AstraZeneca

SH-TPA-0005

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Exanta™

ACTIVE INGREDIENT: Ximelagatran (H 376/95)

Trial title (number): Efficacy and Safety Study of the Oral Direct Thrombin Inhibitor Ximelagatran (H 376/95) Compared with Dose-Adjusted Warfarin (Coumadin®) in the Prevention of Stroke and Systemic Embolic Events in Patients with Atrial Fibrillation (SPORTIF V)

Developmental phase: Phase III Therapeutic confirmatory
First subject recruited: 24 July 2000
Last subject completed:19 June 2003
Approval date: 09 September 2003

OBJECTIVES

Primary

To determine whether the efficacy of fixed oral dose ximelagatran is non-inferior compared to well-controlled dose-adjusted warfarin, aiming for an International Normalized Ratio (INR) of 2.0 to 3.0, for the prevention of all strokes (fatal and non-fatal) and systemic embolic events (SEEs) in patients with chronic nonvalvular atrial fibrillation (AF).

It was a prerequisite that, for the non-inferiority to be formally addressed, the effectiveness of ximelagatran over placebo (utilizing a previous meta-analysis of warfarin over placebo) was established.

Secondary and tertiary

To compare the efficacy of fixed oral dose ximelagatran to that of well-controlled dose-adjusted warfarin, aiming for an INR 2.0 to 3.0:

- For the combined endpoint of prevention of death, non-fatal strokes, non-fatal SEE and non-fatal acute myocardial infarction (AMI).
- For the combined endpoint of prevention of ischemic strokes, transient ischemic attacks (TIAs) and SEE.
- For the prevention of all strokes with a poor outcome (defined by a Modified Rankin score of 3 at 3 months post-stroke or a Barthel score of <60 at 3 months post-stroke).
- For the prevention of all strokes and SEE in patients 75 years of age with AF and to compare this with patients below the age of 75 years.

To assess the safety of fixed oral dose ximelagatran compared with well-controlled dose-adjusted warfarin, aiming for an INR of 2.0 to 3.0, with an emphasis on major and minor bleeding events and any treatment discontinuations.

METHODS

Study design

This was a multicenter, interactive voice response system (IVRS)-randomized, double-blind, double-dummy, 2-arm, parallel-group study. Patients completed a screening period for up to 2 weeks before randomization. Once randomized, patients attended regular visits for assessment. Study drug was administered for a minimum of 12 months and up to 36 months, until 80 primary endpoint events were recorded in the study and until 2000 patient years per treatment group were collected, whichever occurred first. On achieving the target number of primary endpoint events, all patients came to the study center for their End of Treatment Visit and transitioned onto open-label warfarin.

All patients who prematurely discontinued study drug were asked to attend an End of Treatment Visit. If patients agreed, they were followed up, by telephone, for selected endpoint events until the final contact or the study end. A local neurologist or stroke physician at the site performed primary endpoint assessment and the Central Event Adjudication Committee (CEAC) performed endpoint adjudication. Patients with AF were stratified by dynamic allocation according to acetylsalicylic acid (ASA) use and previous stroke/TIA.

Target patient population and sample size

Eligible patients were to be at least 18 years of age, have evidence of chronic AF (persistent or paroxysmal) verified by at least 2 electrocardiograms (ECGs) in the previous year, and at least 1 of the following risk factors for stroke: previous stroke, TIA or SEE, hypertension, left ventricular dysfunction, age ≥75 years, or age ≥65 years with either coronary artery disease or diabetes mellitus.

Patients who had a stroke within 30 days of enrollment, or a TIA within 3 days of enrollment, were to be excluded, together with patients who had conditions associated with an increased risk of bleeding or whose hemostatic function was compromised. Patients were also to be excluded if they had lone AF or transient AF during an acute illness, or if cardioversion was planned. Other cardiac reasons for exclusion were atrial myxoma, left ventricular thrombus, rheumatic valve disease, prosthetic heart valves or hospitalization for acute coronary syndromes or percutaneous coronary artery intervention within 30 days of screening. Patients were not eligible if they had a contraindication for anticoagulation, eg, bacterial endocarditis, pregnancy or liver disease, or if they had a recorded drug addiction or alcohol abuse in the previous 3 years.

