AstraZeneca

SH-TPO-0004

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Exanta™

ACTIVE INGREDIENT: H 376/95 (ximelagatran)

Trial title (number): Dose-finding, safety, and pharmacokinetics of H 376/95 (ximelagatran) given postoperatively as prophylaxis for thromboembolic complications after total knee replacement.

Developmental phase: Phase II
First subject recruited:30 October 1998
Last subject completed:11 January 2000
Approval date:22 June 2001

OBJECTIVES

The primary objective of this study was to determine the optimal dose of orally administered H 376/95 (ximelagatran) given postoperatively following total knee replacement (TKR). Secondary objectives were to determine the safety and pharmacokinetics of H 376/95.

METHODS

Methodology: Multicenter, randomized, parallel design study. Patients who were eligible for study entry were randomized to receive twice daily (bid) administration of one of four oral dosages of H 376/95 (8 mg, 12 mg, 18 mg, or 24 mg) or subcutaneously administered enoxaparin 30 mg. The dose of H 376/95 was blinded, while enoxaparin was administered under open-label conditions. The first dose of study medication was to be administered 12 hours to 24 hours after TKR. Patients were to receive treatment for a minimum of 6 days and a maximum of 12 days. On the last day of treatment, a unilateral contrast venogram of the operated leg was to be performed. Patients were to return for a clinical visit 4 weeks after TKR surgery. An amendment to the protocol (28 September 1999) discontinued enrollment of patients in the H 376/95 8 mg dose group.

Number of Patients (Planned and Analyzed): 500 planned; 600 randomized; 443 evaluable for intention to treat (ITT) efficacy analysis; 415 evaluable for per protocol efficacy analysis (including three patients with PE); 594 evaluable for safety analysis.

Diagnosis and Main Criteria for Inclusion: Adult male or female patients, whose body weight was between 88 lbs and 275 lbs and who were scheduled for elective primary unilateral TKR surgery. Patients with a history of confirmed deep vein thrombosis (DVT) or pulmonary embolism (PE), who required concomitant therapy with agents known to affect coagulation or platelet function, or who had any history of bleeding episodes were not eligible for entry.

Test Product, Dose and Mode of Administration, Batch or Lot Number:
H 376/95 tablets 8 mg Lot H-1360-02-01-01
H 376/95 tablets 12 mg Lot H-1359-02-01-01
H 376/95 tablets 18 mg Lot H-1393-01-01-01
H 376/95 tablets 24 mg Lot H-1360-02-01-01

Duration of Treatment: 6 days to 12 days

Reference Therapy, Dose and Mode of Administration, Batch or Lot Number:
Enoxaparin syringe 30 mg Lot 861

Criteria for Evaluation:

Efficacy : Occurrence of venous thromboembolic events (VTE), ie, DVT in the distal or proximal veins or PE.

Safety: Bleeding complications occurring following TKR surgery; incidence and severity of adverse events; clinical laboratory parameters (hematology, blood chemistry, urinalysis); vital signs (body weight, pulse rate, blood pressure, respiration rate, temperature).

Pharmacokinetics/Pharmacodynamics: Plasma concentrations of melagatran, activated partial thromboplastin time (APTT), and ecarin clotting time (ECT). Correlation of plasma levels with VTE status.

Statistical Methods: The presence and absence of DVT and PE were assessed locally at each investigative site and by a central adjudication site blinded to treatment group, local assessment, or 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) within treatment groups and the observed differences in proportions (with 95% confidence intervals) between selected treatment groups. Dose response (on the log dose) was assessed using the Cochran-Armitage test for trend. Secondary efficacy analyses of proximal DVT and PE, and local VTE rates were performed similarly.

The frequency of bleeding complications, volume of postoperative blood loss, and units of transfused red blood cells, were analyzed with 95% confidence intervals using methods similar to those above. Dose response for blood loss and transfusion parameters were assessed using analysis of variance methods. Analyses of adverse events, laboratory parameters, and vital signs were summarized descriptively.

Plasma melagatran, APTT, and ECT concentrations were summarized descriptively at each time point. The incidence of VTE was also described as a function of plasma concentrations across all H 376/95 dosage groups combined.

