AstraZeneca

SH-TPV-0001

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Exanta™

ACTIVE INGREDIENT: H 376/95 (ximelagatran)

Trial title (number): Efficacy and safety of the oral thrombin inhibitor H 376/95 (ximelagatran), given to patients with acute deep venous thrombosis, an international dose-finding study (THRIVE I)

Developmental phase: II dose-guiding/-finding
First subject recruited: October 1998
Last subject completed: March 2000
Approval date:25 February 2002

OBJECTIVES

Primary objectives

To find the optimal, initial dose of H 376/95(ximelagatran), given as tablets twice daily to patients with acute DVT.

Efficacy was assessed with regard to changes in the size of the thrombus, according to the Marder score and clinical symptoms. Safety was measured with regard to bleeding episodes and other AEs.

Secondary objectives

To evaluate the pharmacokinetics and the pharmacodynamic profile, estimated by the plasma levels of melagatran, APTT and ECT.

To measure major resource utilisation related to route of administration (comparator drug) and safety of study drugs.

METHODS

STUDY DESIGN

This was a randomised, controlled, parallel group, multicentre, international dose-guiding/-finding study comparing the efficacy and safety of four different doses (24 mg bid, 36 mg bid, 48 mg bid and 60 mg bid) of H 376/95 and standard treatment with dalteparin/warfarin. The study was double-blind regarding the dosage of H 376/95 and open as regards the reference group.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Patients were included in the study if the following criteria were met:

- Acute proximal or distal DVT with onset of symptoms or signs within 14 days. In case the clot did not extend up to the popliteal vein (distal DVT), the clot height had to be $\geq$ 7cm. The upper limit of the thrombus had to be visible.
- 18 to 85 years of age.

Patients were excluded from the study if any of the following criteria were met:

- Thrombus extending into the caval vein
- Clinical signs of PE
- Renal impairment (a calculated CrCL below 40 ml/min)

A number of other standard criteria related to contraindications, restrictions in concomitant medication and common clinical study practice were also to be met.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

- H 376/95 12 mg H 1359-02-01-01
- H 376/95 24 mg H 1360-02-01-01
- Placebo H 1383-01-01-01

Patients received treatment of either 24 mg bid, 36 mg bid, 48 mg bid and 60 mg bidorally. The study was double-blind regarding the H 376/95 groups.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

- Dalteparin sodium 0.4 ml H 1369-01-02- 01, 02, 03, 04, 05, 06, 07, 08, 09
- Dalteparin sodium 0.5 ml H 1369-01-03- 01, 02, 03, 04, 05, 06, 07, 08, 09
- Dalteparin sodium 0.6 ml H 1369-01-04- 01, 02, 03, 04, 05, 06, 07, 08, 09
- Dalteparin sodium 0.72 ml H 1369-01-05- 01, 02, 03, 04, 05, 06, 07, 08, 09, 10

The dose of dalteparin was 200 U/kg body weight od, and was given sc, according to the standard dosing instructions, however, it did not exceed 18000 U. Syringes with a concentration of 25000 U/ml were used.

- Warfarin sodium 2.5 mg H 0724-02-01- 01, 03, 04, 05, 06, 08, 09

The dose of warfarin was given orally and was adjusted with the aim for a plasma prothrombin time (P-PT) INR 2-3. Dalteparin and warfarin were given at the same time od according to standard procedure.

DURATION OF TREATMENT

Twelve to 16 days.

MAIN VARIABLES:

- **EFFICACY**

  Efficacy was assessed with regard to changes in the size of the thrombus, according to the Marder score, and clinical symptoms.

  PHARMACOKINETICS AND PHARMACODYNAMICS

  Main pharmacokinetic variables were clearance and volume of distribution for melagatran after oral dosing of H 376/95. Pharmacodynamics was assessed by APTT and ECT.

- **SAFETY**

  Safety was assessed with regard to bleeding episodes and other AEs.

STATISTICAL METHODS

The efficacy and safety of the 4 dose levels of H 376/95 were assessed with the dalteparin/warfarin group as a reference. The percentage of patients with change in thrombus extension and change in Marder score were presented together with 95% confidence intervals using both the ITT and the PP population. Laboratory variables, blood pressure, heart rate, and clinical signs and symptoms were assessed using descriptive statistics.

