AstraZeneca

SH-TPC-0001

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Exanta™

ACTIVE INGREDIENT: Ximelagatran (H 376/95)

Trial title (number): Efficacy and Safety of H 376/95 (ximelagatran), in Combination with Aspirin, in Patients with a Recent Acute Coronary Syndrome with Elevated Biochemical Markers of Myocardial Damage. A Multicentre, Double-Blind, Controlled, Dose-Guiding Study (ESTEEM)

Developmental phase: Therapeutic exploratory (II)
First subject recruited:31 January 2001
Last subject completed:20 September 2002
Approval date:16 October 2003

OBJECTIVES

Primary:

To investigate the relationship between the dose of ximelagatran (H 376/95) and the frequency of the composite clinical endpoint of death (all cause mortality), myocardial infarction (MI) and severe recurrent ischaemia (SRI) during 6 months' treatment in patients with a recent history of myocardial damage.

Secondary:

1. To investigate the relationship between the dose of ximelagatran and the frequency of the composite clinical endpoint of cardiovascular death, MI, ischaemic stroke, and severe recurrent ischaemia during 6 months' treatment.

2. To investigate the relationship between the dose of ximelagatran and the frequency of the composite clinical endpoint of death (all cause mortality) and MI during 6 months' treatment.

3. To assess the safety and tolerability of 4 doses of ximelagatran in combination with 160 mg aspirin (acetylsalicylic acid; ASA), compared to 160 mg ASA with special regard to bleeding during 6 months' treatment.

Tertiary:

1. To investigate the relationship between the dose of ximelagatran and the incidence of the composite clinical endpoint of death (all cause mortality), MI and unscheduled[a] coronary revascularisation during 6 months' treatment.
2. To investigate the relationship between the dose of ximelagatran and the incidence of the composite clinical endpoint of death (all cause mortality) and hospitalisation during 6 months' treatment.
3. To investigate the relationship between the dose of ximelagatran and the incidence of death (all cause mortality) during 6 months' treatment.
4. To investigate the relationship between the dose of ximelagatran and the incidence of cardiovascular death during 6 months' treatment.

a Coronary revascularisation was altered to unscheduled coronary revascularisation following Protocol Amendment 02.

METHODS

Study design

This was a multicentre, multinational, double-blind, placebo controlled, parallel group, dose-guiding study comparing the efficacy and safety of 4 doses of ximelagatran versus placebo when given to aspirin-treated patients during a 6-month period following a recent Acute Coronary Syndrome (ACS) with elevated biochemical markers of myocardial damage.

An independent Clinical Event Adjudication Committee (CEAC) reviewed the following efficacy and safety endpoint events: death, myocardial infarction, severe recurrent ischaemia, stroke and major bleeding.

Target patient population and sample size

It was planned that approximately 1800 eligible patients would be randomised into this study. Eligible patients were to be at least 18 years of age and have ACS, with associated elevated biochemical markers of myocardial damage within the previous 14 days. In addition, patients had to present with at least one of the following ACS risk factors: age ≥ 65 years; diabetes mellitus; additional previous MI (excluding index ACS); multivessel disease (significant lesions in at least 2 major coronary vessels) demonstrated by angiography; previous ischaemic stroke (confirmed by CT and/or MRI scan); peripheral arterial occlusive disease (PAOD); symptomatic congestive heart failure or left ventricular ejection fraction (LVEF) <40%; new or previously unknown left bundle branch block; new or previously unknown ST-segment depression ≥ 0.1 mV in any electrocardiogram (ECG) associated with the index ACS; or a history of hypertension (added following Protocol Amendment 02).