Concomitant treatment with antiplatelet agents, fibrinolytic agents, other anticoagulants or continuous treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) was prohibited during the study, although ASA ≤100mg/day was allowed.

Elevated liver enzymes had been observed in 5% to 6% of patients taking ximelagatran in previous studies, therefore, patients with persistent raised liver enzymes ≥2x the upper limit of normal (ULN) were excluded as a precaution.

It was planned that approximately 3000 eligible patients would be randomized. After a protocol amendment this number was increased to 4000. The combined rate of ischemic stroke, hemorrhagic stroke, and systemic embolism for patients in this study was estimated to be 3.1% per year for each treatment group. To obtain 90% statistical power, adopting a 1-sided α=0.025, approximately 1600 patient years of follow-up per treatment group would be required to establish non-inferiority of ximelagatran compared to dose-adjusted warfarin within 2% per year. However, as a consequence of the non-inferiority criterion chosen, power was sensitive to overall incidence of the primary endpoint. To maintain a power of at least 90% for incidences up to 4.0% per year, a minimum of 2000 patient years per treatment group were required. The average duration of a patient's participation in the study was expected to be 16 months, thereby requiring that at least 3000 patients be randomized into the study.

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

Ximelagatran tablets, **36 mg bid**, 6 batches: H 1384-02-01-04, H 1384-02-01-07, H 1384-02-01-08, H 1384-02-01-09, H 1384-02-01-12, H 1384-02-01-15.

Matching placebo to ximelagatran, 4 batches: H 1444-01-01-03, H 1444-01-01-04, H 1444-01-01-05, H 1444-01-01-06.

Warfarin (Coumadin®) tablets with doses titrated according to local clinical practice, aiming for a target INR of 2.0 - 3.0. **1 mg**, 8 batches: A01234, A01316, 00A019, 00A020, 00C043, 01A001, 01A006, 99J160. **2.5 mg**, 9 batches: A01235, A01285, 00A021, 00A023, 00A024, 00J139, 01A002, 99M181, 99M182.

Matching placebo to warfarin. 1 mg placebo, 4 batches: A01277, 00C041, 00M164, 99J159. 2.5 mg placebo, 6 batches: A01247, A01295, 00A017, 00A018, 00M165, 99J161.

Doses were administered in a double-dummy fashion to maintain the blind. Patients were randomized to either:

(1) ximelagatran 36 mg tablets taken twice a day (bid) and placebo capsules labeled as warfarin taken once daily in the evening (the number and dose of the placebo given depended on the dose schedule specified by the investigator based on the sham [INR] value generated by the IVRS)
or
(2) warfarin 1.0 mg and/or 2.5 mg capsules taken once daily in the evening and titrated to a target INR range of 2.0 to 3.0 and a placebo tablet matching ximelagatran 36 mg taken twice a day.

Duration of treatment

Minimum of 12 months and up to a maximum of 36 months. The study was planned to continue until exposure to study drug reached 2000 patient years per treatment group, and at least 80 primary endpoints were reached, or an interim stopping rule was met.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable: the composite clinical endpoint defined as the incidence of stroke (fatal and non-fatal) or an SEE (fatal or non-fatal).
- Secondary variables: the composite endpoint defined as the incidence of death, a non-fatal stroke, a non-fatal SEE, a non-fatal TIA or a non-fatal AMI; the composite endpoint defined as an ischemic stroke, TIA, or SEE.
- Tertiary variables: the occurrence of a stroke with a poor outcome (measured using the Modified Rankin Score, the Barthel Score or fatal stroke) and re-examination of the primary endpoint according to subgroups of <75 years and ≥75 years of age.

In addition to the variables above, plasma samples were collected at Months 1, 12, and 24, or at the End of Treatment Visit to quantify trough plasma melagatran concentrations.

