treatment group	**%**	**(n/N)**	**95% CI**	**%**	**95% CI**	**p-value[a]**
Major bleeding events						
Ximelagatran 36 mg	1.0	(12/1151)	(0.5, 1.8)	0.6	(-0.1, 1.3)	0.087
Warfarin	0.4	(5/1148)	(0.1, 1.0)			
Minor bleeding events						
Ximelagatran 36 mg	4.2	(48/1151)	(3.1, 5.5)	0.8	(-0.8, 2.3)	0.327
Warfarin	3.4	(39/1148)	(2.4, 4.6)			
Major/minor bleeding events						
Ximelagatran 36 mg	5.0	(58/1151)	(3.8, 6.5)	1.2	(-0.5, 2.9)	0.158
Warfarin	3.8	(44/1148)	(2.8, 5.1)			

[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.

No statistically significant differences were detected between the ximelagatran and warfarin groups in the volumes of postoperative fluid loss or the need for fluid replacement, overall wound appearance, or individual wound characteristics ($p \geq 0.227$). With the exception of a significantly higher incidence of unusual bruising or hematoma on postoperative Day 3 in the ximelagatran group compared with the

warfarin group (p=0.015), there were no significant differences between treatment groups at any other time point in the incidence of any other wound assessments ($p \geq 0.245$).

During the treatment and follow-up periods, 10 patients who underwent surgery and were randomly allocated to study drug died; 7 of these patients had received ximelagatran and 3 had received warfarin. Of the 7 deaths in the ximelagatran group, 4 occurred during treatment and 3 occurring during the follow-up period. Only 1 of the deaths in the ximelagatran group and none in the warfarin group was considered related to study drug by the investigator (gastrointestinal [GI] hemorrhage). Of the 7 patients in the ximelagatran group who died, 1 was the result of a centrally adjudicated major bleeding event (GI hemorrhage) and for 3 additional patients, the ICAC could not exclude PE as the cause of death (verbatim term: myocardial infarction [MI], n=2; death due to an unknown cause). None of the deaths in the warfarin group were attributed by the ICAC to a PE or bleeding event. Deaths occurring during treatment with ximelagatran included ventricular fibrillation and cardiomyopathy, GI hemorrhage, sudden death, and MI, while those occurring during the follow-up period included MI, pneumonia, and death from an unknown cause. Of the 3 deaths in the warfarin group, 2 occurred during treatment (cardiac arrest in combination with AV block, MI) and 1 occurred during the follow-up period (MI).

Similar proportions of patients in the ximelagatran and warfarin groups (6.9%) experienced an SAE, few of which were considered related to study drug by the investigator (1.1% and 1.6%, respectively). The most common SAE in both treatment groups was postoperative complications, occurring in 2.1% of ximelagatran patients and 1.4% of warfarin patients. Few of the serious postoperative complications were considered related to study drug (5 of 24 in the ximelagatran group; 4 of 16 in the warfarin group). Four (0.3%) patients in the ximelagatran group and 3 (0.3%) in the warfarin group experienced a serious GI hemorrhage, all but 1 (in the ximelagatran group) of which was considered related to study drug by the investigator.

Adverse events led to discontinuation of study drug in 2.4% of patients in the ximelagatran group and 3.0% of patients in the warfarin group. No individual AE resulted in the premature discontinuation of study drug in more than 1.0% of patients in either treatment group. The most common treatment-limiting AE in both treatment groups were postoperative complications (preferred term coding for events such as anemia, pain, wound infection, and bleeding) and occurred in 5 (0.4%) ximelagatran patients and 8 (0.7%) warfarin patients. Five patients in the ximelagatran group discontinued study drug prematurely due to a major bleeding event (intracranial hemorrhage [verbatim term, exacerbation of a chronic intracranial subdural hematoma], GI hemorrhage [2 patients], melena, hemorrhoids). Centrally adjudicated major bleeding events prompted discontinuation of study drug in 2 patients in the warfarin group (hemarthrosis, postoperative complications).

Changes from baseline in clinical chemistry parameters, including elevations in LFTs and reductions in hematology parameters, reflected surgical intervention and recovery and were generally comparable in the 2 treatment groups. These changes generally occurred during the immediate postoperative course of treatment and at the time of the End of Treatment Period Study Visit with a return to near baseline levels at follow-up. Postoperative anemia and increased levels of GGT were the most common laboratory abnormalities reported as AEs, and occurred in 5.5% and 6.2% of patients in the ximelagatran group, respectively, and 5.4% and 5.0% of patients in the warfarin group, respectively.

There were no appreciable differences between treatment groups in mean baseline or mean changes from baseline values for any vital sign parameter, nor were there any appreciable differences in the proportion of patients with vital sign measurements outside the extended reference limits.

Reference:

1. Colwell CW, Berkowitz SD, Comp PC, Lieberman JR, Ginsberg JS, Paiement G, McElhattan JL, Roth AW, Francis CW. Randomized, double-blind comparison of ximelagatran, an oral direct thrombin inhibitor, and warfarin to prevent venous thromboembolism (VTE) after total knee replacement (TKR): EXULT B. Blood 2003;102(11 Pt 1 Part 1):14A, Abs 39.

2. Colwell CW, Berkowitz SD, Comp PC, Lieberman JR, Ginsberg JS, Paiement G, McElhattan JL, Roth AW, Francis CW. Oral Direct Thrombin Inhibitor Ximelagatran Compared with Warfarin for Prevention of Venous Thromboembolism after Total Knee Replacement. J Bone Joint Surg Am 2005. In press.

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Exanta™ (ximelagatran), Healthcare Professionals should view their specific country information