Patients were to be excluded from the study if any of the following criteria applied. Patients in whom it was likely that a therapeutic coronary artery intervention (PCI with or without stent placement, or CABG) would take place within 60 days of randomisation. This criterion was incorporated in Amendment 02. Prior to Amendment 02, if the above-specified procedures were planned within 6 months following randomisation, patients were to be excluded. Patients were to be excluded if PCI had been undertaken within 4 months of the index ACS. This criterion was included in Amendment 02. Prior to Amendment 02, patients were to be excluded if PCI had been undertaken within 6 months of the index ACS. Other exclusion criteria included an angiogram performed after the index event showing normal coronary arteries. A stroke within 30 days prior to receiving study medication. Concomitant treatment with oral anticoagulant or oral platelet inhibitory drugs other than ximelagatran and study ASA. Contraindications for ximelagatran/melagatran or ASA treatment. Increased risk of bleeding. Renal impairment (if S-creatinine >ULN, calculated creatinine clearance <30 mL/min). Known active liver disease or persistent elevation of hepatic enzymes (≥ 2xULN), prior to the Index ACS.

A total of 1800 patients (600 in the placebo group and 300 in each ximelagatran dose group) were estimated to be required for 81.3% power to reject the hypothesis of no relationship between dose and response.

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

The following products were administered: ximelagatran 24 mg, 36 mg, 48 mg or 60 mg twice daily (bid); and placebo bid. All treatments were given in combination with ASA 160 mg tablets once daily (od). The ASA dose could be reduced to 75 mg od for any patient experiencing side effects that were judged by the investigator to be possibly related to the ASA treatment. Doses of ximelagatran and placebo were given in a double-blinded manner.

Batch numbers:

Ximelagatran, 24 mg: H 1360-03-01-09, H 1360-03-01-10; 36 mg: H 1384-02-01-08, H 1384-02-01-13, 48 mg: H 1445-01-01-02;
Placebo: H 1431-01-01-05, H 1444-01-01-03, H 1444-01-01-05, H 1444-01-01-06, H 1444-01-01-07, H 1446-01-01-01, H 1446-01-01-02;
ASA, 75 mg: H 1063-03-01-01, H 1063-03-01-02, H 1063-03-01-03; ASA 160 mg: H 1485-01-01-03, H 1485-01-01-04, H 1485-01-01-05, H 1485-01-01-07, H 1485-01-01-08.

Duration of treatment

Six-month treatment period.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable: time to first occurrence of the composite clinical endpoint of:
  - death (all cause mortality), MI and severe recurrent ischaemia.

- Secondary variables: time to first occurrence of the composite clinical endpoint of:
  - cardiovascular death, MI, ischaemic stroke and severe recurrent ischaemia
  - death (all cause mortality) and MI.

- Tertiary variables: time to first occurrence of the composite clinical endpoint of:
  - death (all cause mortality), MI and unscheduled[a] coronary revascularisation
  - death (all cause mortality) and hospitalisation
  - death (all cause mortality)
  - cardiovascular death.

- Main pharmacokinetic variables of melagatran: oral clearance and area under the plasma concentration time curve (AUC).

a Coronary revascularisation was altered to unscheduled coronary revascularisation following Protocol Amendment 02.

Safety
Adverse events; bleeding assessments; laboratory assessments, urinalysis and faeces analysis; ECG; vital signs; and physical examination.

Statistical methods

Unless otherwise stated, all statistical analyses have been based on the Intention To Treat (ITT) approach. In this approach all patients receiving at least one dose of study medication were included until the end of the study, irrespective of their protocol adherence. Patients were to be excluded from the study if likely to undergo (scheduled) PCI/ CABG within 60 days of randomisation. If an unscheduled PCI/ CABG were to be undertaken then the procedure would be deemed an endpoint, triggered by a worsening of underlying disease, eg, an occurrence of severe recurrent ischaemia. A patient would be censored at time of PCI/ CABG intervention.