RESULTS

Efficacy Results: Oral treatment with the 24 mg bid regimen of H 376/95 beginning 12 hours to 24 hours following TKR surgery was associated with the lowest incidence of VTE compared with H 376/95 dosage regimens of 8 mg, 12 mg, or 18 mg bid. Moreover, the incidence rate of VTE was numerically lower with the H 376/95 24 mg bid oral treatment than with enoxaparin 30 mg injected sc (Display I).

The observed treatment differences in VTE incidence ranged from 4% to 12.9% between the H 376/95 24 mg group and each of the other H 376/95 dosage groups and was 6.9% between the H 376/95 24 mg and enoxaparin groups. Despite the numerically lower VTE incidence rate for H 376/95 24 mg, the statistical test for dose response among the H 376/95 groups and the pairwise comparison with the enoxaparin group were not statistically significant ($p \geq 0.297$ and $p \geq 0.273$, respectively). Subgroup analyses based on demographic characteristics and operation details generally showed similarly lower VTE incidence rates with H 376/95 24 mg compared with the other H 376/95 dosage groups and enoxaparin 30 mg group in preventing VTE following TKR.

Display I: VTE Frequency: ITT Population

Treatment Group	VTE Endpoint	Proximal DVT/PE
H 376/95 8 mg po	27.0%(17/63)	6.6%(4/61)
H 376/95 12 mg po	19.8%(20/101)	2.0%(2/101)
H 376/95 18 mg po	28.7%(25/87)	5.8%(5/86)
H 376/95 24 mg po	15.8%(15/95)	3.2%(3/95)
Enoxaparin 30 mg sc	22.7%(22/97)	3.1%(3/97)

Safety Results:

H 376/95 was well tolerated following oral dosing for 6 days to 12 days among patients undergoing TKR and the safety profile of H 376/95 was generally similar to that observed following sc administration of enoxaparin. An overall summary of the safety findings in this study is provided in the following display.

Display II: Overall Summary of Safety Findings

Category	H 376/95 8 mg po (N=84)	H 376/95 12 mg po (N=134)	H 376/95 18 mg po (N=124)	H 376/95 24 mg po (N=127)	Enoxaparin 30 mg sc (N=125)
No. (%) Pts. with Major Bleed	0(0.0%)	0(0.0%)	3(2.4%)	0 (0.0%)	1 (0.8%)
No. (%) Pts. with Significant Bleed	0(0.0%)	2(1.5%)	3(2.4%)	2 (1.6%)	2 (1.6%)
No. (%) Pts. with at Least One Trt-Emergent AE	72(85.7%)	113(84.3%)	110(88.7%)	105(82.7%)	116(92.8%)
No. (%) Pts. with at Least One Drug-Related Trt-Emergent AE[a]	19(22.6%)	26(19.4%)	30(24.2%)	26 (20.5%)	33 (26.4%)
No. (%) Pts. with Trt-Emergent SAE[b]	1(1.2%)	11(8.2%)	19(15.3%)	11 (8.7%)	7 (5.6%)
No. (%) Pts. Discontinued for a Trt-Emergent AE	1(1.2%)	4(3.0%)	8(6.5%)	3 (2.4%)	5 (4.0%)
No. (%) Pts. with a Fatal Trt- Emergent SAE	0(0.0%)	1(0.7%)	0(0.0%)	1 (0.8%)	0 (0.0%)

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

[b] Includes fatal and nonfatal serious adverse events.

Confirmed major bleeding events following TKR were uncommon and were reported for three of the 469 patients (0.6%) treated with oral H 376/95 and one of the 125 (0.8%) patients receiving sc enoxaparin. The rates of clinically significant bleeding events were also comparably low for the H 376/95 (1.5%) and enoxaparin (1.6%) treatments. The rate for any bleeding event (major + minor) was similar following oral treatment with H 376/95 24 mg bid (9.4%) and treatment with sc enoxaparin 30 mg bid (9.6%). The volumes of postoperative blood loss and wound drainage, however, were lower following prophylactic treatment with H 376/95 24 mg bid compared with enoxaparin 30 mg bid. There was no increase in blood loss or wound drainage with increasing H 376/95 dose.

