AstraZeneca

SH-TPO-0007

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Exanta™

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

Trial title (number): A randomized, double-blind, double-dummy, parallel-group, phase III, multicentre study comparing the efficacy and safety of melagatran and ximelagatran with enoxaparin after total hip or knee replacement (EXPRESS)

Developmental phase: Therapeutic confirmatory
First subject recruited: 10 April 2001
Last subject completed: 28 February 2002
Approval date: 24 May 2002

OBJECTIVES

Primary
The primary objective was assessed in a sequential closed-testing procedure of two stages. The first stage of the primary objective was to show that treatment with sc melagatran and oral ximelagatran, according to the stated regimen is non-inferior to enoxaparin 40mg subcutaneous (sc) once daily, started the evening before surgery, in subjects undergoing total hip replacement (THR) or total knee replacement (TKR) by assessment of the first stage composite endpoint consisting of:

- proximal deep venous thrombosis (DVT) verified by bilateral venography on the final day of the study drug period and/or
- clinically suspected and venographically verified proximal DVT up to the final day of the study drug period and/or
- clinically suspected and radiologically verified pulmonary embolism (PE) up to the final day of the study drug period and/or
- death by PE or unknown cause where PE cannot be ruled out, up to the final day of the study drug period.

Referred to as ‘proximal venous thromboembolism (VTE)’.

If the first stage of the primary objective was met, the second stage was to show that treatment with sc melagatran and oral ximelagatran, according to the stated regimen, is superior to that of enoxaparin in subjects undergoing THR or TKR by assessment of the second stage composite endpoint consisting of:

- proximal and/or distal DVT, ie total DVT, verified by bilateral venography on the final day of the study drug period and/or
- clinically suspected and venographically verified DVT up to the final day of the study drug period and/or
- clinically suspected and radiologically verified PE up to the final day of the study drug period and/or
- death by all causes up to the final day of study drug period

Referred to as ‘total VTE’.

Secondary
Secondary objectives of the study were:

- to investigate the rate of verified symptomatic VTE and death during the study, including the follow-up period
- to assess the safety of melagatran and ximelagatran by recording Adverse Events (AEs), bleeding (such as adjudicated severe bleeding, measurements of blood loss and transfusions) and laboratory variables

METHODS:

STUDY DESIGN

This was an international, multicentre, double-blind, randomized, double dummy, parallel group study comparing the efficacy and safety of melagatran and ximelagatran versus enoxaparin in the prevention of VTE in major elective orthopaedic surgery.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Subjects aged ≥ 18 years scheduled for primary elective unilateral THR or TKR that provided written informed consent were included in the study, provided that none of the following main exclusion criteria was met:

- Trauma with immobilisation within 30 days prior to surgery
- Major surgical procedure within 30 days prior to surgery
- Treatment with anticoagulant or antiplatelet drugs within 7 days prior to surgery (Nota Bene (N.B.) Acetylsalicylic acid (ASA) up to 500 mg daily and short-acting nonsteroidal anti-inflammatory drugs (NSAID) with $t_{½}$ < 20 h were 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
- Active malignancy
- Cytostatic treatment within the past 6 months
- Severe renal impairment as judged by the investigator. As a recommended basis of judgement, the calculated creatinine clearance value should be above 30 mL/min for the subject to be included
- 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 and a negative pregnancy test was obtained before randomization)

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Melagatran, 2mg sc formulation, supplied by AstraZeneca R&D Mölndal, Sweden
A solution of melagatran in saline in the concentration of 10 mg/mL, pH 5.0, was supplied in prefilled syringes with white pistons containing 0.2 mL. Batch no H-1334-03-01-01.

Melagatran, 3mg sc formulation, supplied by AstraZeneca R&D Mölndal, Sweden
A solution of melagatran in saline in the concentration 15 mg/mL, pH 5.0, was supplied in prefilled syringes with white pistons, containing 0.2 mL. Batch no H-1391-02-01-01.

Ximelagatran, oral formulation, supplied by AstraZeneca R&D Mölndal, Sweden
Coated tablets in the strength of 24mg were supplied in blister packs. The coating contained iron oxides and titanium dioxide. Batch no H-1360-03-01-08.

Melagatran 2mg sc was given immediately before surgery, followed by post-operative sc melagatran 3mg bid, until oral ximelagatran 24mg bid could be given. If the subject had markedly reduced gastrointestinal function, oral administration could be postponed until the morning of post-operative day 3 at the most.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Enoxaparin, sc formulation, (Aventis)
A solution of enoxaparin at the concentration of 10000 anti-Xa U/mL was supplied in prefilled syringes with yellow pistons containing 40mg in a volume of 0.4 mL. Batch no H-1413-01-02-06.

Enoxaparin 40mg sc was given once daily in the evenings, starting the day before surgery.

DURATION OF TREATMENT

Active treatment was given for 8-11 days.

MAIN VARIABLE(S):

- **EFFICACY**

The rate of proximal or distal DVT, PE and/or death during the study treatment period.