Safety

Major and minor bleeding events and adverse events (AEs); withdrawals and discontinuations; hematology, clinical chemistry, and INR measurement; ECG; blood pressure and heart rate; physical examination; plasma cholecystokinin (CCK) concentration (subset of patients); pancreas computerized tomography (CT) scan (subset of patients); and plasma melagatran concentration.

Statistical methods

The primary objective of the study was addressed with an intention-to-treat (ITT) approach using events adjudicated by the CEAC. In this approach, all randomized patients were included until study closure, irrespective of their protocol adherence and their continued participation in the study.

All statistical analyses of composite endpoints containing AMI or major bleeding related to secondary and tertiary endpoints were based on an on-treatment (OT) approach using adjudication from the CEAC. In addition, with regard to the primary endpoint, a sensitivity analysis was made based on the OT approach. The OT approach included all ITT patients but only their time on study medication was used for analysis. No analyses according to a per-protocol approach were performed.

All patients taking at least 1 dose of study medication and having post randomization data were included in the safety population and were used in the analysis of AEs.

A Data Safety Monitoring Board (DSMB) formally compared the 2 treatment groups for safety regarding the following 4 outcomes:

- All-cause mortality
- All-cause mortality, all strokes, and all SEEs

- All strokes and all SEEs
- Major bleeding.

This evaluation was done when approximately 12.5%, 25%, 50%, and 75% of the expected total number of patient years exposure was reached. Stopping rules were predefined.

RESULTS

Patient population

In total 3922 patients were randomized into the study, 3907 received treatment (1954 to ximelagatran, 1953 to warfarin) and 3336 patients completed the study (1660 in the ximelagatran group, 1676 in the warfarin group). All 3922 randomized patients were included in the ITT population and the OT analysis. Fifteen patients did not take study drug and one patient who took only one dose of study drug did not return for follow-up, therefore, the safety population comprised 3906 patients (Table S1).

The cohort consisted of a moderate to high risk group with well-controlled hypertension and well-controlled serum lipid concentrations. Patients in both treatment groups demonstrated excellent medication compliance rates; for the ximelagatran group 71% of patients were >90% compliant and for the warfarin group 78% were >90% compliant.

Although more ximelagatran patients discontinued study drug during SPORTIF V than discontinued warfarin (37% versus 33% in the warfarin group, p=0.014), the majority of this difference is explained by the protocol-mandated drug discontinuation with increased alanine aminotransferase (ALAT) values. Despite the challenges of participating in a double-blind, double-dummy anticoagulation trial, withdrawal rates remained relatively low at 15%, with less than 1.0% of patients lost to follow-up at the time of study closure.

Table S1 **Patient population and disposition (SPORTIF V)**

Parameter		Ximelagatran	Warfarin	Total
Population				
N randomized (N planned)		1960(2000)	1962(2000)	3922(4000)
Demographic characteristics				
Sex, n (%)	Male	1365(69.6%)	1353(69.0)	2718(69.3%)
	Female	595(30.4%)	609(31.0)	1204(30.7%)
Age, years	Mean (SD)	71.6(9.2)	71.6(9.0)	71.6(9.1)
	Range	30 to 97	35 to 92	30 to 97
Race, n (%)	Caucasian	1875(95.7%)	1888(96.2%)	3763(95.9%)
	Black	67(3.4%)	58(3.0%)	125(3.2%)
	Oriental	15(0.8%)	10(0.5%)	25(0.6%)
	Other	3(0.2%)	6(0.3%)	9(0.2%)
Disposition				

N (%) of patients who	Completed	1660(84.7%)	1676(85.4%)	3336(85.1%)
	Withdrew study	300(15.3%)	286(14.6%)	586(14.9%)
	Discontinued study drug	720(36.7%)	646(33.0%)	1366(34.8%)
N (%) analysed for safety[a]		1953(99.6%)	1953(99.5%)	3906(99.6%)
N analysed for efficacy ITT (Patient years)		1960(3193.1)	1962(3211.7)	3922(6404.8)
N analysed for efficacy OT (Patient years)		1960(2621.7)	1962(2751.9)	3922(5373.6)

[a] Number of patients taking at least 1 dose of study medication and having post randomization data.
ITT Intention-to-treat; OT On-treatment; SD Standard deviation.

