SH-TPV-0002/SH-TPV-0005

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Exanta™

ACTIVE INGREDIENT: Ximelagatran

Trial title (number): Efficacy and safety of the oral direct thrombin inhibitor ximelagatran versus standard therapy (enoxaparin and warfarin) for acute, symptomatic deep vein thrombosis with or without pulmonary embolism. A double-blind, international study (THRIVE Treatment)

Developmental phase: Therapeutic confirmatory (III)
First subject recruited: 22 September 2000
Last subject completed:11 December 2002
Approval date: 09 October 2003

OBJECTIVES

The primary objective was to demonstrate that ximelagatran, an oral direct thrombin inhibitor, is not clinically inferior to the standard treatment regimen (low molecular weight heparin [LMWH] and vitamin K antagonist [VKA]) in the prevention of recurrent venous thromboembolism (VTE) in patients who present with lower extremity deep vein thrombosis (DVT) with or without pulmonary embolism (PE).

The secondary objectives were to compare ximelagatran with the standard treatment with respect to:

- All-cause mortality
- A combined endpoint of symptomatic, objectively confirmed recurrent VTE and/or major bleeding
- Safety, with special regard to bleeding

For use in health economic evaluations of ximelagatran, the proportion of patients who require professional help with the administration of enoxaparin injections was recorded in selected countries in SH-TPV-0002.

METHODS

Study design

An international, double-blind, double-dummy, randomised, parallel group efficacy and safety study comparing the oral direct thrombin inhibitor ximelagatran with standard treatment (enoxaparin and warfarin) in 6 months treatment of patients with acute symptomatic, objectively confirmed DVT with or without PE

Target patient population and sample size

Male and female patients, 18 years or older, with acute, symptomatic, objectively confirmed lower extremity DVT, with or without PE.

The inclusion was to continue until it could be concluded that approximately 50 centrally adjudicated events of venous thromboembolism (VTE) were obtained. In the later phase of the recruitment, this was judged to be reached with approximately 2500 randomised patients.

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

Investigational product: ximelagatran, 36 mg orally twice daily, or placebo ximelagatran.

Comparators: enoxaparin 1.0 mg/kg subcutaneously twice daily or placebo enoxaparin during initial 5-20 days and warfarin orallyonce daily or placebo warfarin to a targeted International Normalised Ratio between 2.0 and 3.0.

Multiple batches were used. For ximelagatran 10 batches, for enoxaparin 13 batches, for warfarin 1 mg 12 batches, for warfarin 2.5 mg 12 batches, for placebo ximelagatran 10 batches, for placebo enoxaparin 7 batches, for placebo warfarin 1 mg 7 batches, and for placebo warfarin 2.5 mg 9 batches.

Duration of treatment

6 months.

Criteria for evaluation (main variables)

Efficacy

Primary variable:

- Time to symptomatic, objectively confirmed recurrent VTE event (fatal or nonfatal) during 6 months of treatment

Secondary efficacy variables:

- Time to death from any cause during 6 months of treatment
- Time to symptomatic, objectively confirmed recurrent VTE and/or major bleeding during 6 months of treatment

Safety

- Time to major bleeding event during 6 months of treatment
- Time to major or minor bleeding event during 6 months of treatment
- Time to any bleeding event during 6 months of treatment
- Adverse events
- Laboratory measurements
- Vital signs
- Physical examinations
- ECG (only SH-TPV-0005)

Statistical methods

The experimental treatment was to be declared non-inferior to the standard treatment comparator if the upper boundary of a 95% confidence interval for the difference in estimated cumulative risk

for objectively confirmed recurrent VTE was less than 4 percentage points. The cumulative risk estimate of VTE events at 6 months (182 days) was based on the varaible time to event using the Product-limit (Kaplan-Meier) estimator. The non-inferiority criterion of 4 percentage point was adopted on the basis of expected recurrence rate of VTE with standard therapy as estimated from published literature and by external experts, and discussed with regulatory authorities.

Evaluation of other efficacy endpoints and bleeding events was done by the same statistical method, but with no pre-adopted non-inferiority limit. The primary objective of the study was addressed with both Intention to treat (ITT) approach and On treatment (OT) approach, the ITT approach being declared as the primary.