Plasma concentrations of melagatran, APTT and ECT were described with descriptive statistics.

AE data were presented descriptively.

RESULTS

PATIENTS

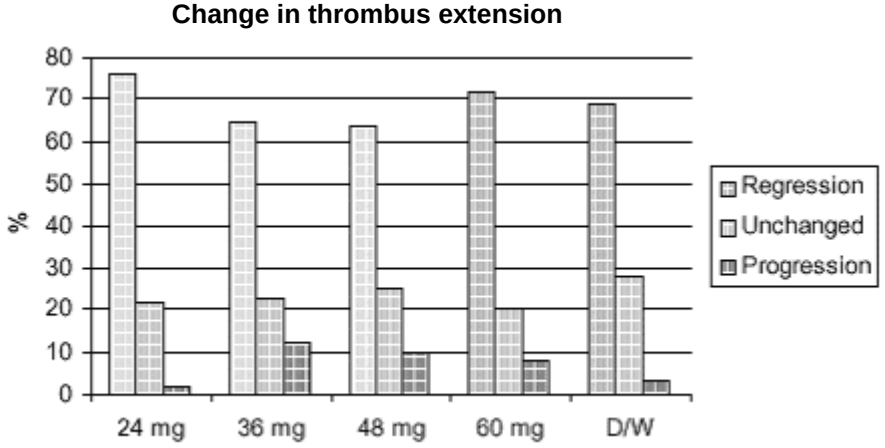
	H 376/95				Dalteparin/ Warfarin	Total
	24mg	**36mg**	**48mg**	**60mg**		
No. planned (evaluable patients) for efficacy	60	60	60	60	60	300
No. randomised and treated	68	65	73	71	73	350
Males/Females	40/28	35/30	45/28	40/31	41/32	201/149
Mean age (range)	58.1 (21-85)	60.5 (20-80)	59.7 (21-83)	59.5 (24-83)	58.2 (20-85)	59.2 (20-85)
Thrombus extension	54	57	59	60	65	295
Marder score	55	57	59	60	65	296
No. analysed for safety	68	65	73	71	73	350
No. completed study drug treatment	64	62	67	68	70	331

The treatment groups seemed to be comparable regarding size and characteristics.

SUMMARY

- **EFFICACY RESULTS**

Change in thrombus extension between baseline and the final day of study treatment, by treatment group (24 - 60 mg ref = H 376/95, D/W = dalteparin/warfarin).



The efficacy of H 376/95 was similar to that in the dalteparin/warfarin group and no dose-response relationship between the different dosages of H 376/95 regarding thrombus extension and Marder score was shown. Nor were there any notable differences regarding effect on clinical symptoms (pain, oedema, calf and ankle circumference).

PHARMACOKINETICS

The pharmacokinetics was predictable with moderate variability. The plasma concentrations of melagatran were proportional to the dose of H 376/95. The elimination rate was positively correlated to the calculated CrCL and the volume of distribution to the body weight. Smoking did not influence the pharmacokinetics of melagatran.

PHARMACODYNAMICS

APTT and ECT levels were correlated to the plasma concentration of melagatran and were within expected ranges.

HEALTH ECONOMICS

Most of the patients (88%) randomised to dalteparin/warfarin received help from a nurse with at least one study drug injection.

- **SAFETY RESULTS**

The AEs reported in this study were those expected to occur in this population. In the H 376/95 groups there were two deaths during the treatment period and two deaths during the follow-up period. There was one death in the dalteparin/warfarin group but it occurred after the follow-up period had ended. Possible adverse drug reactions such as bleeding events did not differ between the H 376/95 groups and the dalteparin/warfarin group. The prevalence of occult blood in faeces and urine did not seem to be related to the dose of H 376/95 and the

highest dose group tended to have a lower prevalence than the dalteparin/warfarin group. Increases in liver enzymes were more common on dalteparin/warfarin than on H 376/95.

HEALTH ECONOMICS

Insufficient data were collected on resource utilisation related to safety of study drugs.

Reference:

Eriksson H, Wåhlander K, Gustafsson D, Welin LT, Frison L, Schulman S. A randomized, controlled, dose-guiding study of the oral direct thrombin inhibitor ximelagatran compared with standard therapy for the treatment of acute deep vein thrombosis: THRIVE I. Journal of Thrombosis and Haemostasis 2003;1(1):41-7.

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