Efficacy and pharmacokinetic results

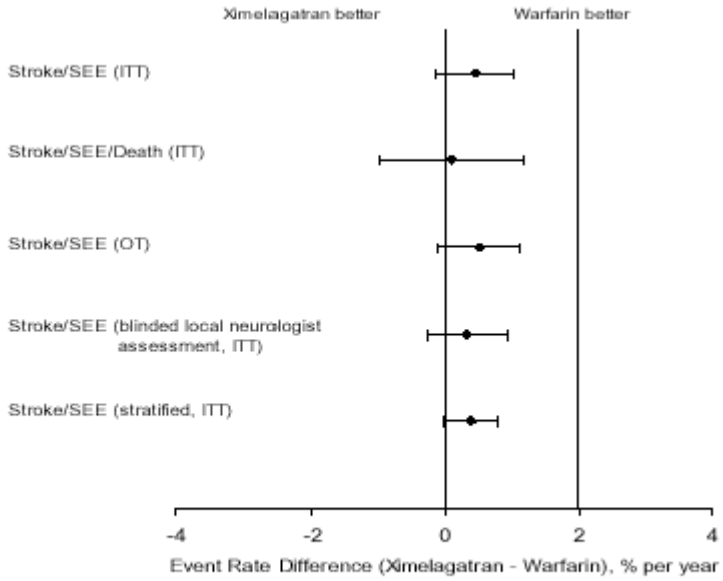
SPORTIF V met its primary objective of demonstrating non-inferiority of fixed oral dose ximelagatran to well-controlled warfarin, dose-adjusted to an INR 2.0 to 3.0, for the chosen non-inferiority margin, with the upper limit of the confidence interval (CI) for the difference in event rates being less than 2%/year (1.03%/year). Fifty-one patients in the ximelagatran group had a primary event (1.6%/year) compared to 37 patients in the warfarin group (1.2%/year), yielding a difference of 0.45%/year (95% CI –0.13 to 1.03) (Table S2 and Figure S1).

Table S2 **Efficacy comparison ximelagatran vs warfarin: number of patients with stroke and/or SEE and estimated event rates within treatment groups and between groups, with 2-sided 95% CI (ITT population) (SPORTIF V)**

Treatment group	Events[a]	Patient years	Event rate (%/year)	95% CI		p-value[b]
				Lower	Higher	
Ximelagatran	51	3160	1.61	1.17	2.06	
Warfarin	37	3186	1.16	0.79	1.54	
Ximelagatran - warfarin			0.45	-0.13	1.03	0.133

a Number of patients with events according to CEAC.
b p-value for difference between treatment groups.
CEAC Clinical Event Adjudication Committee; SEE Systemic embolic event; ITT Intention-to-treat; CI Confidence interval.

Figure S1 **Summary of primary efficacy variable and its sensitivity analyses; all confidence intervals are for between-group comparisons (SPORTIF V)**



ITT Intention-to-treat; SEE Systemic embolic event; OT On-treatment.

A relative risk reduction for stroke/SEE of 50% compared to placebo was calculated for ximelagatran, based on a putative analysis using historical data for risk reduction of warfarin to placebo.

Sensitivity analyses of the primary endpoint confirmed the primary result of non-inferiority of ximelagatran to warfarin in stroke prevention (Figure S1). Results in SPORTIF V are consistent across several endpoint event clusters.

SPORTIF V results support the use of ximelagatran in a fixed oral dose of 36 mg bid without routine coagulation monitoring. The patients receiving warfarin benefited from excellent control of warfarin-induced anticoagulation as revealed by their periodic INR determinations. Overall, patients were within the INR range 2.0 to 3.0 for 68% of the time.