- **SAFETY**

AEs
Adjudicated severe bleeding
Volume of blood loss
Number of subjects with transfusion
Laboratory measurements

STATISTICAL METHODS

The Intention To Treat (ITT) population was used for the main analysis of the endpoints. No interim analysis was made. The ITT population was defined as all subjects that fulfilled the following criteria:

- Randomized
- Received study drug
- Underwent primary THR or TKR

Non-inferiority of melagatran and ximelagatran in comparison to enoxparin was assessed for the primary composite endpoint (assessed at the first stage) of proximal VTE with a one-sided upper limit and 97.5% confidence interval for the risk difference between treatment groups. In the absence of any published data, an absolute margin of non-inferiority of 2% was chosen, based on the expected incidence of this endpoint with the comparator enoxaparin. This choice was discussed with the study external experts and the French, German and Swedish health authorities (AFSSAPS, BfArM and MPA). If the upper limit of the confidence interval fell below the adopted non-inferiority margin of 2%, this was taken as proof that melagatran and ximelagatran were non-inferior to enoxaparin with respect to the first stage endpoint.

At the second stage of the testing procedure (to be formally assessed only if successful at the first stage), Fisher's exact test of the hypotheses of no difference between treatment groups on a 5% level against a two-sided alternative was used to assess the composite endpoint of total VTE for superiority.

For the secondary endpoint, comparisons between treatment groups were done mainly using descriptive statistics.

RESULTS:

SUBJECTS

	melagatran and ximelagatran	enoxaparin	Total
No. planned	1300	1300	2600
No. randomized and treated	1403	1418	2821
Males/Females (ITT)	509/868	542/845	1051/1713
Mean age (range) (ITT)	66.3 (24-88)	65.8 (20-89)	66.1 (20-89)
No. analysed for efficacy			
• 1st stage	1138	1178	2316
• 2nd stage	1141	1184	2325
No. analysed for safety	1403	1418	2821
No. completed*	1301	1325	2626

*completed both study drug and follow-up period

SUMMARY

- EFFICACY RESULTS

Table I Difference in rate of 1st stage primary efficacy endpoint

Between treatment rate of 1st stage primary efficacy endpoint in the ITT population with approximative 95% CI. An upper limit of the confidence interval below the adopted margin of non-inferiority (two percentage points) will be taken as proof of non-inferiority.

Surgery	Event rate (%)		Difference	95% CI	
	mel and ximel	enoxaparin		Lower	Upper
THR + TKR	2.28	6.28	-4.00	-5.63	-2.36
THR	1.81	5.47	-3.66	-5.47	-1.84
TKR	3.29	8.17	-4.88	-8.27	-1.50

Table II Difference in rate of 2nd stage primary efficacy endpoint

Between treatment rate of 2nd stage primary efficacy endpoint in the ITT population with approximative 95% CI and the hypotheses of no difference in risk between treatment groups assessed with Fisher's test. A p-value less than 0.05 will be taken as proof of superiority.

Surgery	Event rate (%)		Difference	95% CI		P-value
	mel and ximel	enoxaparin		Lower	Upper	
THR + TKR	20.25	26.60	-6.36	-9.79	-2.93	0.0003
THR	12.94	18.23	-5.29	-8.86	-1.71	0.004
TKR	35.11	44.13	-9.02	-15.95	-2.09	0.012

- The rate of proximal VTE (1st stage of primary objective) for melagatran and ximelagatran was statistically significantly lower than for enoxaparin (p=0.0000018), and thus superiority over enoxaparin was demonstrated.

- The total VTE rate (2nd stage of primary objective) for melagatran and ximelagatran was statistically significantly lower than for enoxaparin (p=0.0003), which also demonstrated superiority over enoxaparin.

- Symptomatic VTE events were rare: during the active treatment they were numerically lower for melagatran and ximelagatran compared with enoxaparin; during the entire study period, including follow-up, they were not statistically significantly different between the treatment groups.

- **SAFETY RESULTS**

  - The frequency of adjudicated bleeding events was higher in the melagatran and ximelagatran group in comparison with enoxaparin, except for TKR subjects.

  - SAEs and AEs leading to discontinuation respectively were more common in the melagatran and ximelagatran group compared to the enoxaparin group and were mainly due to bleeding.

  - The mortality in this study was low (0.2%, six out of 2765) and similar to what has been seen in previous large studies within this indication.

  - The overall safety conclusion is that treatment with melagatran and ximelagatran and the present dose regimen was generally well tolerated but caused higher frequency of bleeding compared to enoxaparin, although fatal bleeding, critical site bleeding and bleeding leading to re-operations were not different.

Reference:

1. Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Lassen MR, Mouret P, Rosencher N, Kalebo P, Panfilov S, Eskilson C, Andersson M. The direct thrombin inhibitor melagatran followed by oral ximelagatran compared with enoxaparin for the prevention of venous thromboembolism after total hip or knee replacement: the EXPRESS study. Journal of Thrombosis and Haemostasis 2003;1(12):2490-6.