AstraZeneca

# SH-TPO-0005

## SUMMARY

## ASTRAZENECA PHARMACEUTICALS

**FINISHED PRODUCT:** Exanta™

**ACTIVE INGREDIENT:** Ximelagatran (H 376/95)

**Trial title (number):** A randomized, double-blind, comparative study of ximelagatran (H 376/95) and enoxaparin for the prevention of venous thromboembolism following total hip arthroplasty. (PLATINUM Hip)

**Developmental phase:** III
**First subject recruited:** 03 March 2000
**Last subject completed:**18 April 2001
**Approval date:** 31 January 2002

## OBJECTIVES

The primary objective of this study was to establish the non-inferior efficacy of ximelagatran compared to enoxaparin for prevention of venous thromboembolic events (VTE) in patients following total hip arthroplasty (THA). Secondary objectives were to compare the incidence of proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE) during the treatment period as well as the incidence of bleeding events between the 2 treatments.

## METHODS

### Study design

This was a multicenter, randomized, double-blind, double-dummy, parallel group, active comparator study to establish the non-inferior efficacy of ximelagatran compared with enoxaparin for the prevention of VTE in patients undergoing THA. Unilateral venography was used to detect asymptomatic DVT.

### Target patient population and sample size

Adult male or female patients whose body weight was between 88 and 275 lbs, inclusive, and who were scheduled for primary unilateral THA. 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. A total of 1280 evaluable patients undergoing THA, derived from 1600 randomized patients, were required for 90% power to demonstrate non-inferiority using a 5% margin with a one-sided 97.5% confidence interval (CI).

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

Ximelagatran (H 376/95), 24 mg orally (po) twice daily (bid), or enoxaparin (LOVENOX®, Aventis); 30 mg subcutaneously (sc) bid. Doses were given in double-dummy fashion due to the difference in route of administration. Both treatments were started the morning after surgery (minimum of 12 hours postsurgery). Batch (lot) numbers were: ximelagatran (given as one 24-mg tablet), 1360-03-01-02 and 1360-03-01-03; enoxaparin (given as a pre-filled syringe), 30059, 30158, and 30239; placebo to match ximelagatran, 1431-01-01-01 and 1431-01-01-03; placebo to match enoxaparin, 1363-01-05-01 and 1363-01-05-02.

**Duration of treatment**

7 to 12 days

**Criteria for evaluation (main variables)**

**Efficacy and pharmacokinetics**

**Primary variable:** Incidence of VTE (ie, DVT in the distal or proximal veins or PE)

**Secondary variables:** Incidence of proximal DVT/PE; average plasma concentrations of melagatran at trough.

**Safety**

Safety assessments included bleeding complications occurring following THA (both during treatment and throughout the study); surgical site evaluations; adverse event reports; clinical laboratory data (hematology, clinical chemistry, and urinalysis), vital signs, and electrocardiograms (ECG).

**Statistical methods**

The presence or absence of DVT and PE were assessed locally at each investigative site and by the Central Adjudication Committee blinded to treatment group, local assessment, and other test/clinical findings. The primary statistical analysis was performed using the central evaluations. The primary efficacy variable, the frequency of VTE, was estimated using the observed proportions (with 95% CI) for each treatment group. The difference in the proportion of patients with verified VTE (ximelagatran – enoxaparin) was assessed using a one-sided 97.5% CI, based on normal approximation. Secondary efficacy analyses of proximal DVT and PE were performed similarly. Prespecified subgroup analyses were performed on the frequency of VTE. Sensitivity analyses of overall VTE and proximal DVT/PE were performed by substituting local assessments for central assessments. 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 of the operated leg or objectively-confirmed, symptomatic DVT/PE while on treatment.

The frequency of bleeding events (major and/or minor) was estimated using the observed proportions (with 95% CI) for each treatment group. Differences between treatment groups were examined using Fisher's Exact Test. The overall appearance of the surgical wound and bleeding complications of the surgical wound were summarized for each treatment group and between-group differences tested using Fisher's Exact Test. Characteristics of the wound appearance were summarized by percentage of patients for whom the particular characteristic was "worse than expected". Fluid loss associated with surgery was summarized descriptively by treatment group, while the volume of blood loss, postoperative wound drainage, transfusion requirements, and bleeding index were estimated using the observed mean levels (with 95% CI) for each treatment group. Between-group differences were tested using an analysis of variance. Subgroup analyses were performed on the frequency of bleeding events. Analyses of adverse events, laboratory parameters (including hemoglobin, hematocrit, and platelet count), vital signs, and ECG measurements were summarized descriptively. Trough plasma melagatran concentrations obtained on Day 3 were summarized descriptively. The incidence rates of VTE and bleeding events were also described as a function of plasma concentrations for the ximelagatran group.