Trough melagatran plasma concentrations, determined at 1, 12, and 24 months demonstrated stable concentrations over time.

Safety results

The overall incidence of AEs was high in this study not only reflecting a high level of compliance to protocol-required AE reporting, this being the basis of endpoint collection, but also reflecting the severity of the underlying disease, the long duration of the study and the elderly cohort. The treatment groups did not differ with respect to the number of patients with deaths, AEs, and serious adverse events (SAEs). More discontinuations of study treatment due to AEs (DAEs) occurred in the ximelagatran group, mainly due to the protocol-required withdrawal of patients who experienced elevations in ALAT, resulting in a longer mean exposure to study drug in the warfarin group. The total number of AEs was numerically greater in the warfarin group than the ximelagatran group (Table

S3). Numerical differences for AEs that occurred in >4% of either cohort span multiple system classes and are most notable for purpura, accident/injury, epistaxis, cardiac failure, all more frequent in the warfarin group, and hepatic enzymes increased more frequently in the ximelagatran group (Table S4).

Table S3 **Number (%) of patients who had an AE in any category by study period (safety population) (SPORTIF V)**

	N (%) of patients who had an AE in each category[a]					
	Pre-treatment		Ximelagatran 36 mg	Warfarin INR 2.0 to 3.0	During or after Follow-up	
Category of AEs	Ximelagatran N=1946	Warfarin N=1952	Ximelagatran N=1953	Warfarin N=1953	Ximelagatran N=1879	Warfarin N=1881
Any AE	225(11.6)	206(10.6)	1861(95.3)	1866(95.5)	1421(75.6)	1432(76.1)
Fatal SAE	0(0.0)	0(0.0)	33(1.7)	41(2.1)	83(4.4)	82(4.4)
Non-fatal SAE	19(1.0)	13(0.7)	600(30.7)	609(31.2)	296(15.8)	265(14.1)
DAE	0(0.0)	0(0.0)	354(18.1)	300(15.4)	0(0.0)	0(0.0)
Total number of AEs[b]						
Any AE[b]	295	278	12430	13674	4880	5197
SAEs[b]	25	16	1066	1162	591	563
DAEs[b]	0	0	376	341	0	0

[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 one occurrence of the event is counted.

AE Adverse event; SAE Serious adverse events; DAE Adverse event leading to discontinuation of a patient from study drug.

Table S4 **Number (%) of patients with the most commonly reported AEs during the study treatment period (safety population) (SPORTIF V)**

	Ximelagatran N=1953		Warfarin N=1953		Total N=3906	
Preferred term[a]	n	(%)	n	(%)	n	(%)
Total number of patients with AEs	1827	(93.5)	1834	(93.9)	3661	(93.7)
Respiratory infection	438	(22.4)	458	(23.5)	896	(22.9)

