AstraZeneca

SH-TPV-0003

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Exanta™

ACTIVE INGREDIENT: Ximelagatran

Trial title (number): Oral Thrombin Inhibitor Ximelagatran given to Patients as Prolonged Prophylaxis after a Six-month Anticoagulation Treatment for Venous Thromboembolism. An International Multicentre Double-blind Placebo Controlled Study (THRIVE III)

Developmental phase: Therapeutic confirmatory (III)
First subject recruited: 02 November 1999
Last subject completed:19 April 2002
Approval date: 30 April 2003

OBJECTIVES

Primary

To assess whether the oral thrombin inhibitor ximelagatran given as prolonged prophylaxis after a six-month anticoagulation treatment for venous thromboembolism (VTE) reduces the recurrence rate of symptomatic objectively confirmed VTE events compared to placebo (time to event).

Secondary

- To estimate all-cause mortality
- To assess the safety of treatment with ximelagatran with special regard to bleeding
- To evaluate the pharmacokinetics of melagatran during long term treatment with ximelagatran

METHODS

Study design

This was a double-blind, randomised, placebo-controlled, parallel-group multicentre study comparing the efficacy and safety of ximelagatran 24 mg twice daily with placebo when given orally as long term secondary prevention for 18 months to patients after a six-month anticoagulation treatment for VTE.

Target patient population and sample size

Male and female patients, 18 years or older, with symptomatic, objectively confirmed VTE, treated with anticoagulants for six months.

It was assumed that during the 18-month treatment period, VTE rates of 6% in the placebo group and 2% in the ximelagatran group would be observed. It was further anticipated that drop-out rates would be 25% in both groups. Using the log-rank test, with a two-sided significance level of 5%, a 90% statistical power was obtained with 600 patients randomised to each of the two treatment groups.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Tablets of ximelagatran (H 376/95), 24 mg orally twice daily, or placebo.

The batch numbers were as follows.
Ximelagatran: from H 1360-03-01-01 to H 1360-03-01-04
Placebo: from H 1431-01-01-01 to H 1431-01-01-03 and H 1431-01-01-05

Duration of treatment
The duration of treatment was 18 months.

Criteria for evaluation (main variables)
Efficacy and pharmacokinetics

Primary variable

- Time to symptomatic objectively confirmed VTE over a period of 18 months of treatment or until premature study discontinuation.

Secondary variables

- Time to all-cause mortality over a period of 18 months of treatment or until premature study discontinuation.
- Pharmacokinetic parameters
  - Clearance
  - Volume of distribution
  - AUC
  - $t_{1/2}$

Safety
Secondary variables

- Time to major bleeding event during the 18 months of treatment or until premature discontinuation of the study.
- Time to any bleeding event, during the 18 months of treatment or until premature discontinuation of the study.
- Adverse events (AEs)
- Laboratory measurements
- Vital signs, ECG, physical examination

Statistical methods
Time to event was compared between the treatment groups using a log-rank test. A proportional hazard model was used to estimate the hazard ratio. The primary analysis was based on the intention to treat (ITT) population.

RESULTS

Patient population

Table S1 Patient population and disposition

		Ximelagatran	Placebo	Total
Population				
N randomised (N planned)		617(600)	616(600)	1233(1200)
Demographic characteristics				
Sex (n and % of patients)	Male	331(54%)	313(51%)	644(53%)
	Female			579(47%)

		Ximelagatran	Placebo	Total
Age (years)	Mean (SD)			
	Range	18 to 87	19 to 90	18 to 90
Race (n and % of patients)	Caucasian	571(93%)	569(93%)	1140(93%)
	Black	1(0%)	4(1%)	5(0%)
	Oriental	1(0%)	0	
	Other	34(6%)	34(6%)	1(0%)
	Hispanic	5(1%)	4(1%)	68(6%)
				9(1%)
Baseline characteristics				
Weight	Mean (SD)	82(16)	82(16)	82(16)
	Range	45 to 145	47 to 150	45 to 150
No VTE event before initial VTE (n and % of patients)		534(87%)	514(84%)	1048(86%)
Type of initial VTE (n and % of patients)	DVT only	406(66%)	389(64%)	795(65%)
	PE only	106(17%)	93(15%)	199(16%)
	DVT and PE	100(16%)	128(21%)	228(19%)
Malignancy according to baseline stratification		34(6%)	32(5%)	66(5%)
Disposition				
N of patients who	completed	468	435	903
	discontinued	149	181	330
N analysed for efficacy and safety (ITT) [a]		612	611	1223
N analysed for efficacy (PP)		498	517	1015
N with all data analysed for efficacy (PP)		341	385	725

a The intention to treat (ITT) population is all randomised patients who had taken at least 1 dose of study treatment and had at least 1 data point after randomisation. The safety population included the same patients as in the ITT population.

