Drug product:		SYNOPSIS	
Drug substance(s):	Ximelagatran		
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Long-Term Treatment with the Oral Direct Thrombin Inhibitor H 376/95, Compared to Warfarin, as Stroke Prophylaxis in Patients with Atrial Fibrillation. An Open 10-Year Follow-up Study. Final report at 7 years (Supplement to 5-year interim analysis report)

SPORTIF IV (SH-TPA-0004) is an open long-term follow-up study of patients who participated in SPORTIF II (SH-TPA-0002). Information on both studies is combined in this report.

All clinical studies with ximelagatran (including SPORTIF IV) were stopped following an adverse event report of serious liver injury in the EXTEND clinical trial, reviewed in the context of the hepatic findings previously observed during clinical trials of chronic use. The AE report indicated a potential risk of severe liver injury, with an observation of rapid onset of signs and symptoms in the weeks following the end of the 35 days treatment. This specific observation had not previously been made in relation to ximelagatran, and indicated that regular liver function monitoring might not mitigate the possible risk. Therefore, in the interests of patient safety, AstraZeneca took the precautionary measure of withdrawing Exanta® from the market and discontinuing all ongoing clinical studies with ximelagatran. This decision was taken on 14 February 2006.

Study centres

This was an international, multicentre study carried out in 23 centres in Belgium, Czech Republic, Denmark, Finland, Norway, Poland, Sweden, UK and the USA (also France and Germany in SPORTIF II).

Publications

Bååthe S, Hamren B, Karlson MO, Wollbratt, M, Grind M, Eriksson UG. Population pharmacokinetics of melagatran, the active form of the oral direct thrombin inhibitor ximelagatran, in atrial fibrillation patients receiving long-term anticoagulation therapy in practice. Clin Pharmacokinetics 2006;45(8):803-19.

Eriksson UG, Bååthe S, Hamren B, Wollbratt M, Wolzt M, Grind M. Predictable pharmacokinetics of ximelagatran, an oral direct thrombin inhibitor, in nonvalvular atrial fibrillation patients receiving long-term treatment. Pathophysiol Haemost Thromb 2002;32(Suppl 2):56.

Grind M, Hamren, B, Bååthe S, Wollbratt M, Eriksson UG. Pharmacokinetics of the oral direct thrombin inhibitor ximelagatran in patients with nonvalvular atrial fibrillation receiving long-term treatment: a population analysis by nonlinear mixed effect modeling. Clin Pharmacol Ther 2002; 71(2):31.

Olsson SB, Petersen P, on behalf of the SPORTIF II and IV Investigators. Ximelagatran: a long-term oral direct thrombin inhibitor for stroke and systemic embolism prevention nonvalvular atrial fibrillation patients. Eur Heart J 2002;23 Abstr. Suppl (Aug/Sept):239.

Petersen P on behalf of the SPORTIF II and IV Investigators. A long-term follow-up of ximelagatran as an oral anticoagulant for the prevention of stroke and systemic embolism in patients with atrial fibrillation. Blood 2001;98(11):706a.

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Petersen P, Grind M, Adler J for the SPORTIF II Investigators. Ximelagatran Versus Warfarin for Stroke Prevention in Patients with Nonvalvular Atrial Fibrillation. SPORTIF II: A Dose-Guiding, Tolerability and Safety Study. J Am Coll Cardiol 2003;41:1445-1451.

Study dates		**Phase of development**
First subject enrolled	9 August 1999	Therapeutic exploratory (II)
Last subject completed	3 April 2006	

The study was stopped prematurely; following an adverse event report of serious liver injury in the EXTEND clinical trial AstraZeneca took the precautionary measure of closing all

clinical trials, and on 14 February 2006 investigators were asked to contact all patients and stop study treatment within one week.

Objectives

The primary objective of SPORTIF II was to evaluate tolerability of 3 different doses of ximelagatran (H 376/95) compared with warfarin during 12 weeks' treatment in atrial fibrillation patients with a moderate increased risk for stroke. The primary variable was the number of adverse events (AEs), with special regard to bleeding and thromboembolic events.

The primary objective of SPORTIF IV was to evaluate tolerability of long-term treatment with ximelagatran (H 376/95) compared to warfarin. The primary variable was the number of adverse events, with special regard to bleeding, thromboembolic events and discontinuation of treatment.

Secondary objectives (SPORTIF II only) were to study the pharmacokinetics of ximelagatran in the patient population, and to test the feasibility of the study design to optimise the dose of the large Phase III trials.