**RESULTS**

**Patient population**

Of the 2075 patients who were enrolled in this study, 1838 were eligible for entry and were randomly assigned to receive treatment with ximelagatran 24 mg po bid (n=918) or enoxaparin 30 mg sc bid (n=920). Despite randomization to a treatment group, 22 patients did not receive at least 1 dose of study medication (12 ximelagatran; 10 enoxaparin) and were excluded from all analysis populations. Of the 1816 randomized patients who received at least 1 dose of study medication (safety population), 259 did not have an evaluable venogram or objectively-confirmed

symptomatic DVT/PE and were excluded from the efficacy ITT population. An additional 74 patients had prespecified protocol deviations and were further excluded from the per protocol (PP) population. Thus, the numbers of patients included in the safety, efficacy ITT, and PP populations was 906, 782, and 747 in the ximelagatran group, respectively, and 910, 775, and 736 in the enoxaparin group, respectively. Among all randomized patients, the proportion of patients who discontinued treatment prematurely was comparable in the ximelagatran and enoxaparin groups (6.9% vs. 7.2%) and the most common reasons for discontinuation in these 2 groups were adverse events (2.8% vs. 2.3%), consent withdrawn (2.1% for each), and other reasons (1.9% vs. 2.5%). Table S1 presents an overview of the disposition of all randomized patients and the demographic and baseline characteristics of patients included in the safety population. The population was generally evenly distributed between males and females and had a mean age of 64.3 years. Among patients included in the efficacy ITT population, the most common reason for THA in both the ximelagatran and enoxaparin groups was osteoarthrosis (89.4% and 87.1%, respectively). The length of surgery averaged approximately 100 minutes in both groups and 99% of surgeries were performed using either an antero-lateral approach (58.6%) or a posterior approach (40.7%). Approximately two-thirds of the patients in both groups had general anesthesia and approximately 50% of patients in both groups had a non-cemented prosthesis. The time to first dose of study medication was comparable in both the ximelagatran (20.5 hours) and enoxaparin (20.2 hours) groups.

**Table S1 Patient population and disposition**

| | | Ximelagatran | | Enoxaparin | | Total | |
|---|---|---|---|---|---|---|---|
| **Population** | | | | | | | |
| N randomized (N planned) | | 918 | (800) | 920 | (800) | 1838 | (1600) |
| **Disposition (all randomized patients)** | | | | | | | |
| N (%) of patients who | completed | 855 | (93.1%) | 854 | (92.8%) | 1709 | (93.0%) |
| | discontinued[a] | 63 | (6.9%) | 66 | (7.2%) | 129 | (7.0%) |
| N analyzed for safety [b] | | | 906 | | 910 | | 1816 |
| N analyzed for efficacy (ITT) | | | 782 | | 775 | | 1557 |
| N analyzed for efficacy (PP) | | | 747 | | 736 | | 1483 |
| **Demographic characteristics (safety population)** | | | | | | | |
| Sex (n and % of patients) | Male | 414 | (45.7%) | 439 | (48.2%) | 853 | (47.0%) |
| | Female | 492 | (54.3%) | 471 | (51.8%) | 963 | (53.0%) |
| Age (years) | Mean (SD) | 64.6 | (12.9) | 64.1 | (13.1) | 64.3 | (13) |
| | Range | | 20-93 | | 27-92 | | 20-93 |
| Race (n and % of patients) | Caucasian | 852 | (94.0%) | 859 | (94.4%) | 1711 | (94.2%) |
| | Black | 45 | (5.0%) | 46 | (5.1%) | 91 | (5.0%) |
| | Oriental | 5 | (0.6%) | 1 | (0.1%) | 6 | (0.3%) |
| | Other | 4 | (0.4%) | 4 | (0.4%) | 8 | (0.4%) |
| Country | United States | 537 | (59.3%) | 551 | (60.5%) | 1088 | (59.9%) |
| (n and % of patients) | Canada | 249 | (27.5%) | 244 | (26.8%) | 493 | (27.1%) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Rest of world[c] | 120 | (13.2%) | 115 | (12.6%) | 235 | (12.9%) |
| **Baseline characteristics** | | | | | | | |
| Weight (kg) | Mean (SD) | 80.4 | (17.3) | 81.2 | (17.6) | 80.8 | (17.5) |
| | Range | 40-145 | | 45-156 | | 40-156 | |
| Body mass index ($kg/m^2$) | Mean (SD) | 28.3 | (5.3) | 28.4 | (5.3) | 28.4 | (5.3) |
| | Range | 15.8-58.9 | | 15.6-49.2 | | 15.6-58.9 | |
| Estimated CrCl (mL/min)[d] | Mean (SD) | 99.9 | (41.1) | 99.7 | (39.8) | 99.8 | (40.5) |
| | Range | 26.4-310 | | 14.1-313.3 | | 14.1-313.3 | |