The primary objective was addressed using a Cox-regression model with time from randomisation to the first occurrence of the composite clinical endpoint as response variable and log-transformed dose as explanatory variable. Patients undergoing a PCI/CABG that was scheduled prior to randomisation were censored at the date of the intervention . For computational reasons a dose of 1 mg has been used for the control group ie, zero on the log scale. If the estimated regression coefficient for log-transformed dose of ximelagatran was statistically significantly different from zero (adopting a 2-sided 5% significance level) this has been taken as evidence of a relationship between dose of ximelagatran and the frequency of the composite clinical endpoint. Pairwise comparisons between the treatment groups have also been performed.

At each review of the study, the DSMB was able to confirm to the Executive Committee and the sponsor that there were no safety issues and the study could progress as per protocol.

RESULTS

Patient population

In total 1900 patients were randomised with 1883 patients (1245 ximelagatran, 638 placebo) taking at least one dose of study drug. Seventeen patients were randomised but did not receive study drug (see Table S1). The cohort in this study comprised patients with recent ACS in accordance with published criteria (The Joint European Society of Cardiology/ American College of Cardiology 2000). MI patients with ST-segment elevation (STEMI) and non-STEMI patients were included.

The patients in the ITT and safety populations were predominantly Caucasian (99%), 69% male and 31% female with a mean age 67.0 (range 27 to 93 years). Thirty-seven percent were non-smokers, 34% were previous smokers and 29% were either occasional or habitual smokers. Index ACS events were diagnosed as unstable angina pectoris for 111 (6%) patients, as non-Q-wave MI for 816 (43%) patients and as Q-wave MI for 951 (51%) patients. The mean number of days between the index event and randomisation was 7 days. Overall, the treatment groups were balanced for demographic and baseline characteristics, and representative of a moderate to high-risk population of patients with ACS.

Of the 1883 patients who received study drug, 686 (36%) patients discontinued study drug prematurely. The proportion of patients in the 24 mg ximelagatran group and placebo group were similar, 34% and 32%, respectively. The most common reasons for premature discontinuation of study drug were endpoint events (315 patients), adverse events other than endpoint events (229 patients) and consent withdrawal (92 patients).

Table S1 Patient population and disposition

		Ximelagatran				Placebo
		24 mg	36 mg	48 mg	60 mg	
Population						
N randomised (N planned)		309(300)	309(300)	315(300)	326(300)	641(600)
N received at least one dose[a]		307	303	311	324	638
Baseline characteristics						
Sex (%)	Male	210(68%)	205(68%)	211(68%)	222(69%)	442(69%)
	Female	97(32%)	98(32%)	100(32%)	102(31%)	196(31%)
Age (years)	Mean (SD)	67.0(11.7)	67.1(10.7)	66.7(10.9)	66.2(11.5)	67.5(10.9)
	Range (years)	38 - 91	31 - 88	27 - 91	29 - 89	30 - 93
Race (%)	Caucasian	304(99%)	300(99%)	308(99%)	323(100%)	634(99%)
	Black	1(0%)	2(1%)	1(0%)	1(0%)	1(0%)
	Oriental	1(0%)	1(0%)	2(1%)		3(0%)
	Other	1(0%)				
Medical	Previous MI	65(21%)	67(22%)	64(21%)	76(23%)	142(22%)
History	Previous stroke	9(3%)	13(4%)	11(4%)	14(4%)	34(5%)
	PCI	14(5%)	15(5%)	10(3%)	19(6%)	28(4%)
	CABG	18(6%)	13(4%)	16(5%)	21(6%)	51(8%)
	Angina Pectoris	98(32%)	107(35%)	102(33%)	113(35%)	212(33%)
	Hypertension	160(52%)	171(56%)	149(48%)	174(54%)	339(53%)
	Hypercholesterol-aemia	157(51%)	169(56%)	152(49%)	179(55%)	330(52%)
	Diabetes Mellitus	67(22%)	69(23%)	73(23%)	72(22%)	137(21%)
	Smokers[b]	86(22%)	87(29%)	92(30%)	99(30%)	177(28%)
ECG:	ST-elevation	213(69%)	195(65%)	203(66%)	207(64%)	412(65%)
Index Event	ST-depression[c]	54(18%)	67(22%)	64(21%)	63(20%)	136(21%)
	T-wave inversion[d]	31(10%)	20(7%)	31(10%)	40(12%)	58(9%)
	UAP (unstable angina pectoris)	20(7%)	21(7%)	16(5%)	16(5%)	38(6%)
	Non Q-wave MI	139(45%)	114(38%)	140(45%)	140(43%)	283(4%)
	Q-wave MI	147(48%)	167 (55%)	154(50%)	168(52%)	315(49%)
Days-IE[e]	-	7	7	7	7	7
Days-IE[e]	(range)	(3-13)	(3-13)	(3-12)	(3-13)	(3-12)
Disposition						
N (%) of:	Completed	274(89%)	270(87%)	270(86%)	273(84%)	563(88%)
	Discontinued	35(11%)	39(13%)	45(14%)	53(16%)	78(12%)
N analysed for safety		307	303	311	324	638
N analysed for efficacy (ITT)		307	303	311	324	638
N analysed for efficacy (OT)		307	303	311	324	638

