AstraZeneca

SH-TPO-0010

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 refinement of dose (EXULT 290A). The confirmation of safety and efficacy (EXULT 290B) methods and results are described in a separate Clinical Study Report

Developmental phase: Therapeutic confirmatory (III)
First subject recruited: 22 May 2001
Last subject completed: 25 April 2002
Approval date: 18 April 2003

OBJECTIVES

The purpose of this study was to determine the better of the two doses of ximelagatran for the prevention of venous thromboembolism (VTE) using two different doses (24 mg and 36 mg) in patients undergoing primary elective total knee replacement (TKR). Each dose was given twice daily by oral administration, starting as early as possible on the morning after surgery. The primary analysis was to focus first on showing that 36 mg ximelagatran had superior efficacy compared with warfarin followed by an analysis of the 24 mg ximelagatran dose on the primary composite endpoint of proximal and distal deep vein thrombosis (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; for the primary composite endpoint according to on-site evaluations; and for the incidence of major and total bleeding during the study drug treatment period.

METHODS:

Study design

This study 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 3 treatment groups: ximelagatran 24 mg **or** ximelagatran 36 mg (both initiated as early as possible on the morning after surgery) **or** warfarin initiated the evening of surgery. The goal was to determine the better of the two doses of ximelagatran when compared with warfarin for the prevention of VTE. Bilateral venography performed at the End of Treatment Period study visit was used to determine total DVT. Objectively confirmed symptomatic VTE events, bilateral venography, bleeding events and deaths were evaluated by an Independent Central Adjudication Committee (ICAC).

Target patient population and sample size

Adult male or female patients whose body weight was between 88 and 300 lbs, 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 30% incidence of VTE in patients treated with warfarin, a total of 1700 evaluable patients undergoing TKR, derived from 2250 randomized patients, provided more than 90% power to detect a 33% 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), 24 or 36 mg orally (po) twice daily (bid), and the comparator was warfarin sodium (COUMADIN®, Bristol-Myers Squibb) po given once a day 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 the matching placebo dummy) was started the morning after surgery (minimum of 12 hours postsurgery). Batch numbers were: ximelagatran 24 mg tablet H 1360-03-01-10; ximelagatran 36 mg tablet H 1384-02-01-08 and H 1384-02-01-09; warfarin sodium capsule 2.5 mg 00J139; placebo to match ximelagatran 24 mg H 1431-01-01-05 and to match ximelagatran 36 mg H 1444-01-01-05; placebo to match warfarin 00A017 and 00A018. Lot numbers for study drug were: AM-491, AM-556 and AM-557.

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

During this study, trough plasma samples of melagatran were collected at postoperative Day 3 and the End of Treatment Period study visit and related to key efficacy (total VTE and/or all-cause mortality) and safety (major/minor bleeding) parameters. Methodology and results for the trough melagatran samples are detailed in this clinical study report.

The pharmacokinetic substudy samples collected during this study will be combined with the pharmacokinetic substudy samples collected in 290B. The combined results will be analyzed and reported in the EXULT 290B clinical study report. No further reference will be made to the PK substudy in this report.

Safety

Safety assessments included bleeding complications occurring after TKR; surgical site evaluations; adverse event 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 Independent Central Adjudication Committee. 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). If this comparison was statistically significant ($p<0.05$), then ximelagatran 24 mg was to be compared to warfarin, also at a significance level of 0.05. If the comparison of ximelagatran 36 mg vs. warfarin was not statistically significant ($p>0.05$), then no further statistical testing was to be performed. All secondary 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. The main analysis of efficacy was performed on the efficacy intention-

to-treat (ITT) population, ie, all randomized and treated patients with an evaluable venogram or objectively confirmed, symptomatic DVT/PE or death while on treatment.

The frequency of 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 and bilateral). The overall appearance of the surgical wound and bleeding complications of the surgical wound were summarized by type of surgery. INR values recorded at postoperative Day 3 and the End of Treatment Period study visit were summarized descriptively for warfarin patients, with and without confirmed bleeding events. 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. Surgical site evaluation was performed on postoperative Day 3, at the End of Treatment Period Study visit (ie, on the day of venography) and at the 4-week follow-up visit. Liver function test results were summarized according to the proportion of patients with results greater than 2, 3, 5, and 7 times the upper limit of normal. Analyses of adverse events, laboratory parameters (including hemoglobin and platelet count), and vital signs were summarized descriptively.