[a] Includes 22 patients (12 ximelagatran, 10 enoxaparin) who did not received study medication.

[b] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing.

[c] Includes Argentina, Israel, Mexico, and South Africa

[d] Cockcroft-Gault equation.

ITT Intention to treat; N Number; PP Per protocol; SD standard deviation

### Efficacy and pharmacokinetic results

In the efficacy ITT population, the rate of VTE following unilateral THA was 7.9% in the ximelagatran group compared with 4.6% in the enoxaparin group. Statistical non-inferiority could not be established since the upper limit of the 95% CI (5.7%) surrounding the between group difference of 3.3% was >5%. The incidence of proximal DVT + PE was 3.6% in the ximelagatran group and 1.2% in the enoxaparin group. For both VTE and proximal DVT/PE, the lower limit of the 95% CI (0.9% for both) was greater than 0%, indicating that there was a statistical difference in favor of enoxaparin. The results of the analyses of the frequency of VTE and proximal DVT/PE are shown in Table S2. There were only 9 cases of verified PE during this study, 4 during the treatment period (all in the ximelagatran group) and 5 (3 ximelagatran, 2 enoxaparin) during the follow-up period.

Subgroup analyses 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. A sensitivity analysis of the incidence of VTE which substituted local assessments for the assessments of the Central Adjudication Committee showed similar findings to the primary analysis. There were no differences in mean plasma trough concentrations of melagatran among patients with or without confirmed VTE ( 0.117 µmol/L vs. 0.124 µmol/L , respectively ).

**Table S2 Frequency of VTE and proximal DVT/PE (Efficacy intention-to-treat population)**

| Type of event | Treatment group | % | (n/N) | Exact 95% CI | Ximelagatran vs. Enoxaparin % | 95% CI |
|---|---|---|---|---|---|---|
| **VTE** | Ximelagatran | 7.9 | (62/782) | (6.1,10.0) | 3.3 | (0.9,5.7) |
| | Enoxaparin | 4.6 | (36/775) | (3.3,6.4) | | |
| **Proximal DVT/PE**[a] | Ximelagatran | 3.6 | (28/782) | (2.4,5.1) | 2.4 | (0.9,3.9) |
| | Enoxaparin | 1.2 | (9/774)[b] | (0.5,2.2) | | |

[a] Proximal DVT/PE included patients with a confirmed DVT of the proximal veins by venography as well as any patient who had objectively confirmed signs or symptoms of proximal DVT/PE.

[b] One patient (501/2838) in the enoxaparin group was not included in the analysis of proximal DVT/PE because she had objectively confirmed symptomatic distal DVT rather than proximal DVT. VTE venous thromboembolic event; DVT deep vein thrombosis; PE pulmonary embolism; CI confidence interval

**Safety results**

Oral administration of ximelagatran following unilateral THA was associated with a safety and tolerability profile generally comparable to enoxaparin. An overall summary of the safety findings in this study is provided in Table S3. The incidence of on-treatment major bleeding events, an established consequence of anticoagulant therapy, was <1% following treatment with ximelagatran and enoxaparin (p=1.000). The volumes of postoperative blood loss and wound drainage were also comparable following prophylactic treatment with ximelagatran and enoxaparin. Fewer than 10% of patients in either treatment group experienced bleeding complications (eg, wound hematoma, bruising, etc.) at any point following surgery, and <2.5% of patients in the ximelagatran and enoxaparin groups required an intervention for their bleeding complication. At any scheduled visit during the study, overall wound appearance was rated as expected for the majority of patients in the ximelagatran and enoxaparin groups (90.0% and 93.6%, respectively). Overall during the study and at follow-up (ie, at any time point), wound appearance was rated as "worse than expected" at least once for 9.5% of patients in the ximelagatran group compared with 6.1% of patients in the enoxaparin group (nominal p=0.019). There were no differences in mean plasma trough concentrations of melagatran among patients with or without a confirmed bleeding event (0.154 µmol/L vs. 0.124 µmol/L).