RESULTS

Patient population

Table S1 Patient population and disposition

			Ximelagatran 36 mg bid	Enoxaparin/ Warfarin	Total
Population					
N randomised (N planned)			1258(1250)	1270(1250)	2528(2500)
ITT population[a]			1240	1249	2489
Demographic characteristics					
Sex (n and % of patients)		Male	654(53%)	665(53%)	1319(53%)
		Female	586(47%)	584(47%)	1170(47%)
Age (years)		Mean (SD)	56.7(16.4)	57.1(16.5)	56.9(16.4)
		Range	18 to 93	18 to 97	18 to 97
Race (n and % of patients)		Caucasian	1112(90%)	1128(90%)	2240(90%)
		Black	42(3%)	28(2%)	70(3%)
		Oriental	45(4%)	46(4%)	91(4%)
		Other	41(3%)	47(4%)	88(4%)
Baseline characteristics					
Type of initial VTE (n)	Distal DVT without PE		107	108	215
	Proximal DVT without PE		660	681	1341
	DVT and PE		461	455	916
	Other[b]		12	5	17
Disposition					
N[c] (%) of patients who		Completed	1187(94%)	1176(93%)	2363(93%)
		Withdrawals after randomisation	71	94	165
N[c] analysed for efficacy and safety[a]			1240	1249	2489

[a] Number of randomised patients who took at least one dose of study drug and for whom post-dose information was available

[b] Unknown type of DVT, PE only, or VTE not confirmed

[c] N=number

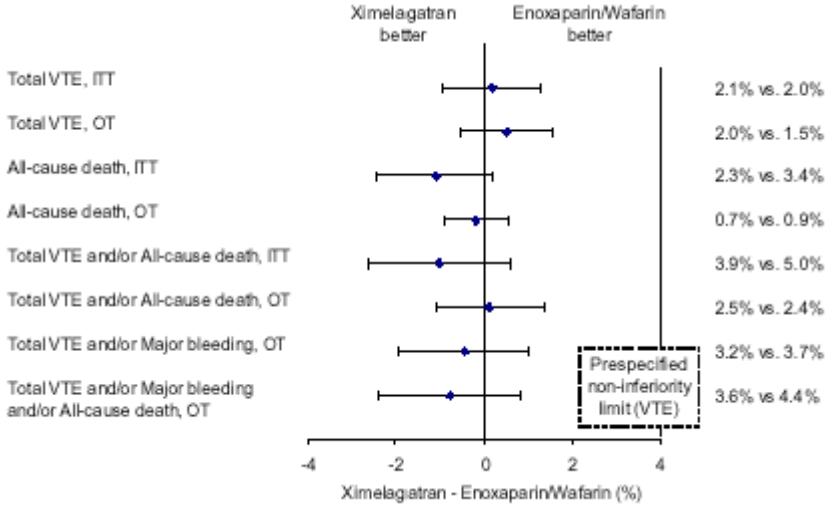
The study population, as demonstrated by baseline demographic characteristics, was mainly composed of Caucasians, and included a rather small proportion of patients with malignancy. In other respects it adequately represents the target population: patients with DVT with or without PE. Important exclusions from the study population were patients with severe renal and hepatic impairment, children and pregnant women. Patients with proximal DVT and patients with PE at the start of the treatment period were well represented: 2180 patients had a symptomatic proximal DVT and 916 patients had an objectively confirmed PE. Patients with varying potential VTE risk factors were included.

Treatment compliance was satisfactory and the treatment groups were comparable in all important aspects.

Efficacy results

The primary objective of establishing non-inferiority for a fixed dose of ximelagatran 36 mg twice daily for 6 months with no coagulation monitoring versus standard therapy, enoxaparin/warfarin, in prevention of recurrent VTE in patients with DVT, with or without PE was met. Analyses of the primary and secondary variables are illustrated in Figure 1.

Figure 1 Efficacy endpoints; absolute treatment differences



The upper boundary of the confidence intervals were well below the pre-specified non-inferiority margin of 4 percentage points for the total VTE endpoint, in both ITT and OT analyses. The outcome for the endpoint all-cause-mortality was in favour of the ximelagatran treatment (p=0.094). The outcome for the combined endpoint of recurrent VTE and/or major bleeding was similar in the two groups (p=0.531).

Odds ratios did not demonstrate any significant difference in risk of recurrent VTE between the two treatment groups relative to substrata.

Safety results

A tendency for a reduced risk of bleeding events with ximelagatran treatment as compared to standard treatment was indicated. There were 14 patients with a major bleeding event in the ximelagatran treatment group (estimated cumulative risk 1.3%) versus 26 in the enoxaparin/warfarin group (estimated cumulative risk 2.2%), %), treatment difference –1.0% (CI –2.1% to 0.1%; p=0.074). Bleeding events were numerically fewer in the ximelagatran treatment group also in the other bleeding endpoint categories, ie, major or minor bleeding events, and total bleeding events. The treatment difference for total bleeding events was statistically significant. This endpoint included, in addition to major and minor bleeding events, also reported events that were adjudicated by ICAC as not clinically significant. The consistency in the comparisons indicate that a fixed oral dose of ximelagatran 36 mg twice daily, with no coagulation monitoring, has a lower bleeding propensity than a regimen with dose adjusted, well controlled warfarin in conjunction with enoxaparin/warfarin regimen, despite the fact that the study was not powered to show superiority for bleeding events.

