AstraZeneca

SH-TPO-0003

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Exanta™

ACTIVE INGREDIENT: Melagatran /H 376/95(ximelagatran)

Trial title (number): Efficacy and safety of melagatran and H 376/95 (ximelagatran) compared with enoxaparin as prophylaxis against venous thromboembolism after total hip- or knee replacement (METHRO III)

Developmental phase: Therapeutic confirmatory
First subject recruited:08 November 1999
Last subject completed:13 July 2000
Approval date:21 June 2001

OBJECTIVES

To assess efficacy and safety in the following study populations:

- All study patients (total hip replacement [THR] and total knee replacement [TKR])
- THR patients separately
- TKR patients separately

Primary objectives

Due to new Committee for Proprietary Medicinal Products (CPMP) documents concerning endpoints in non-inferiority studies in this indication that came into use during the study, the endpoint consisting of **proximal** deep vein thrombosis (DVT) and/or pulmonary embolism (PE,fatal or non-fatal) and/or unexplained death was promoted from a secondary endpoint to a primary endpoint. This results in two endpoints under the primary objectives, as outlined below. The primary is to assess efficacy in patients with THR or TKR with respect to these endpoints.

The following parts comprise the primary endpoint under the primary objective, in this document referred to as **overall venous thromboembolism (VTE):**

- **overall** deep vein thrombosis (DVT) verified by venography on the final day of the study drug period
- clinically suspected and verified **overall** DVT/pulmonary embolism (PE) up to the final day of the study drug period
- fatal PE or unexplained death up to the final day of the study drug period

Patients meeting any of the criteria above are considered to have met the **overall VTE** endpoint.

The following parts comprise the secondary endpoint under the primary objective, in this document referred to as **proximal VTE**:

- **proximal** DVT verified by venography on the final day of the study drug period
- clinically suspected and verified proximal DVT/PE up to the final day of the study drug period
- fatal PE or unexplained death up to the final day of the study drug period

Patients meeting any of the criteria above are considered to have met the **proximal VTE** endpoint.

Secondary objectives

(1) To assess safety by recording AEs and measurements of bleeding, transfusions and laboratory variables.

(2) To assess the incidence of verified symptomatic DVT/PE occurring between the end of the drug period and the follow-up visit (4-6 weeks after surgery).

(3) To collect data on resource utilisation to provide data for future modelling of the health economic properties of melagatran and H 376/95 in comparison with enoxaparin as short-term prophylaxis in connection with orthopaedic surgery.

METHODS:

STUDY DESIGN

International, multicentre, randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of melagatran and H 376/95 versus enoxaparin. The patients were randomized to receive one of two treatment regimens.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Patients were eligible for enrolment in the study if the following criteria were met:

1. Scheduled for primary, elective total hip- or knee replacement.
2. Age $\geq$ 18 years
3. Weight $\geq$ 40 kg
4. Signed, informed consent to participate in the study

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

- Trauma with immobilization within 30 days prior to the surgery
- Major surgical procedure within 30 days prior to surgery
- Treatment with anticoagulant or antiplatelet drugs within 7 days prior to surgery (N.B. ASA up to 500 mg daily, and short-acting NSAID with $t_{1/2} \leq 20$ h, are allowed)
- Known disorder associated with increased risk of bleeding
- History of intracranial bleeding
- Ischaemic stroke during the last 30 days
- Known intraocular bleeding during the last year
- History of gastrointestinal bleeding disorder within the preceding 3 months
- Endoscopically verified ulcer disease within the last 14 days prior to surgery
- Ongoing malignancy
- Cytostatic treatment within the past 6 months
- Severe renal impairment (corresponding to a calculated creatinine clearance $\leq$ 30 mL/min.)
- Known active liver disease or liver insufficiency as judged by the investigator
- Childbearing potential, pregnancy, lactation and inadequate contraception (women of childbearing potential were eligible for inclusion, provided that an adequate method of birth control, as judged by the investigator, was used).

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Melagatran, sc formulation, supplied by AstraZeneca AB.
Solutions of melagatran in saline in the concentration of 15 mg/mL, pH 5.0, were supplied in prefilled syringes, containing 0.2 mL. Batch no H 1391-02-01-01.

H 376/95, oral formulation, supplied by AstraZeneca AB.
Coated tablets in the strength of 24 mg were supplied in blister packs. The coating contains iron oxides and titanium dioxide. Batch no H 1360-03-01-02 and H 1360-03-01-05.

Melagatran, 3 mg, given as a sc injection, started the evening after surgery (at least 4 hours after completion of surgery), followed by 24 mg H 376/95 given as a tablet bid, for the remaining treatment period. The last tablet was given the morning of the day of venography.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Enoxaparin, sc formulation, (Rhône-Poulenc Rorer).
Prefilled syringes containing enoxaparin at a concentration of 10000 anti-Xa U/mL were used in this study. 40 mg was supplied in a volume of 0.4 mL. Batch no H 1413-01-02-01 and H 1413-01-02-02.

Enoxaparin, 40 mg, given as a sc injection qd, started the evening before surgery and then continued every evening until the evening before venography.

DURATION OF TREATMENT

Test product and comparator: The total active study drug period comprised 8-11 days.