	Ximelagatran N=1953		Warfarin N=1953		Total N=3906	
Preferred term[a]	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Purpura	298	(15.3)	428	(21.9)	726	(18.6)
Accident and/or injury	314	(16.1)	381	(19.5)	695	(17.8)
Dizziness	327	(16.7)	312	(16.0)	639	(16.4)
Pain	276	(14.1)	320	(16.4)	596	(15.3)
Dyspnea	265	(13.6)	295	(15.1)	560	(14.4)
Diarrhea	240	(12.3)	242	(12.4)	482	(12.4)
Edema peripheral	207	(10.6)	247	(12.6)	454	(11.6)
Fatigue	229	(11.7)	222	(11.4)	451	(11.6)
Epistaxis	151	(7.7)	282	(14.4)	433	(11.1)
Chest pain	197	(10.1)	224	(11.5)	421	(10.8)
Back pain	177	(9.1)	218	(11.2)	395	(10.2)
Headache	187	(9.6)	185	(9.5)	372	(9.6)
Coughing	183	(9.4)	175	(9.0)	358	(9.2)
Arthralgia	166	(8.5)	163	(8.3)	329	(8.4)
Bronchitis	158	(8.1)	164	(8.4)	322	(8.2)
Nausea	144	(7.4)	160	(8.2)	304	(7.8)
Sinusitis	139	(7.1)	145	(7.4)	284	(7.3)
Rash	128	(6.6)	132	(6.8)	260	(6.7)
Urinary tract infection	128	(6.6)	130	(6.7)	258	(6.7)
Abdominal pain	108	(5.5)	137	(7.0)	245	(6.3)
Cardiac failure	95	(4.9)	144	(7.4)	239	(6.2)
Insomnia	107	(5.5)	116	(5.9)	223	(5.7)
Hematuria	109	(5.6)	105	(5.4)	214	(5.5)
Rhinitis	106	(5.4)	95	(4.9)	201	(5.1)
Dyspepsia	104	(5.3)	90	(4.6)	194	(5.0)
Anemia	82	(4.2)	106	(5.4)	188	(4.8)
Gout	88	(4.5)	95	(4.9)	183	(4.7)
Pneumonia	74	(3.8)	106	(5.4)	180	(4.6)
Tooth disorder	105	(5.4)	75	(3.8)	180	(4.6)
Flu-like disorder	82	(4.2)	97	(5.0)	179	(4.6)
Hyperglycemia	88	(4.5)	86	(4.4)	174	(4.5)
Constipation	59	(3.0)	110	(5.6)	169	(4.3)
Hypertension aggravated	62	(3.2)	90	(4.6)	152	(3.9)
Asthenia	72	(3.7)	78	(4.0)	150	(3.8)
Myalgia	61	(3.1)	79	(4.0)	140	(3.6)
Cellulitis skin	52	(2.7)	80	(4.1)	132	(3.4)
Hypercholesterolemia	52	(2.7)	86	(4.4)	138	(3.5)
Hepatic enzymes increased	90	(4.6)	23	(1.2)	113	(2.9)

[a] This table uses a cut-off of 4%. A patient is counted once per preferred term if he/she had 1 or more events with that term. AEs are sorted by decreasing order of frequency as summarized over both treatment groups.

AE Adverse event.

SPORTIF V showed numerically lower but statistically similar major bleeding rates for ximelagatran (2.4%/year) versus warfarin (3.1%/year) and statistically significant reduced total bleeding rates (major and minor) with ximelagatran (37%/year) compared to warfarin (47%/year) ($p<0.0001$).

Six percent of patients taking ximelagatran in SPORTIF V demonstrated serum ALAT concentrations above 3x ULN at least once during the study, compared with 0.8% of warfarin patients ($p<0.0001$). Thorough review of the SPORTIF V database did not disclose any prognostic factor for ALAT >3x ULN.

Two patients who developed large elevations in ALAT subsequently died of massive gastrointestinal hemorrhage. One patient had documented liver failure and a liver biopsy consistent with drug-induced hepatotoxicity. He died following erosion of a large duodenal ulcer into the pancreas; autopsy revealed hepatocellular regeneration. The other patient died of a massive gastrointestinal hemorrhage 17 days after a routine laboratory sample returned ALAT of 4.5x ULN and shortly after presenting with hemoglobin of 4 g/dL and hypovolemic shock.

Plasma CCK and serial CT scan data do not support the hypothesis that ximelagatran exerts a trophic effect on the pancreas. Pancreatic-related AEs were few and numerically similar between the treatment groups.

Ximelagatran treated patients in SPORTIF V did not exhibit clinical rebound when they stopped taking study drug. One ximelagatran patient and no warfarin patients had a stroke during drug transition. The similar numbers of bleeding events and AEs during or after the follow-up period in the treatment groups indicate no additional risk in switching from ximelagatran to other anticoagulants.

Reference:

Halperin JL, Albers GW, Diener HC, Frison L, Grind M, Nevinson M, Partridge S, Horrow J, Olsson SB, Petersen P, Vahanian A. Executive Steering Committee on behalf of the SPORTIF V Investigators. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: A randomized trial. JAMA 2005;293(6):690-8

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