Risk of major bleeding was related to age in both treatment groups, but no clear relationship between risk of major bleeding and CrCL was identified within the ximelagatran group. Importantly, the outcome of the combined endpoint VTE recurrence and major bleeding was similar for both treatment groups in all substrata, indicating that the net risk-benefit balance for these outcomes was independent of subgroup.

Overall AE frequency was similar in both treatment groups, see Table S2. There was an even distribution of causes of death between treatment groups. Discontinuations due to adverse events were more common in the ximelagatran treatment group. The numerical difference can be attributed largely to discontinuations due to elevated liver enzymes that were required according to protocol stipulations. Discontinuations due to bleeding events were fewer with ximelagatran treatment. The most common AEs are listed in Table S3.

The estimated cumulative risk for an ALAT elevation >3xULN was 10.9% in the ximelagatran group versus 2.1% in the enoxaparin/warfarin group, corresponding to an incidence rate of 9.6% and 2.0%, respectively. The onset of the elevations typically occurred during the second and third treatment months in the ximelagatran group and during the first 2 weeks in the enoxaparin/warfarin group. A resolution of the elevation was established for nearly all patients, both among those who discontinued study drug and those who continued. The ALAT elevations were generally not associated with specific clinical symptoms. One case of suspected drug-induced hepatitis without known alternative explanation recovered after cessation of ximelagatran. No case of drug induced liver failure was identified in this study. It is unclear if the study drug contributed to the fatal course in one case of fulminant hepatitis B in the ximelagatran treatment group. There was no evidence from this study that the hepatic enzyme elevations associated with the ximelagatran treatment causes persistent liver function disorder.

Table S2 Number (%) of patients who had at least one adverse event in any category, and total numbers of adverse events (safety population)

	N(%) of patients[a] who had an adverse event in each category	
	During treatment	**During treatment**
Drug	**ximelagatran**	**enoxaparin/warfarin**
No of patients	**(n=1236)**	**(n=1248)**
Category of adverse events		
Any adverse events	930(75.2)	934(74.8)
Serious adverse events	220(17.8)	191(15.3)
Serious adverse events leading to death	8(0.7)	9(0.7)
Serious adverse events not leading to death	218(17.6)	183(14.7)
Discontinuations of study treatment due to adverse events	177(14.3)	126(10.1)

Number of adverse events[b] in any category (safety population)		
	During treatment	**During treatment**
Drug	**ximelagatran**	**enoxaparin/warfarin**
No of patients	**(n=1236)**	**(n=1248)**
Category of adverse events		
Any adverse events	3266	3149
Serious adverse events	299	259
Discontinuations adverse events	232	166

[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 the most commonly reported adverse events (>3% in any treatment group), sorted by decreasing order of total frequency as summarised over all treatment groups (safety population)

Preferred term	During treatment ximelagatran (n=1236)		During treatment enoxaparin/warfarin (n=1248)	
	n	(%)	n	(%)
Pain	144	(11.7)	135	(10.8)
Purpura	57	(4.6)	130	(10.4)
Oedema peripheral	92	(7.4)	89	(7.1)
Headache	92	(7.4)	80	(6.4)
Respiratory infection	74	(6.0)	87	(7.0)
Diarrhoea	75	(6.1)	65	(5.2)
Chest pain	68	(5.5)	59	(4.7)
Accident and/or injury	54	(4.4)	64	(5.1)
Epistaxis	39	(3.2)	76	(6.1)
Back pain	57	(4.6)	57	(4.6)
Nausea	57	(4.6)	54	(4.3)
Arthralgia	55	(4.4)	55	(4.4)
Dyspnoea	47	(3.8)	50	(4.0)
Constipation	46	(3.7)	43	(3.4)
Haematuria	35	(2.8)	51	(4.1)
Urinary tract infection	45	(3.6)	41	(3.3)
SGPT increased	66	(5.3)	19	(1.5)
Abdominal pain	48	(3.9)	33	(2.6)
Insomnia	45	(3.6)	36	(2.9)
Hepatic enzymes increased nos	48	(3.9)	9	(0.7)
SGOT increased	39	(3.2)	10	(0.8)

Reference:

Fiessinger JN, Huisman MV, Davidson BL, Bounameaux H, Francis CW, Eriksson H, Lundström T, Berkowitz SD, Nyström P, Thorsen M, Ginsberg JS. Ximelagatran vs low-molecular-weight heparin and warfarin for the treatment of deep vein thrombosis: A randomized trial. JAMA 2005;293(6):681-9.

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