RESULTS:

Patient population

Of 2656 patients enrolled in 116 centers, 2301 were randomized to treatment at 114 centers. The first patient entered the study on 22 May 2001 and the last patient completed the study on 25 April 2002. Randomization occurred following the patient's elective surgery. Sixteen randomized patients were excluded from the safety analysis population because they did not receive study drug. Of 2285 patients in the safety population, data from 1851 patients were analyzed for efficacy in the ITT population and data from 1754 patients were analyzed for efficacy in the per-protocol population. There were no appreciable differences among treatment groups in the proportion of patients in the per-protocol population. Approximately 92% of patients completed the study from each treatment group. 3.0% of patients withdrew because of adverse events in each ximelagatran treatment group and 1.7% withdrew in the warfarin treatment group.

Demographic and key baseline characteristics of study patients were well matched among treatment groups. Slightly more than 60% of patients were female in each treatment group, 96% of all patients were Caucasian in each treatment group, and most patients were enrolled at centers in the United States or Canada. The mean age of patients in each treatment group was approximately 68. Approximately 95% of patients in each treatment group underwent TKR because of osteoarthrosis; from 3% to approximately 4% underwent TKR because of rheumatoid arthritis. More than 95% of patients in each treatment group underwent unilateral knee surgery. Prostheses were cemented in place in approximately 90% of the patients in each treatment group.

Table S1 Demographic and baseline characteristics (safety population)

Demographic or baseline characteristic		**Ximelag 24 mg** N=757		**Ximelag 36 mg** N=769		**Warfarin** N=759	
Demographic characteristics							
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 (years)	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)

Efficacy results

Ximelagatran 36 mg was both clinically effective and superior compared to warfarin (p=0.003) in reducing total VTE and/or all-cause mortality among patients with TKR, according to blinded ICAC assessment. The absolute reduction in the frequency of total VTE and/or all-cause mortality in patients randomized to ximelagatran 36 mg was 7.3% relative to patients randomized to warfarin (p=0.003). The corresponding absolute reduction for patients in the ximelagatran 24 mg treatment group was 2.7% (p=0.282). The frequency of total VTE and/or all-cause mortality among patients was 24.9% for patients randomized to ximelagatran 24 mg, 20.3% for patients randomized to ximelagatran 36 mg, and 27.6% for patients randomized to warfarin.

Table S2 Summary of efficacy analyses (efficacy intention-to-treat population)

Analysis					**Ximelag vs Warfarin**	
Treatment Group	**%**	**(n/N)**	**Exact 95% CI**	**%**	**95% CI**	**CMH p-value[a]**
Frequency of total venous thromboembolism[b] and/or all-cause mortality – ICAC assessment						
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)			
Frequency of proximal deep vein thrombosis, pulmonary embolism, and/or all-cause mortality						
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)			
Frequency of total venous thromboembolism[b] and/or all-cause mortality – local assessments						
Ximelag 24 mg	33.4	(211/631)	(29.8, 37.3)	–4.3	(–9.6, 1.0)	0.108
Ximelag 36 mg	29.6	(188/636)	(26.0, 33.3)	–8.2	(–13.3, –3.0)	0.002
Warfarin	37.7	(240/636)	(34.0, 41.6)			

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

[b] Total venous thromboembolism includes pulmonary embolism.

CI Confidence interval.

Ximelagatran 36 mg was clinically more effective with a statistically significant improvement compared to warfarin (p=0.002) in reducing total VTE and/or all-cause mortality according to local assessments. The absolute reduction in the frequency of total VTE and/or all-cause mortality in patients randomized to ximelagatran 36 mg was 8.2% relative to patients randomized to warfarin (p=0.002) according to local assessments. The corresponding absolute reduction for patients in the ximelagatran 24 mg treatment group was 4.3% (p=0.108) according to local assessments. The locally assessed frequency of total VTE and/or all-cause mortality was 33.4% for patients randomized to ximelagatran 24 mg,

29.6% for patients randomized to ximelagatran 36 mg, and 37.7% for patients randomized to warfarin. Results obtained from data in the efficacy ITT population were confirmed by analyses of data from patients in the per-protocol population.