Study design

SPORTIF II was a multicentre, randomised, parallel group, dose-guiding study in patients with nonvalvular atrial fibrillation (AF); patients were randomised to receive either ximelagatran (20, 40 or 60 mg bid in a double-blinded fashion), or warfarin (aiming for an International Normalised Ratio for Prothrombin Time (INR) of 2.0-3.0). SPORTIF IV was a multicentre, open-label, extension study of SPORTIF II to compare the long-term safety and tolerability of ximelagatran 36 mg bid (initially 40 mg bid) with warfarin (aiming for an INR of 2.0 - 3.0) in patients completing SPORTIF II.

Target subject population and sample size

Eligible patients aged at least 18 years; weight 50 - 120 kg; history of chronic or intermittent nonvalvular atrial fibrillation, verified by at least 2 ECG readings; and at least one of the following risk factors for stroke: history of hypertension, age ≥65 years, previous cerebral ischaemic attack (stroke or transient ischaemic attack, TIA), previous systemic embolism, left ventricular dysfunction, diabetes mellitus or coronary artery disease. Patients completing SPORTIF II Visits 1 to 7 were eligible to participate in SPORTIF IV.

Patients were excluded from the study if they had stroke and/or systemic embolism within the previous 2 years; AF secondary to other reversible disorders eg, thyrotoxicosis; mechanical heart valves; diagnosis of left ventricular aneurysm or atrial myxoma; myocardial infarction, CABG or PTCA within the previous 3 months; continuous NSAID treatment other than acetylsalicylic acid (ASA) ≤160 mg daily; treatment with fibrinolytic drugs within one week; contraindications for warfarin treatment; conditions associated with increased risk of bleeding; hypertension; renal impairment; known active liver disease or liver insufficiency; anaemia; platelet count $<100x10^9$/L; pregnant or lactating; other serious diseases that give a calculated

life survival less than 24 months; planned cardioversion or surgery during the study, or history of rheumatic valvular disease.

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

Initially ximelagatran tablets 20 mg, Batch numbers H 1309-02-01-01 & H 1309-02-01-02, dosage 40 mg bid. Replaced by proposed commercial formulation: ximelagatran tablets 36 mg, Batch numbers H 1384-02-01-01/03/05/06/09/11/14/15/17/18; H 1384-03-02-01. Dosage: 36 mg bid.

Warfarin tablets, administered according to hospital routines aiming for an INR of 2.0-3.0. Batch numbers: H 0724-02-01-09/10/14, H 1441-01-02-01/04/06, H 1432-01-01-04, H 1432-02-02-05/06, H 1433-03-02-01, 100 41 284, 101 26 182, 0055 699, AM-259, AC 4-1, BL 1-1, ZL 8-1, AI 7-2, ZM 9-2, AI 9-2, CB 1-2, BL 12-4, H 0724-02-01-16, H 0724-02-01-17, H 1441-01-02-07, H 1432-02-02-07, H 0724-03-01-04, H 1432-01-01-05, H 1432-03-01-03, H 1433-05-01-03.

Duration of treatment

Study treatment was planned to continue for up to 10 years, but the study was stopped prematurely. This report covers the period of approximately 7 years until study closure (6 years, 9 months, including SPORTIF II).

Criteria for evaluation (main variables)

Primary variable: number of adverse events, with special regard to bleeding, thromboembolic events and discontinuation of treatment. All suspected stroke/TIA events were independently adjudicated by a blinded Clinical Event Adjudication Committee (CEAC). CEAC opinion superseded investigator opinion.

Statistical methods

The safety and tolerability of ximelagatran 36 mg bid during long-term treatment in patients with atrial fibrillation was assessed exploratively with warfarin as a reference. The baseline for all analyses is Visit 1 in SPORTIF II; therefore the SPORTIF IV Visit 1 is referred to as 3 months' treatment. Hence all data presented in this report are the combined SPORTIF II and SPORTIF IV datasets. The baseline for the adverse event analysis in this report was the date of first dose in SPORTIF II.

Estimates of proportions for the occurrences of minor and major bleeding, thromboembolic events and discontinuation of treatment during time since start of treatment within groups and differences in proportions between groups with 95% confidence intervals are given. As the number of dropouts was expected to be substantial due to the long treatment period, these proportions were estimated using life table analysis. Patients dropping out from the study for reasons other than adverse events or thromboembolic events were treated as censored at the time of withdrawal, except for the analysis of proportions of discontinuation of treatment, where they have been included as failures. Estimated cumulative curves are also presented.

Plasma concentrations and pharmacokinetic parameters of melagatran, APTT and ECT were described with descriptive statistics and, where appropriate, depicted graphically versus time since last intake of study drug and/or achieved plasma concentrations of melagatran.