DVT deep vein thrombosis; N Number; PE pulmonary embolism; PP Per protocol

Overall, the treatment groups were comparable for demographic characteristics, baseline parameters, treatment compliance and use of concomitant medication.

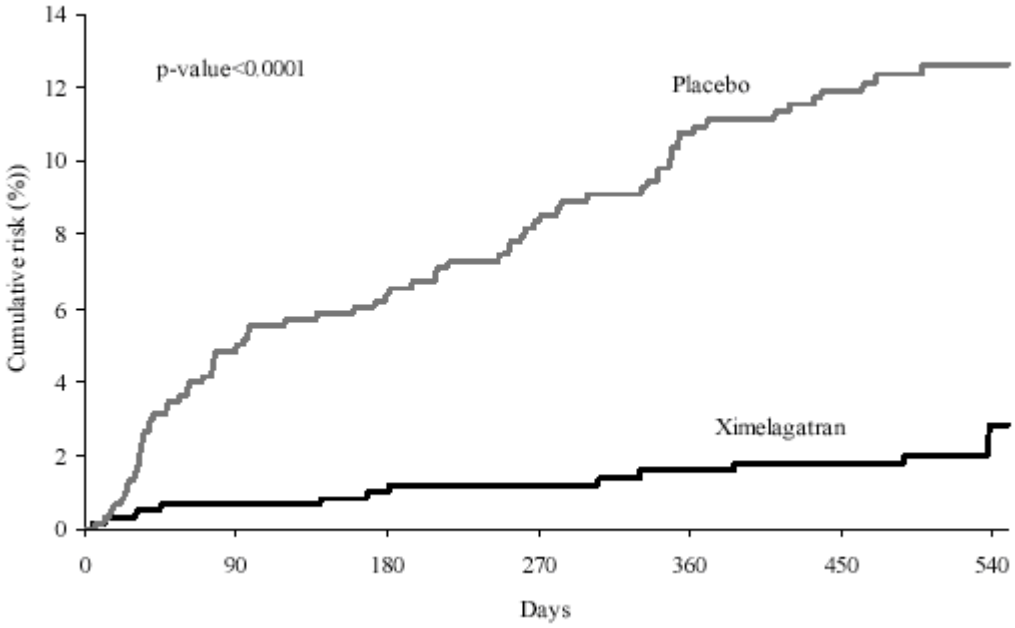
The most common reason for discontinuation of study, except for locally confirmed VTE in the placebo group, was adverse event in both treatment groups.

The study population, as demonstrated by baseline characteristics, includes important subgroups of a general patient population of patients with previous VTE.

Efficacy and pharmacokinetic results

Ximelagatran significantly reduced the recurrence rate of symptomatic objectively confirmed VTE events (DVT and/or PE) as compared to placebo. The estimated cumulative risk of an event during 18 months of treatment was 2.80% and 12.61% for patients on ximelagatran and placebo, respectively (hazard ratio 0.16; $p<0.0001$).

Figure S1 **VTE events, cumulative risk versus time after randomisation, ITT population**



There were few deaths, and these were evenly distributed, 6 in the ximelagatran group and 7 in the placebo group. Three deaths due to VTE occurred in the placebo group and none in the ximelagatran group.

Safety results

Overall, the safety profile of ximelagatran was acceptable as compared to placebo.

The incidence of major bleedings was low and similar in the two groups (n=6 for ximelagatran and n=5 for placebo). There were no fatal bleedings. Major and/or minor bleedings were numerically somewhat more common with ximelagatran (hazard ratio 1.19; p=0.1703). As shown in Table S2, the total number of adverse events (AEs) was similar in the two treatment groups, taking into account that the average exposure time was longer for ximelagatran. However, if VTE events are excluded, AEs of all categories were more common in the ximelagatran group, except for fatal serious AEs. The most common AEs are listed in Table S3. According to this table, accidents and/or injuries were more frequent in the ximelagatran group. AEs within the System Organ Class (SOC) Liver and biliary system disorders were also more frequent with ximelagatran than with placebo. The difference was explained by elevated liver function tests (LFTs) reported as AEs. The estimated cumulative risk of developing ALAT > 3 x ULN during the study was 6.4 % in the ximelagatran group as compared to 1.2 % in the placebo group. These elevations mainly occurred within the first 6 months of treatment and were of a transient nature. After 6 months the incidence was low and similar in the two treatment groups. There was not any specific pattern of symptoms or signs associated with the elevations. However, eleven ximelagatran patients discontinued study treatment due to elevated liver enzymes, which was thereby the most