a 1900 patients were randomised to the study but only 1883 took at least one dose of study treatment and had at least one data point after dosing

b Smokers = occasional plus habitual smokers,

c ST-depression without elevation,

d T- wave inversion without ST-changes

e Days-IE: the mean number of days between index event and randomisation

n= number, ITT= Intention To Treat - the population includes all randomised patients receiving at least one dose of study drug, ir respective of their protocol adherence.

OT= On-Treatment - The OT population included patients in the ITT population but only their time on study drug was used for analysis. The "On-Treatment" period started at the first dose intake and included the period to 48 hours following the last dose intake

Efficacy and pharmacokinetic results

Primary variable

The study fulfilled its primary objectives, showing a statistically significant dose-response in the positive direction for ximelagatran. This positive dose-response was

driven by the efficacy of all ximelagatran groups combined, not by differences between dose levels of ximelagatran.

Oral ximelagatran in combination with ASA was superior to ASA alone (placebo) in reducing the composite endpoint of death, non-fatal MI and SRI as demonstrated by the primary dose-response regression analysis including placebo as dose zero (p=0.0357; Figure S1). There was no evident difference in efficacy among the individual ximelagatran doses, suggesting a flat dose-response in the dose range studied, see Figure S2. The cumulative risk at 6 months for the primary endpoint was 12.7% for the combined ximelagatran groups (range 12.1–13.7%), compared with 16.3% in the placebo group, hazard ratio 0.76 (95% CI 0.59, 0.98; p=0.0317; Figure S3). Consistent results were observed for the on-treatment analysis with a hazard ratio of 0.68 (95% CI 0.51, 0.89; p=0.0052) for the primary endpoint. The Kaplan-Meier curve of the occurrence of the first event of death, MI or SRI demonstrated that the difference appeared during the first month of treatment and was maintained during the 6-months' treatment period (Figure S3).

Figure S1 **Composite endpoint of death, MI and SRI. Estimated dose-response relationship (ximelagatran/placebo) with a 95% confidence bound and pairwise comparisons (ITT population)**