Laboratory variables, blood pressure, heart rate and ECG recordings were assessed using descriptive statistics.

Adverse event data were presented descriptively. Analyses and evaluation of safety were performed on the safety population, defined as all patients who received at least one dose of (randomised) investigational product, and for whom post-dose data were available.

Subject population

In total, 254 patients randomised into SPORTIF II received treatment (187 ximelagatran; 67 warfarin). Of the 207 patients who completed SPORTIF II, 167 patients (125 ximelagatran, 42 warfarin) continued in the follow-up study SPORTIF IV, of whom 101 patients (75 ximelagatran, 26 warfarin) completed 5 years treatment and 87 completed the study (69 ximelagatran, 18 warfarin) (Table S1). The total exposure was 615 patient years on ximelagatran and 206.4 patient years on warfarin.

There were more male than female patients (61% *vs* 39%), and 72% of patients were aged ≥65 years at the start of the study. Overall, the baseline characteristics of the patient population in this study resembled those of the target population in terms of current medical histories, presence of other risk factors for stroke/TIA in addition to AF, and concomitant medication usage. The majority of patients (77%) had 2 or more risk factors in addition to AF, indicating a moderate-to-high risk for stroke/TIA.

Of the patients originally randomised into SPORTIF II, 87 remained at study closure (69 on ximelagatran and 18 on warfarin). All 101 patients who completed the 5-year follow-up continued in the study. Fourteen patients (6 on ximelagatran and 8 on warfarin) discontinued treatment during the 5-7 year period, of whom 8 died (5 on ximelagatran and 3 on warfarin). The actual maximum individual time in study was 6 years, 9 months, 13 days for ximelagatran and 6 years, 9 months, 19 days for warfarin.

When patient characteristics at 5 years for the 101 patients continuing beyond 5 years were compared with baseline (entry to SPORTIF II), mean age had increased (as expected, from 66.3 years to 71.3 years); mean bodyweight decreased (from 87.2 kg to 86.3 kg), and mean BMI decreased (from 29.7 kg/m^2 to 29.4 kg/m^2). Mean calculated CrCL increased slightly (from 74.7 mL/min to 79.2 mL/min). The ximelagatran and warfarin groups remained comparable for these patient characteristics.

Table S1 Patient population and disposition (SPORTIF II/IV)

	Ximelagatran 36 mg bid	Warfarin	Total
No. received study drug	187	67	254
Males / Females	117 / 70	37 / 30	154 / 100
Mean age (range)	69.4 (39 – 95)	70 (44 – 93)	69.5 (39 – 95)
No. completed 5-year follow-up	75	26	101
No. completed study	69	18	87
[a]No. (%) premature discontinuations	*87 (46.5%)*	*37 (55.2%)*	*124 (48.8%)*

a Another 40 patients (28 on ximelagatran and 12 on warfarin) completed SPORTIF II but did not participate in SPORTIF IV

Efficacy results

Three CEAC-adjudicated TIAs (one ximelagatran, 2 warfarin) were reported during the first 3 months of the study (ie, during SPORTIF II); no further TIAs were reported during SPORTIF IV. CEAC-adjudicated strokes were reported in 7 ximelagatran patients (4 non-fatal ischaemic and 3 fatal haemorrhagic), and in 4 warfarin patients (one non-fatal ischaemic and 3 haemorrhagic, 2 of which were fatal). Estimated event rates (%/patient year, %/py) for stroke alone were 1.13%/py for ximelagatran patients and 1.93%/py for warfarin patients; the event rate difference was not statistically significant. One patient in the ximelagatran group experienced an additional thromboembolic event (deep vein thrombosis). Over the complete study period (SPORTIF II and SPORTIF IV) estimated event rates for stroke/TIA/thromboembolic event were 1.46%/py for ximelagatran patients and 2.98%/py for warfarin patients; the event rate difference of -1.52% was not statistically significant (p=0.221). Estimated event rates of stroke alone were 1.13%/py for ximelagatran patients and 1.93%/py for warfarin patients; the event rate difference was not statistically significant. The efficacy results at the end of the study were consistent with those reported at 5 years.