There were 34 symptomatic thromboembolic events over the entire study period, 10 (1.6%) in the ximelagatran 24 mg treatment group, 13 (2.1%) in the ximelagatran 36 mg treatment group, and 11 (1.8%) in the warfarin treatment group. There were 28 symptomatic thromboembolic events during the on-treatment period, 8 (1.3%) in the ximelagatran 24 mg treatment group, 10 (1.6%) in the ximelagatran 36 mg treatment group, and 10 (1.6%) in the warfarin treatment group. There were no appreciable differences among treatment groups in the incidences of clinical DVT, clinical PE, death, or any clinical event.

Asymptomatic DVTs occurred more frequently distally than proximally. Asymptomatic distal DVTs occurred most commonly ipsilaterally.

Subgroup analyses performed on the frequency of total VTE and/or all-cause mortality based on prespecified demographic and other characteristics were comparable to those for the total population and no statistically significant interactions were found between treatment and any of the subgroup factors ($p \geq 0.1$). At the time of venography, 58.3% of patients in the warfarin treatment group were within the therapeutic INR range of 1.8 to 3.0, 76.2% of patients had an INR 1.8 or higher and 23.8% of patients were subtherapeutic (INR <1.8). There was no appreciable difference in mean INR between patients on warfarin with confirmed VTE and with no confirmed VTE at the postoperative Day 3 and End of Treatment Period study visits, although the patients with confirmed events had a mean INR slightly below that for patients with unconfirmed events (2.30 and 2.36, respectively for patients at postoperative Day 3; 2.31 and 2.43, respectively for patient at the End of Treatment Period study visit). The frequencies of patients with and without confirmed VTE were not appreciably different to the corresponding distribution of patients below, within, and above the therapeutic range of INR.

Among patients treated with ximelagatran who had plasma melagatran levels available on postoperative Day 3 and/or at venography, there was a lack of consistent relationship between concentration of melagatran and incidence of thrombotic event (VTE and/or all-cause mortality). Melagatran levels were similar in patients with and without confirmed VTE and/or all-cause mortality. There was considerable overlap in melagatran plasma concentrations in all groups. The data suggest no obvious correlation between plasma concentration of melagatran, as measured in this study, and thrombotic event (VTE and/or all-cause mortality).

Safety results

Overall, oral administration of ximelagatran 24 mg and 36 mg twice daily (mean number of days on treatment was approximately 8 days) was well tolerated. The incidences of adverse events in each ximelagatran treatment group were similar to those seen in the warfarin treatment group (Table S3). More than 60% of patients in each treatment group experienced at least 1 adverse event. The incidence of discontinuations attributed to adverse events was slightly higher in the ximelagatran treatment groups than in the warfarin group. The most common adverse event was postoperative complications (preferred term coding for events such as anemia; pain; wound infection; bleeding and delayed wound healing) as experienced by 20.4% of all patients; the incidence of postoperative anemia was 9.0%. The other common adverse events experienced by at least 5% of all patients were fever (7.0%), nausea (6.9%), increased serum levels of gamma glutamyl transferase (6.4%) and constipation (5.0%) (Table S4). The common adverse events attributed to study drug by the investigator that were experienced by at least 1% of patients were increased serum levels of gamma glutamyl transferase (4.3%), postoperative complications (3.1%), alkaline phosphatase (2.8%), alanine aminotransferase (2.6%) and aspartate aminotransferase (1.7%).