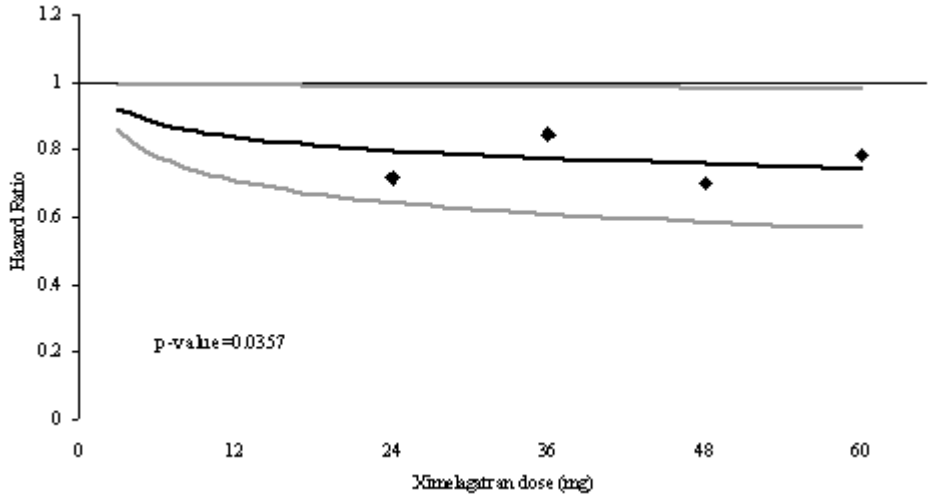


Figure S2 **Composite endpoint of death, MI and SRI. Cumulative risk (%) versus time after randomisation (ITT population)**

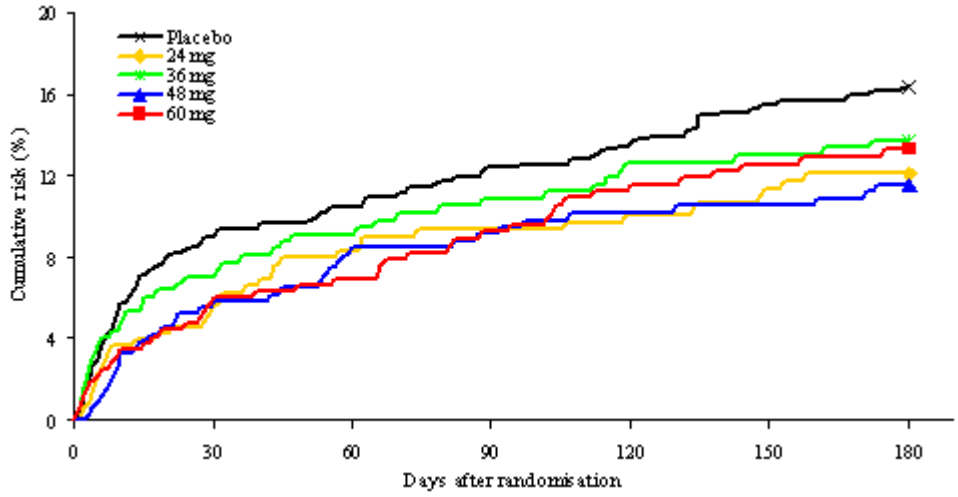
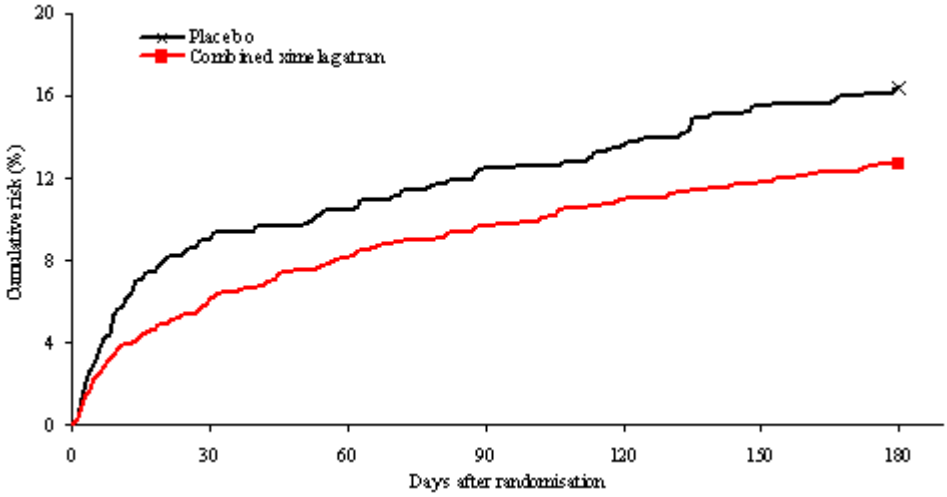