Pharmacokinetic and Pharmacodynamic results

Ximelagatran is rapidly absorbed and metabolised to melagatran via the 2 intermediate metabolites H 415/04 and H 338/57. The concentrations of the parent drug ximelagatran and the intermediate metabolites were low compared to the main metabolite melagatran. The pharmacokinetics of melagatran in AF patients are predictable and remain constant over time. The plasma concentrations observed during SPORTIF II were similar to those observed during the 5-year follow-up study, thus indicating no accumulation has taken place during the treatment period. The maximum plasma concentration of melagatran was observed between 1.5 and 6 hours after dosing, and the mean half-life was 5.1 hours. The variability (CV%) in the pharmacokinetic parameters AUC_{τ} and C_{max} was 56% and 38%, respectively. Clearance was positively correlated to renal function and volume of distribution to body weight. Concomitant medication with the most common drugs (ie, digoxin, ACE inhibitors, organic nitrates, loop diuretics, β-blocking agents, verapamil, dihydropyridine derivatives) in the

population had no impact on melagatran pharmacokinetics. Population PK analysis was performed on the pooled SPORTIF II, IV and VI dataset.

The results of coagulation tests are fully summarised in the 5-year report. The majority of warfarin patients were mostly within the recommended INR range of 2.0-3.0 during the 5-year follow-up period, with INR values between 2.0-3.0 for 64.3% of the time, and between 1.8-3.2 for 81.5% of the time. Mean INR values ranged between 2.3-2.6, and occasionally, when fewer patients were available, the value was more variable. Similar prolongations were observed for both ECT and APTT during treatment with ximelagatran, showing that the effect was consistent over time. ECT followed the plasma melagatran concentration curve well.

Safety results

A summary of all adverse events reported during treatment in SPORTIF II/IV is presented in Table S2.

Table S2 Summary of patients (n=254) who had an AE in any category, during treatment (Safety population, SPORTIF II/IV)

Category of adverse events ximelagatran [a]	Ximelagatran (n=187)		Warfarin (n=67)	
Any adverse events	160	(85.6)	56	(83.6)
Serious AEs	83	(44.4)	30	(44.8)
Serious AEs leading to death [b]	15	(8)	5	(7.5)
Serious AEs not leading to death	75	(40.1)	27	(40.3)
Discontinuation of study treatment due to AEs	46	(24.6)	16	(23.9)
Severe AEs	57	(30.5)	21	(31.3)

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 This table includes only deaths during the treatment period. The number of deaths in Table S4 includes deaths occurring during treatment and after treatment discontinuation.

Ximelagatran was generally well tolerated compared to warfarin: 86% of the patients on ximelagatran and 84% patients on warfarin reported at least one adverse event (AE) at any time during SPORTIF II/IV, with 46 (24.6%) patients discontinuing ximelagatran and 16 (23.9%) discontinuing warfarin because of AEs. There were 21 deaths (3.4%/py) in the ximelagatran group and 6 deaths (2.9%/py) in the warfarin group during SPORTIF II/IV; the difference did not reach statistical significance (p=0.825). All deaths but 4 (2 exceptions in each group) were attributable to cardiovascular disease or malignancy, which could be expected in an elderly population with atrial fibrillation.

Non-fatal SAEs were reported by 75 (40.1%) ximelagatran and 27 (40.3%) warfarin patients during treatment. The most commonly reported non-fatal SAEs in the ximelagatran group were cardiac failure (4.8%) and angina pectoris (4.3%), while cardiac failure (7.5%) and cerebrovascular disorder (the preferred term for stroke or TIA) (6%) were the most common SAEs in the warfarin group. The most common DAE in both groups was cerebrovascular disorder (preferred term for stroke/TIA), with 6 (3.2%) and 3 (4.5%) discontinuations in the

ximelagatran and warfarin groups, respectively. No specific AE was the reason for discontinuation in the ximelagatran group.

Table S3 below summarises the most frequently reported AEs, by preferred term.

Table S3 Number (%) of patients with the most commonly reported adverse events during treatment, (Safety Population); SPORTIF II/IV

The 20 most common AEs, by preferred term, sorted by decreasing order of frequency, as summarised over both treatment groups.

Preferred term	Ximelagatran (n=187)		Warfarin (n=67)	
Haematuria	29	(15.5)	17	(25.4)
Accident and/or injury	18	(9.6)	8	(11.9)
Respiratory infection	21	(11.2)	5	(7.5)
Purpura	16	(8.6)	8	(11.9)
Cardiac failure	16	(8.6)	7	(10.4)
Back pain	18	(9.6)	3	(4.5)
Bronchitis	14	(7.5)	6	(9)
Dizziness	12	(6.4)	6	(9)
Diarrhoea	12	(6.4)	5	(7.5)
Oedema peripheral	11	(5.9)	5	(7.5)
Epistaxis	10	(5.3)	6	(9)
Hypertension	10	(5.3)	5	(7.5)
Sgpt increased	14	(7.5)	1	(1.5)
Hyperglycaemia	9	(4.8)	6	(9)
Arthralgia	11	(5.9)	4	(6)
Headache	10	(5.3)	4	(6)
Bradycardia	12	(6.4)	2	(3)
Melaena	10	(5.3)	4	(6)
Dyspnoea	9	(4.8)	5	(7.5)
Pain	12	(6.4)	2	(3)

Bleeding events were less common in the ximelagatran group than in the warfarin group. Major bleeds were reported by 5 ximelagatran patients (0.8%/py) and 4 warfarin patients (2.0%/py). Minor bleeding outcome rates were 5.7%/py (31 patients) and 8.6 %/py (14 patients), in the ximelagatran and warfarin groups, respectively.