common reason for discontinuation due to AE in the ximelagatran group. Diarrhoea and abdominal pain were more common with ximelagatran (reported by 5.2 and 4.2 % of the patients who received ximelagatran, respectively, with corresponding values of 2.8 and 2.5 % for patients who received placebo). Myocardial infarctions were reported in 1.8% of the ximelagatran treated patients compared to 0.5% in the placebo group. Other expressions of coronary heart disease (angina, myocardial ischaemia) were similar in the two treatment groups. There was no indication of allergic reactions caused by ximelagatran.

Table S2 **Number (%) of patients who had an adverse event in any category (ITT population)**

Category of adverse events	**N(%) of patients who had an adverse event in each category[a]**	
	ximelagatran (n=612)	**placebo (n=611)**
Any adverse events	517(84.5)	503(82.3)
Serious adverse events	126(20.6)	173(28.3)
Serious adverse events leading to death	6(1.0)	7(1.1)
Serious adverse events not leading to death	124(20.3)	169(27.7)
Discontinuations of study treatment due to adverse events	80(13.1)	125(20.5)
Severe adverse events	81(13.2)	104(17.0)
	Total number of adverse events	
Any adverse events[b]	1811	1735

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] Events are counted by preferred term ie, for patients with multiple events falling under the same preferred term, only 1 occurrence of the event is counted.

Table S3 **Number (%) of patients with most commonly reported adverse events, sorted by decreasing order of frequency as summarised over treatment group ≥ 5% in any of the treatment arms**

Preferred term	**Run-in ximelagatran (n=611) n (%)**	**Run-in placebo (n=609) n (%)**	**ximelagatran (n=612) n (%)**	**placebo (n=611) n (%)**	**TOTAL (n=1223) n (%)**
Accident and/or injury	5 (0.8)	0	79 (12.9)	50 (8.2)	129 (10.5)
Pain	5 (0.8)	3 (0.5)	63 (10.3)	66 (10.8)	129 (10.5)
Respiratory					

Preferred term	Run-in ximelagatran (n=611) n (%)	Run-in placebo (n=609) n (%)	ximelagatran (n=612) n (%)	placebo (n=611) n (%)	TOTAL (n=1223) n (%)
infection	6 (1.0)	2 (0.3)	58 (9.5)	54 (8.8)	112 (9.2)
Back pain	2 (0.3)	0	49 (8.0)	38 (6.2)	87 (7.1)
Headache	3 (0.5)	3 (0.5)	33 (5.4)	42 (6.9)	75 (6.1)
Arthralgia	3 (0.5)	0	37 (6.0)	36 (5.9)	73 (6.0)
Bronchitis	3 (0.5)	4 (0.7)	43 (7.0)	29 (4.7)	72 (5.9)
Thrombosis deep venous	0	0	12 (2.0)	60 (9.8)	72 (5.9)
Purpura	1 (0.2)	1 (0.2)	31 (5.1)	34 (5.6)	65 (5.3)
Haematuria	4 (0.7)	4 (0.7)	38 (6.2)	24 (3.9)	62 (5.1)
Hypertension	0	1 (0.2)	23 (3.8)	32 (5.2)	55 (4.5)
Diarrhoea	3 (0.5)	2 (0.3)	32 (5.2)	17 (2.8)	49 (4.0)
SGPT increased	1 (0.2)	1 (0.2)	42 (6.9)	7 (1.1)	49 (4.0)
Embolism pulmonary	0	0	4 (0.7)	31 (5.1)	35 (2.9)
SGOT increased	0	1 (0.2)	31 (5.1)	4 (0.7)	35 (2.9)

SGPT=ALAT; SGOT= ASAT

Reference:

Schulman S, Wåhlander K, Lundström T, Billing Clason S, Eriksson H. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. New England Journal of Medicine 2003;349(18):1713-21.

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