Table S3 Summary of treatment-emergent adverse events (safety population)

Category	Ximelag 24 mg N=757		Ximelag 36 mg N=769		Warfarin N=759	
	n	(%)	n	(%)	n	(%)
At least 1 adverse event	482	(63.7)	493	(64.1)	469	(61.8)

Drug-related adverse event	83	(11.0)	98	(12.7)	85	(11.2)
Serious adverse event	45	(5.9)	44	(5.7)	33	(4.3)
Discontinued due to adverse event	23	(3.0)	23	(3.0)	13	(1.7)
Death	2	(0.3)	4	(0.5)	2	(0.3)

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

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

Approximately 5% of patients in each treatment group had major (approximately 1%) or minor (approximately 4%) bleeding events, as determined by ICAC adjudication, while receiving study medication (Table S5). Approximately 5 to 6% of patients in each treatment group had major or minor bleeding events during the entire study (period from the last administration of study medication until the follow-up visit); thus, most bleeding events occurred while the patients were receiving study medication. There were no statistically significant differences between the ximelagatran and warfarin treatment groups in the frequency of major, minor, or combined major or minor bleeding events while receiving study medication (p 0.461). Similarly, there were no statistically significant differences between ximelagatran 24 mg and 36 mg in the frequencies of these bleeding events while receiving study medication (p 0.490). The most common treatment-emergent bleeding complication, as reported by the investigators was coded under postoperative complications (5.1%).

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

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

Warfarin	4.5	(34/759)	(3.1, 6.2)			

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

Among patients treated with ximelagatran who had plasma melagatran levels available on postoperative Day 3 and/or at venography, there was a lack of consistent relationship between concentration of melagatran and incidence of bleeding event. Melagatran levels were similar in patients with and without confirmed bleeding events. There was considerable overlap in melagatran plasma concentrations in all groups. The data suggest no obvious correlation between plasma concentration of melagatran, as measured in this study, and bleeding event.

Eight patients who underwent surgery and were randomized to study drug died; 6 patients received ximelagatran and 2 patients received warfarin. No patient death was considered by an investigator to be related to ximelagatran. One patient death was considered by an investigator to be related to warfarin. Deaths in the warfarin treatment group were attributed to myocardial infarction (in-hospital on postoperative Day 2) and cardiac arrest (in-hospital, adjudicated by the ICAC as cannot rule out PE). Deaths in the ximelagatran treatment groups were attributed to: PE (2 patients treated with ximelagatran 36 mg, one patient 4 days from the last dose of ximelagatran and the other patient 12 days from the last dose of ximelagatran); myocardial infarct (1 patient treated with ximelagatran 36 mg, the AE onset was 1 day from the start of treatment and the death occurred 7 days from the start of treatment); hypotension, gastrointestinal bleeding, and multiorgan failure (1 patient treated with ximelagatran 36 mg, the AE onset was 1 day from the start of treatment and the death occurred 46 days from the start of treatment); perforated bowel (1 patient treated with ximelagatran 24 mg, the AE onset was 7 days from the start of treatment and the death occurred 9 days from the start of treatment) and unknown causes (1 patient treated with ximelagatran 24 mg, 23 days from the last dose of ximelagatran).

Postoperative complications (5 patients [0.3%] in the ximelagatran group and 2 patients [0.3%] in the warfarin group) and myocardial infarction (5 patients [0.3%] in the ximelagatran group and 1 patient [0.1%] in the warfarin group) were the adverse events that most frequently led to study drug discontinuation. Other common adverse events that led to discontinuation of study drug were atrial fibrillation, nausea, gastrointestinal hemorrhage, and vomiting.

The most common serious adverse events were postoperative complications (eg, anemia; pain; wound infection; bleeding and delayed wound healing - as defined using preferred terms in the Astra Adverse Event Dictionary) (18 patients [0.8%]) and myocardial infarction (13 patients [0.6%]). Five patients experienced serious gastrointestinal hemorrhage; all were randomized to ximelagatran (4 [0.5%] to the 24 mg dose and 1 [0.1%] to the 36 mg dose).

Changes from baseline in clinical chemistry parameters, including liver function tests, hematology parameters, and vital signs reflected surgical intervention and recovery, and were generally larger at the time of venography than at the follow-up visit, returning to near baseline levels at follow-up. There were few appreciable differences in mean changes from baseline in clinical chemistry parameters or vital signs among treatment groups.

Reference:

Francis CW, Berkowitz SD, Comp PC, Lieberman JR, Ginsberg JS, Paiement G, Peters GR, Roth AW, McElhattan J, Colwell CW Jr. Comparison of ximelagatran with warfarin for the prevention of venous thromboembolism after total knee replacement. New England Journal of Medicine 2003;349(18):1703-12.

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