Thirteen ximelagatran patients had >3xULN ALAT levels at any time in SPORTIF II/IV, of whom 8 patients reached >3xULN ALAT during the first 3 months of treatment. Eleven of the ALAT elevations occurred in the first year of exposure; 2 patients had an elevation during the second and third years, respectively; the presence of possible confounding factors in both cases made a causality assessment uncertain or unlikely. ALAT levels normalised for all 13 patients, of whom 8 normalised during continued ximelagatran treatment; the remaining 5 patients normalised after treatment discontinuation. No patient in the warfarin group had ALAT>3xULN. Hepatobiliary adverse events were noted at a higher incidence in the ximelagatran group (15.5% ximelagatran vs 11.9% warfarin), largely arising from the reporting of elevated liver enzymes as an AE.

AEs related to coronary artery disease were reported during treatment more frequently in the ximelagatran group (19 patients, 10.2%) than in the warfarin group (3 patients, 4.5%). These were mainly angina pectoris; myocardial infarction was reported by one patient in each treatment group. Of the 19 ximelagatran patients who reported a CAD event, 15 had a history of CAD. No conclusion on the incidence of CAD events can be drawn from the small differences in frequency of events in this study.

Other reported AEs and SAEs could reasonably be attributed more to the underlying diseases and/or the old age of the study population of patients with chronic atrial fibrillation. No notable differences between the 2 treatment groups were observed. No late onset adverse reactions have been identified.

The occurrence of a positive U-Hb test was similar between the 2 treatment groups, while a slightly higher proportion of ximelagatran patients had positive tests for F-Hb. However AEs of haematuria and melaena were more frequently reported in the warfarin group: haematuria was reported as an adverse event for 15.5% ximelagatran and 25.4% warfarin patients, and melaena was reported as an AE for 5.3% ximelagatran and 6% warfarin patients. Although it cannot be excluded that the study drugs contributed to the occurrence of positive U-Hb and F-Hb tests, the overall number of positive tests was so small that the same result could also have been obtained in an elderly population without anticoagulant treatment. Except for liver transaminase elevations, there were no deviations in clinical laboratory results suspected to be causally related to ximelagatran, after 7 years of exposure.

Table S4 Summary of clinical events during SPORTIF II/IV. Number of patients with stroke/TIA (adjudicated by CEAC) and/or thromboembolic events (ITT population)

	Ximelagatran (n=187)			Warfarin (n=67)		
	0-5yr	**5-7yr**	**0-7yr**	**0-5yr**	**5-7yr**	**0-7yr**
Primary objective:						
Stroke/TIA/thrombo-embolic events (events/patient years)	9/491 (1.8%)	0/124 (0.0%)	9/615 (1.5%)	5/166 (3.0%)	1/35 (2.9%)	6/201 (3.0%)
TIA	1	0	1	2	0	2
Ischaemic stroke	4	0	4	1	0	1
Haemorrhagic stroke	3 (3)[a]	0	3 (3)	2 (2)	1	3 (2)
Other embolic events	1	0	1	0	0	0
Total number of events	9 (3)[a]	0	9 (3)	5 (2)	1	6 (2)
Deaths (events/patient years)[b]	16/490 (3.3%)	5/129 (3.9%)	21/619 (3.4%)	3/170 (1.8%)	3/38 (7.9%)	6/208 (2.9%)
Major bleeds (events/patient years)	4/490 (0.8%)	1/123 (0.8%)	5/614 (0.8%)	4/165 (2.4%)	0/34 (0.0%)	4/199 (2.0%)
Minor bleed (events/patient years)	25/447 (5.6%)	6/96 (6.2%)	31/543 (5.7%)	13/149 (8.7%)	1/14 (7.1%)	14/163 (8.6%)
Myocardial infarction	0	1	1	1	0	1

a Number in parentheses is the number of fatal cases.
b Deaths occurring during treatment and post-treatment follow-up.

Date of the report

8 December 2006