Figure S3 **Composite endpoint of death, MI and SRI. Cumulative risk (%) versus time after randomisation, all ximelagatran doses combined (ITT population)**



Secondary and tertiary variables

Overall, the results of the secondary and tertiary endpoints were consistent with those of the primary analyses. The secondary composite endpoint of cardiovascular death/MI/ischaemic stroke/SRI was significantly different for the pairwise comparisons between the treatment groups. The dose-response relationship when including placebo in the analysis was statistically significant (p=0.0055), showing that ximelagatran is effective in preventing the composite endpoint of cardiovascular death, MI, ischaemic stroke and SRI. The estimated hazard ratio for all ximelagatran groups combined compared to placebo was 0.71 (95% CI 0.55, 0.90; p=0.0056).

Pharmacokinetics (exploratory)

Plasma concentrations of melagatran were determined in samples collected after one and 26 weeks of treatment in a subgroup of the patients. In total, 2624 observations of melagatran plasma concentrations from 726 patients were used in the pharmacokinetic evaluation.

The pharmacokinetics of melagatran, described by a one compartment model with first order absorption rate, was dose proportional and consistent during the 6-month treatment period. The total variability in oral clearance of melagatran (CL/F) was estimated to approximately 50%, expressed as the coefficient of variation. The covariate analysis showed that CL/F of melagatran was influenced by calculated creatinine clearance (CrCL), age and gender, where CrCL was the most important predictor of interindividual variability. The volume of distribution (V/F) increased linearly with body weight and was influenced by age and gender to the same extent as CL/F. The half-life of melagatran, derived from the typical values of CL/F and V/F, was 5.0 h in both male and female patients.

The influence of chronically administered ACE-inhibitors, β -blocking agents, calcium channel antagonists (dihydropyridine derivatives), HMG-CoA inhibitors (statins), and loop diuretics were estimated to change the AUC of melagatran less than 15%, and were therefore considered to be of no clinical relevance.

Health economics (exploratory)

Approximately 65-70% of the patients had a procedure/operation during the study period. The number of patients with a procedure/operation during the study period was similar. A notable exception is the number of patients undergoing the procedure 'coronary arteriography', 34 (11%) and 105 (16%) in the 24 mg ximelagatran and placebo groups, respectively. The mean number of days in intensive care was lowest in the 24 mg ximelagatran group (3.4 days) compared with placebo (3.9 days). The mean number of total days in hospital during the study period was approximately 15 days.

Safety results

The overall occurrence of adverse events (AEs), serious adverse events (SAEs) and deaths were similar in all treatment groups. AEs belonging to the SOC "Myo-, endo-, pericardial and valve disorders" were most common in each of these categories, and more common in patients receiving placebo. In total, 63 patients died during the study, whereof 29 during treatment (15 ximelagatran, 14 placebo). All 29 deaths during treatment, except one suicide in the placebo group, were reported in terms associated with cardiovascular disease. Discontinuations due to AEs were more common in the ximelagatran groups, which was partly explained by the protocol-specified criteria for discontinuation due to hepatic enzyme elevations (see Table S2, Table S3 and Table S4). Discontinuation of study drug due to a bleeding event was also more frequent in patients receiving ximelagatran. Other reported AEs occurred at a similar incidence in the placebo and ximelagatran treatment groups and were those that commonly occur in an elderly population with a recent ACS.

With regard to bleeding events, the number of bleeding events (minor and/or major, on treatment (OT) analysis) in the placebo group was lower than the ximelagatran group (combined). The dose-response relationship when including placebo in the analysis was statistically significant ($p<0.0001$), showing that treatment with ximelagatran was associated with an increased cumulative risk of bleeding (minor and/or major), and in a dose-related manner. This effect of ximelagatran appears early and is sustained over time. There were few major bleeding events in each group, 3 (0.5%) patients receiving placebo versus 6 (2.0%), 1 (0.3%), 9 (2.9%) and 5 (1.5%) patients in the 24, 36, 48 and 60 mg ximelagatran groups, respectively.