MAIN VARIABLE(S):

- **EFFICACY**

The primary variable was the presence or absence of overall or proximal DVT, PE and/or unexplained death during the study drug period.

- **SAFETY**
    - Volume of blood loss
    - Volume of transfusions
    - Number of severe bleedings
    - General safety

STATISTICAL METHODS

Unless otherwise stated all statistical analyses, figures and tabulations were based on the ITT approach. All patients having undergone total hip- or knee replacement and who received at least one dose of their scheduled study drug were included regardless of their protocol adherence. In addition, with regard to the variables comprising the primary objective, a secondary analysis based on the per protocol (PP) approach was made. All patients presenting major protocol deviations which were defined before the study code was broken, were excluded from the PP analyses.

RESULTS:

PATIENTS			
	melagatran	**enoxaparin**	**Total**
	and H 376/95		
No planned	1300	1300	2600
No randomized and treated	1429	1424	2853
Males/Females	515/884	549/840	1064/1724
Mean age (range)	66.4 (25-93)	65.8 (26-93)	66.1 (25-93)
No analysed for efficacy	1146	1122	2268
No analysed for safety	1429*	1425*	2854*
	1399**	1389**	2788**
* AE & SAE			
** Bleeding, transfusion and lab.			

SUMMARY

- EFFICACY RESULTS

Table I Comparison of risk of overall VTE during study drug period.
Between treatment group risk difference (%) of VTE with asymptotic 95% confidence intervals. Combined surgery population (THR+TKR) as well as each joint separately. All patients in the ITT population, evaluable with respect to VTE.

	Surgery	**Estimate**	**95% CI**	
			Lower	**Upper**
melagatran and H 376/95 - enoxaparin	THR+TKR	3.70	-0.03	7.44
	THR	6.04	1.96	10.12
	TKR	-1.83	-9.35	5.69

Table II Comparison of risk of proximal VTE during study drug period.
Between treatment group risk difference with asymptotic 95% confidence intervals. Combined surgery population (THR+TKR) as well as THR and TKR separately. All evaluable patients in the ITT population.

	Surgery	**Estimate**	**95% CI**	
			Lower	**Upper**
melagatran and H 376/95 - enoxaparin	THR+TKR	-0.52	-2.47	1.43
	THR	0.02	-2.32	2.35
	TKR	-1.86	-5.42	1.69

Overall VTE rates (1st part of primary objective) for melagatran and H 376/95 were slightly higher than for enoxaparin, and thus superiority of melagatran and H 376/95 over enoxaparin could not be demonstrated. However, proximal VTE rates (2nd part of primary objective) for melagatran and H 376/95 were numerically lower than for enoxaparin.

There was a tendency for overall VTE rates to be lower with earlier rather than later administration of the first dose of melagatran after surgery (<8 versus ≥ 8 hours), thus indicating that timing of the first dose in relation to surgery may be an important factor contributing to the overall efficacy of melagatran and H 376/95.

The number of symptomatic events during the entire study period, including follow-up, was consistently numerically lower on melagatran and H376/95 than on enoxaparin.

No conclusions were drawn on resource utilisation for the study drugs.

- **SAFETY RESULTS**

Mortality was low (0.3%) in this study and similar to the previous large study, SH-TPO-0002 , in this programme and exactly the same as in a study with another thrombin inhibitor. Among the 8 patients who died, only 2 died during active treatment (both on melagatran and H 376/95).

There was a tendency toward a lower incidence of severe bleedings and lower bleeding volumes during surgery in the melagatran and H 376/95 group as compared to the enoxaparin group. The amount of blood transfused and the proportion of patients who received blood transfusions were also lower in the melagatran and H 376/95 group. The probable cause of this is the post-operative start of melagatran.

The overall frequency of AEs and SAEs was slightly lower in the melagatran and H 376/95 group as compared to the enoxaparin group. Post-operative complications and non-surgical bleedings also tended to be less frequent in the melagatran and H 376/95 group. Confusion was most likely related to surgery and not to the study drugs. Allergic reactions and urticaria were not related to melagatran and H 376/95.

Laboratory changes were as expected after major orthopaedic surgery. A higher incidence of increased liver enzymes in the enoxaparin group as compared to the melagatran and H 376/95 group was also expected because of the known effect of heparins and LMWHs on liver enzymes.

Reference:

1. Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Mouret P, Rosencher N, Eskilson C, Nylander I, Frison L, Ögren M. Direct thrombin inhibitor melagatran followed by oral ximelagatran in comparison with enoxaparin for prevention of venous thromboembolism after total hip or knee replacement: The METHRO III study. Thrombosis and Haemostasis 2003;89(2):288-96.
2. Dahl OE, Eriksson BI, Agnelli G, Cohen AT, Mouret P, Rosencher N, Panfilov S, Bylock A, Andersson M. Postoperative melagatran/ximelagatran for the prevention of venous thromboembolism following major elective orthopaedic surgery. Effects of timing of first dose and risk factors for thromboembolism and bleeding complications on efficacy and safety. Clinical Drug Investigation 2005;25(1):65-77.

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) or melagatran, Healthcare Professionals should view their specific country information.