AstraZeneca

SH-TPO-0006

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Exanta™

ACTIVE INGREDIENT: Ximelagatran (H 376/95)

Trial title (number): A randomized, double-blind, comparative study of H 376/95 (ximelagatran) and warfarin (COUMADIN®) for the prevention of venous thromboembolism following total knee arthroplasty. (PLATINUM Knee)

Developmental phase:III
First subject recruited:21 March 2000
Last subject completed:25 September 2000
Approval date:12 October 2001

OBJECTIVES:

The primary objective of this study was to establish the superior efficacy of ximelagatran compared with warfarin for the prevention of venous thromboembolic events (VTE) in patients following unilateral or bilateral total knee arthroplasty (TKA). Secondary objectives were to assess whether ximelagatran was superior to warfarin in preventing proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and to compare the incidence of bleeding events between the two treatments .

METHODS:

Methodology:
Multicenter, randomized, double-blind, double-dummy, parallel group study. Patients who were eligible for study entry were randomized to receive twice daily (bid) oral administration of ximelagatran 24 mg or once daily oral administration of warfarin titrated to a target international normalized ratio (INR) of 2.5 (range, 1.8 to 3.0). The first dose of warfarin was administered on the evening of surgery, while the first dose of ximelagatran was administered on the morning of the day after surgery (no sooner than 12 hours postoperatively). Patients were to receive treatment for a minimum of 7 days and a maximum of 12 days. On the last day of treatment, ascending venography of the operated leg(s) was to be performed. Patients were to return for a clinic visit 6 (± 2) weeks after surgery.

Number of Patients (Planned and Analyzed):

600 planned; 680 randomized; 537 evaluable for intention-to-treat (ITT) efficacy analysis; 476 evaluable for per protocol efficacy analysis; 675 evaluable for safety analysis.

Diagnosis and Main Criteria for Inclusion:

Adult male or female patients whose body weight was between 88 and 275 lbs, inclusive, and who were scheduled for elective primary unilateral or bilateral TKA. 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.

Test Product, Dose and Mode of Administration, Batch or Lot Number:

Ximelagatran 24 mg tablet Lot H1360-03-01-03

Duration of Treatment:

7 to 12 days

Reference Therapy, Dose and Mode of Administration, Batch or Lot Number:

Warfarin 2.5 mg capsule Lot 99M181

Placebo tablet Lot H1431-01-01-03

Placebo capsule Lot 99J161

Criteria for Evaluation:

Efficacy:

Incidence of VTE (ie, DVT in the distal or proximal veins or PE); incidence of proximal DVT + PE.

Safety:

Bleeding complications occurring following TKA; surgical site evaluations; incidence and severity of adverse events (AEs); clinical laboratory parameters (hematology, blood chemistry and urinalysis); electrocardiogram (ECG); vital signs (body weight, pulse rate, blood pressure, respiration rate and temperature).

Pharmacokinetics: Plasma concentrations of melagatran and correlation of plasma levels with VTE status and bleeding events.

Statistical Methods:

The presence or absence of DVT and PE was assessed locally at each investigative site and by a central adjudication site 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% confidence intervals) for each treatment group and the observed differences in proportions (with 95% confidence intervals) between the two treatment groups. Treatment group comparisons were tested using the Cochran-Mantel-Haenszel (CMH) chi-square test, stratified by unilateral or bilateral surgery. 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 ITT population, ie, all randomized and treated patients with an evaluable venogram of the operated leg(s) or objectively-confirmed, symptomatic DVT/PE while on treatment.

The frequency of bleeding complications, bleeding complications of the surgical wound, volume of operative blood loss, postoperative wound drainage, and transfusion requirements were analyzed with 95% confidence intervals using methods similar to those above. The overall appearance of the surgical wound was summarized for each treatment group and between-group differences tested using the CMH chi-square test stratified by type of surgery. 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. 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

SUMMARY

EFFICACY RESULTS: The incidence of VTE following treatment with ximelagatran 24 mg bid beginning at least 12 hours following unilateral or bilateral TKA was numerically lower (19.2%) compared to that observed following treatment with warfarin initiated on the evening of surgery (25.7%) ($p = 0.07$). Both study treatments were associated with similar, low frequencies of proximal DVT + PE (3.3% and 5.0%; $p = 0.316$). Subgroup analyses based on prespecified demographic or other characteristics were comparable to those for the total population, with the incidence of VTE consistently lower in the ximelagatran group compared with the warfarin group for most of the factors examined.

EFFICACY RESULTS (Continued): When local venography assessments were analyzed, the frequency of VTE following unilateral or bilateral TKA was statistically significantly lower in the ximelagatran group (25.4%) compared with the warfarin group (33.5%) ($p = 0.043$). The incidence of locally-assessed proximal DVT/PE was also lower in the ximelagatran group compared with the warfarin group (5.7% vs. 9.2%), although the treatment difference was not statistically significant ($p = 0.119$). Among all randomized and treated patients with clinical signs/symptoms of DVT or PE during the treatment period, comparable percentages of patients in the warfarin (1.8%) and ximelagatran (1.7%) groups had confirmed DVT, while four times as many warfarin patients compared with ximelagatran patients (1.2% vs. 0.3%) had confirmed PE.