There were 2 events of haemopericardium, one in the placebo group and one in the 24 mg ximelagatran group. Both patients died a sudden death. There were no other reported bleedings with fatal outcome. There were 2 intracranial bleedings during the study, both in the placebo group. The most common types of bleeding events were epistaxis and haematuria (positive dipsticks included).

The estimated cumulative risk for an ALAT elevation >3xULN was 1.2% for placebo and 7.8, 16.0, 13.6 and 16.0 % for the 24, 36, 48 and 60 mg ximelagatran dose groups, respectively. The corresponding incidence rates were 1.3, 6.5, 12.9, 12.2 and 13.0%. The onset of the elevations in the ximelagatran groups typically occurred during the second and third treatment months. The pattern of ALAT elevations was dose-related. In most cases, the elevations of ALAT were not associated with specific clinical symptoms. No case of drug-induced liver failure was identified in this study. There was no evidence that the hepatic enzyme elevations associated with the ximelagatran treatment causes persistent liver function disorder.

There were no changes in vital signs or ECG causally related to ximelagatran.

Table S2 **Number (%) of patients who had at least one adverse event in any category, and total numbers of adverse events. Treatment vs follow-up period (safety population)**

Category of adverse events	N (%) of patients who had an adverse event in each category[a]			
	Placebo (n=638)	Ximelagatran (n=1245)	Placebo FU (n=609)	Ximelagatran FU (n=1191)
Any adverse events	507(79.5)	991(79.6)	350(57.5)	753(63.2)
Serious adverse events	211(33.1)	379(30.4)	67(11.0)	171(14.4)
Serious adverse events leading to death[b]	14(2.2)	15(1.2)	8(1.3)	27(2.3)
Serious adverse events not leading to death	200(31.3)	367(29.5)	60(9.9)	153(12.9)
Discontinuations of study treatment due to adverse events[c]	140(21.9)	362(29.1)	12(2.0)	32(2.7)

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

b In total, 63 patients died during the study, 29 during treatment (15 ximelagatran, 14 placebo). In addition, there was one patient (Centre 62/Patient 286) who experienced a myocardial infarction in the follow-up period 2 days before study completion and he died one week after study completion.

c Temporary discontinuation due to one AE could proceed to 'permanent' discontinuation due to another AE without resumption of treatment during the intervening period. In such cases, the patient 'enters' the follow-up period at a date that corresponds to the date when study treatment was first stopped. This gives rise to an apparent contradiction ie, discontinuation of treatment due to AEs during the follow-up period.

FU follow-up

Table S3 Number (%) of patients who had at least one adverse event in any category during the treatment period (safety population)

Category of adverse events	N (%) of patients who had an adverse event in each category[a]				
	Placebo	Ximelagatran			
		24 mg	36 mg	48 mg	60 mg
	(n=638)	(n=307)	(n=303)	(n=311)	(n=324)
Any adverse events	507(79.5)	242(78.8)	250(82.5)	237(76.2)	262(80.9)
Serious adverse events	211(33.1)	92(30.0)	95(31.4)	89(28.6)	103(31.8)
Serious adverse events leading to death	14(2.2)	3(1.0)	2(0.7)	3(1.0)	7(2.2)
Serious adverse events not leading to death	200(31.3)	91(29.6)	93(30.7)	86(27.7)	97(29.9)
Discontinuations of study treatment due to adverse events	140(21.9)	74(24.1)	100(33.0)	91(29.3)	97(29.9)

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

Table S4 Number (%) of patients with the most commonly reported [a] adverse events, sorted by decreasing order of frequency as summarised over all ximelagatran groups (safety population)