**Table S3 Overall summary of safety findings (safety population)**

| Category | N (%) of patients in each category[a] | | | |
|---|---|---|---|---|
| | Ximelagatran (N=906) | | Enoxaparin (N=910) | |
| Any on-treatment major bleeding event | 7 | (0.8%) | 8 | (0.9%) |
| Any on-treatment bleeding event (major/minor) | 55 | (6.1%) | 47 | (5.2%) |
| Any treatment-emergent adverse event | 707 | (78.0%) | 712 | (78.2%) |
| Treatment-emergent serious adverse events | | | | |
| Serious adverse events leading to death | 1 | (0.1%) | 1 | (0.1%) |
| Serious adverse events not leading to death | 58 | (6.4%) | 52 | (5.7%) |
| Discontinuations of study treatment due to adverse events | 23 | (2.5%) | 19 | (2.1%) |

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

In both the ximelagatran and enoxaparin groups, the most frequently reported treatment-emergent adverse events were those typical in a postoperative setting, and included postoperative complications (37.0% vs. 33.5%), fever (15.2% vs. 16.7%), nausea (11.4% vs. 11.1%), and constipation (8.5% vs. 7.8%). There were no clinically important differences in reported incidence rates between the ximelagatran and enoxaparin groups. In the safety population, few patients in the ximelagatran group (2.5%) discontinued treatment prematurely as the result of a treatment-emergent adverse event and this incidence was comparable to that in the enoxaparin group (2.1%). The majority (>75%) of treatment-limiting adverse events were considered by the investigator as unlikely to be related to treatment.

Among patients included in the safety population, no patient died during treatment although 2 patients (1 in each treatment group) died within the study-defined 6-week follow-up visit. The ximelagatran-treated patient died as a result of a myocardial infarction, convulsions, bradycardia, and cardiac arrest on postoperative Day 17, 10 days after the end of treatment; the enoxaparin-treated patient died as the result of a cardiac arrest resulting from a possible PE on postoperative Day 49, approximately 6 weeks after the end of treatment. Both deaths were assessed as unlikely to be related to treatment. The incidence of nonfatal, treatment-emergent serious adverse events in the ximelagatran and enoxaparin groups was comparably low during this study (6.4% and 5.7%, respectively) and few (<6%) of the serious adverse events were considered related to treatment.

In general, treatment with oral ximelagatran and subcutaneous enoxaparin following THA was associated with similar changes in the clinical laboratory parameters. Exceptions were gamma GT, ALT (SGPT), and AST (SGOT) where the magnitude of the median elevations were 1.5- to 3-fold larger following treatment with enoxaparin than with ximelagatran. The most common laboratory parameters for which patients had values outside the extended reference range were low hematocrit, low hemoglobin, low RBC count, and elevated gamma GT. While several patients had laboratory abnormalities reported as adverse events, for only 2 patients (both in the ximelagatran group) did the abnormality (postoperative anemia and increased INR) meet the criteria for being serious. Postoperative anemia was the most common laboratory abnormality reported as an adverse event, and occurred with a lower incidence rate in the ximelagatran group (16.7%) compared with the enoxaparin group (19.3%). No clinically meaningful differences between treatment groups were observed in changes from baseline in any of the vital sign, body weight, or ECG parameters during this study. In addition, few patients ( $\leq$ 3%) had vital sign, body weight, or ECG values that were outside the extended reference range during the study.

**Reference:**

Colwell CW Jr, Berkowitz SD, Davidson BL, Lotke PA, Ginsberg JS, Lieberman JR, Neubauer J, Peters GR, Francis CW. Comparison of ximelagatran, an oral direct thrombin inhibitor, with enoxaparin for the prevention of venous thromboembolism following total hip replacement. A randomized, double-blind study. Journal of Thrombosis and Haemostasis 2003;1(10):2119-30.

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