Treatment-emergent adverse events were reported by 85.3% of patients assigned to one of the four H 376/95 dosage groups compared with 92.8% of patients assigned to treatment with enoxaparin 30 mg sc bid. The most frequently reported treatment-emergent adverse events were those typical in a postoperative setting and included nausea, fever, constipation, anemia, vomiting, and postoperative complications. In general, the reported incidence rates for treatment-emergent adverse events did not show a dose-related increase among the H 376/95 groups, and there were few differences in reported incidence rates between the H 376/95 and enoxaparin groups. Exceptions included peripheral oedema, hypertension, and dyspepsia which were reported at higher rates in the H 376/95 18 mg and 24 mg dosage groups compared with the H 376/95 8 mg and 12 mg groups. Peripheral oedema, pruritus, dizziness, and myalgia were reported at lower rates in the enoxaparin group than in at least three of the four H 376/95 dose groups.

There were two deaths in this study, both of which were considered by the investigator to be unrelated to study treatment. One patient assigned to the H 376/95 12 mg group died as the result of a myocardial infarction complicated by a possible GI hemorrhage two days after taking her last dose of study medication. A second patient assigned to the H 376/95 24 mg group died as the result of a pulmonary embolism 7 days after completing study treatment. A total of 47 patients experienced treatment-emergent nonfatal serious adverse events, including 40 (8.5%) assigned to treatment with H 376/95 and seven (5.6%) assigned to treatment with enoxaparin. Most (67%) of these were considered by the investigator to be unrelated to study treatment. The proportion of patients who discontinued study treatment for an adverse event was comparable for the H 376/95 dose groups combined (3.4%) and the enoxaparin group (4.0%). Of the 21 patients in this study who were withdrawn from study treatment for an adverse event, 15 had one or more adverse events that met the criteria for being characterized as serious.

Elevations in clinical laboratory parameters indicative of liver function (ie, AST, ALT, total bilirubin, alkaline phosphatase, LDH), elevations in white blood cell and segmented neutrophil counts, and reductions in total cholesterol, triglycerides, and erythrocyte parameters (ie, hematocrit, hemoglobin, red blood cell counts) occurred in all treatment groups. With the exception of GGT, ALT, and AST, the magnitude of the changes in these laboratory parameters with H 376/95 treatment were similar to those observed with enoxaparin 30 mg. By comparison, elevations in GGT, ALT, and AST levels were larger following treatment with enoxaparin than with any of the four oral doses of H 376/95. Across all five treatment groups the most common laboratory parameters outside of the extended reference range were low hematocrit and low hemoglobin. While several patients had laboratory abnormalities reported as an adverse event, for only four patients did the abnormality meet the criteria for being characterized as serious. Three patients (one in H 376/95 8 mg group, two in the H 376/95 18 mg group) had anemia reported as a serious adverse event, one of whom also had abnormal renal function (8 mg group). The remaining patient had blood in his stool (preferred term: laboratory test abnormal NOS; H 376/95 18 mg) which was considered serious. Anemia was also the most common laboratory abnormality reported as an adverse event, and occurred with a lower incidence rate in the H 376/95 8 mg group (15.5%) than with the other three H 376/95 dose groups (24.2% to 28.4%) or enoxaparin 30 mg group (24.0%). No clinically significant changes were observed in any of the vital signs or in body weight during this study.

Pharmacokinetic/Pharmacodynamic Results:

Among the H 376/95 dose groups, plasma concentrations of melagatran increased in an approximate dose-proportionate manner, with the highest concentrations observed in the 24 mg dose group. The rate of VTE was not clearly related to plasma concentrations of melagatran. The incidence of VTE was also not clearly associated with APTT and ECT concentrations. A dose-proportional increase in mean APTT and ECT concentrations was observed among the H 376/95 treatment groups with ECT having larger changes than APTT.

Reference:

Heit JA, Colwell CW, Francis CW, Ginsberg JS, Berkowitz SD, Whipple J, Peters G. Comparison of the oral direct thrombin inhibitor ximelagatran with enoxaparin as prophylaxis against venous thromboembolism after total knee replacement. Archives of Internal Medicine 2001;161(18):2215-21.

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