Preferred term	Placebo		Ximelagatran							
			24 mg		36 mg		48 mg		60 mg	
	(n=638)		(n=307)		(n=303)		(n=311)		(n=324)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Angina pectoris	101	(15.8)	41	(13.4)	36	(11.9)	37	(11.9)	49	(15.1)
Chest pain	87	(13.6)	33	(10.7)	33	(10.9)	24	(7.7)	43	(13.3)
Dizziness	37	(5.8)	15	(4.9)	26	(8.6)	20	(6.4)	18	(5.6)
Dyspnoea	32	(5.0)	21	(6.8)	21	(6.9)	20	(6.4)	13	(4.0)
Fatigue	29	(4.5)	18	(5.9)	10	(3.3)	16	(5.1)	19	(5.9)
Diarrhoea	23	(3.6)	20	(6.5)	14	(4.6)	11	(3.5)	17	(5.2)
Epistaxis	14	(2.2)	7	(2.3)	11	(3.6)	24	(7.7)	19	(5.9)
Haematuria	18	(2.8)	15	(4.9)	11	(3.6)	16	(5.1)	19	(5.9)
Coronary artery disorder	21	(3.3)	14	(4.6)	22	(7.3)	11	(3.5)	13	(4.0)
Myocardial infarction	51	(8.0)	16	(5.2)	17	(5.6)	13	(4.2)	14	(4.3)
Myocardial ischaemia	37	(5.8)	17	(5.5)	16	(5.3)	12	(3.9)	14	(4.3)
Coughing	30	(4.7)	16	(5.2)	13	(4.3)	12	(3.9)	13	(4.0)
Hepatic enzymes increased nos	1	(0.2)	4	(1.3)	15	(5.0)	18	(5.8)	17	(5.2)
Respiratory infection	26	(4.1)	14	(4.6)	10	(3.3)	15	(4.8)	14	(4.3)
Nausea	28	(4.4)	13	(4.2)	18	(5.9)	10	(3.2)	11	(3.4)
Dyspepsia	28	(4.4)	10	(3.3)	13	(4.3)	8	(2.6)	17	(5.2)
Headache	27	(4.2)	14	(4.6)	14	(4.6)	7	(2.3)	13	(4.0)
Melaena	10	(1.6)	8	(2.6)	12	(4.0)	11	(3.5)	15	(4.6)
Purpura	17	(2.7)	12	(3.9)	11	(3.6)	5	(1.6)	17	(5.2)
Abdominal pain	25	(3.9)	14	(4.6)	9	(3.0)	10	(3.2)	10	(3.1)
Oedema peripheral	10	(1.6)	14	(4.6)	10	(3.3)	6	(1.9)	8	(2.5)
Pain	18	(2.8)	8	(2.6)	11	(3.6)	9	(2.9)	7	(2.2)
SGPT increased	0		4	(1.3)	10	(3.3)	10	(3.2)	11	(3.4)
Hypertension	19	(3.0)	12	(3.9)	9	(3.0)	7	(2.3)	6	(1.9)
Insomnia	17	(2.7)	5	(1.6)	7	(2.3)	11	(3.5)	10	(3.1)
Urinary tract infection	8	(1.3)	8	(2.6)	5	(1.7)	11	(3.5)	9	(2.8)
Cardiac failure	21	(3.3)	8	(2.6)	10	(3.3)	11	(3.5)	3	(0.9)
Constipation	27	(4.2)	8	(2.6)	8	(2.6)	8	(2.6)	7	(2.2)
Anaemia	6	(0.9)	7	(2.3)	6	(2.0)	12	(3.9)	5	(1.5)
Back pain	17	(2.7)	7	(2.3)	8	(2.6)	4	(1.3)	10	(3.1)
Angina pectoris aggravated	21	(3.3)	2	(0.7)	7	(2.3)	4	(1.3)	6	(1.9)

[a] This table uses a cut-off of 3%.

Reference

Wallentin L, Wilcox RG, Weaver WD, Emanuelsson H, Goodwin A, Nyström P, Bylock A. Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial. Lancet 2003;362(9386):789-97.

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.