SAFETY RESULTS: Ximelagatran was well tolerated following oral dosing for 7 to 12 days among patients undergoing unilateral or bilateral TKA and its tolerability profile was comparable to that of warfarin. An overall summary of the safety findings in this study is provided in the following display.

Display I: Overall Summary of Safety Findings

Safety Population

	Ximelagatran		Warfarin	
Category	(N = 345)		(N = 330)	
No. (%) Pts. With Major Bleeding Event[a]	6	(1.7%)	3	(0.9%)
No. (%) Pts. With Any Bleeding Event[a]	31	(9.0%)	23	(7.0%)
No. (%) Pts. With Treatment-Emergent AE	275	(79.7%)	261	(79.1%)
No. (%) Pts. With Drug-Related Treatment-Emergent AE[b]	64	(18.6%)	61	(18.5%)
No. (%) Pts. with Treatment-Emergent Serious Adverse Event[c]	29	(8.4%)	30	(9.1%)
No. (%) Pts. Discontinued for a Treatment-Emergent AE	14	(4.1%)	18	(5.5%)
No. (%) Pts. with a Fatal Serious Adverse Event[d]	0	(0.0%)	2	(0.6%)

[a] No statistically significant difference ($p < 0.05$) using the CMH test.

[b] Adverse events considered possibly or probably related to treatment.

[c] Includes fatal and nonfatal serious adverse events. One warfarin-treated patient had both a fatal and nonfatal serious adverse event.

[d] One patient died after completion of the study-defined 6-week follow-up visit.

In the ximelagatran group, there were only six (1.7%) confirmed major bleeding events, and 31 (9.0%) patients experienced any bleeding event (major or minor) during treatment. The rates of

major and major/minor bleeding events in the warfarin group were 0.9% and 7.0%, respectively. The volumes of postoperative blood loss and wound drainage were comparable in the ximelagatran and warfarin groups. Overall wound appearance was rated as “worse than expected” at one or more points following surgery by a comparably small percentage of patients in the ximelagatran (9.9%) and warfarin (7.9%) groups. In addition, fewer than 10% of patients in either treatment group experienced bleeding complications (eg, wound hematoma, bruising, etc.) at any point following surgery, and fewer than 2% of patients in the ximelagatran and warfarin groups required an intervention for their bleeding complication. The most frequently reported treatment-emergent adverse events were those typical in a postoperative setting, and included postoperative complications, nausea, fever and constipation. There were no clinically important differences in the reported incidence rates between the ximelagatran and warfarin groups.

Only one patient included in the safety population died during treatment or within the study-defined 6-week follow-up visit. This patient was treated with warfarin and died as the result of a PE and cardiac arrest on postoperative Day 3. A second warfarin-treated patient died as the result of colon carcinoma approximately 3.5 months after the end of treatment. One additional patient assigned to the ximelagatran group died as the result of a myocardial infarction following surgery and randomization but prior to receipt of study medication.

SAFETY RESULTS (Continued): Comparable percentages of patients in the ximelagatran and warfarin groups (8.4% and 8.8%, respectively) experienced nonfatal serious adverse events, and most (87%) of the serious adverse events were considered by the investigator to be unrelated to study treatment. The proportion of patients who discontinued study treatment due to an adverse event was also comparable in the ximelagatran (4.1%) and warfarin (5.5%) groups. Of the 32 patients in this study who were withdrawn from study treatment for an adverse event, 17 had one or more adverse events that met the criteria for being characterized as serious.

In general, treatment with ximelagatran and warfarin following unilateral or bilateral TKA was associated with similar changes in clinical laboratory parameters. The most common laboratory parameters for which a comparable proportion of patients in both treatment groups had values outside the extended reference range were low hematocrit, low hemoglobin, low red blood cell counts and elevated GGT. While several patients had laboratory abnormalities reported as an adverse event, for only five patients did the abnormality meet the criteria for being characterized as serious (anemia, laboratory test abnormal [blood in stool], thrombocytopenia in ximelagatran group; prothombin decreased and renal function abnormal in warfarin group). Postoperative anemia was the most common laboratory abnormality reported as an adverse event, and occurred in 18.0% of patients in the ximelagatran group and 14.5% in the warfarin group.

No 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 had vital sign, body weight or ECG values that were outside the extended reference range during the study.

PHARMACOKINETIC RESULTS: Among patients treated with ximelagatran who had plasma melagatran levels available on postoperative Day 3, there was a suggestion of lower levels in those who experienced a VTE compared to those who did not. Melagatran levels were similar in patients with and without bleeding events. There was considerable overlap in melagatran plasma concentrations in these groups, however, and the data should be interpreted with caution.

Reference :

1. Francis CW, Davidson BL, Berkowitz SD, Lotke PA, Ginsberg JS, Lieberman JR, Webster AK, Whipple JP, Peters GR, Colwell CW Jr. Ximelagatran versus warfarin for the prevention of venous thromboembolism after total knee arthroplasty. Annals of Internal Medicine 2002;137(8):648-655

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