Drug product:	EXANTA	**SYNOPSIS**	
Drug substance(s):	Melagatran/Ximelagatran		
Edition No.:	1		
Study code:	D4003C00030		
Date:	31 October 2006		

The "EXTEND" study: A randomized, double-blind, parallel-group, phase III b, multi-centre study evaluating extended prophylactic treatment with melagatran/ximelagatran versus enoxaparin for the prevention of venous thromboembolic events in patients undergoing elective hip replacement or hip fracture surgery.

Study centre(s)

This study was conducted in 1158 patients recruited from 104 centres in 16 countries. Each centre recruited between 1 and 42 patients.

Publications

No publications currently completed.

Study dates

First patient enrolled *7 September 2005*

Last patient completed *30 August 2006*

Phase of development

Therapeutic confirmatory (III)
Therapeutic use (III)

The EXTEND study was prematurely stopped on 13 February 2006, following a report of serious liver injury in one patient after completion of 35 days melagatran/ximelagatran treatment.

The study was planned to include 35 (±3) days treatment and a follow-up period until post-op day 56 (±3). In addition, an independent visit was planned for post-op day 180 (±10).

After the study stop, all melagatran/ximelagatran patients had to attend all scheduled study visits as described in the clinical study protocol plus an additional independent visit with liver enzyme testing on post-op day 90 (±3). Patients who had been randomized to enoxaparin did not have to attend any further study visits but were requested to return any remaining investigational product to the study centre.

Objectives

The overall objective of this study was to evaluate the safety and efficacy of extended prophylactic treatment with melagatran/ximelagatran versus enoxaparin for the prevention of venous thromboembolic events in patients undergoing elective hip replacement or acute hip fracture surgery.

Due to the premature stop of this study, data collection was not completed as planned according to the clinical study protocol. Therefore, it has not been possible to fully evaluate the risk-benefit of melagatran/ximelagatran relative to enoxaparin as specified in the study objectives, and the results are presented as an abbreviated report. In line with FDA guidelines on the contents of an abbreviated study report, all safety related variables are fully reported while efficacy data are only briefly summarised.

Study design

This was an international, multi-centre, randomized, double-blind, parallel-group study comparing the efficacy and safety of melagatran/ximelagatran versus enoxaparin for the prevention of venous thromboembolic events in patients undergoing elective hip replacement or acute hip fracture surgery. To maintain the balance between the two treatment groups within each type of surgery, the randomization list was stratified by type of surgery; elective hip replacement or acute hip fracture surgery. The aim was that both types of surgery would contribute to at least one third of the randomized patient population.

Three independent Adjudication Committees provided blinded assessments of the events comprising the primary efficacy composite endpoint, all bleeding events and events suspected to represent myocardial infarctions, respectively. An independent Data Safety Monitoring Board was set up to regularly monitor the safety in the study.

Target patient population and sample size

Female or male patients aged 18 years and above, scheduled for elective hip replacement surgery or patients requiring surgery for hip fracture, such as osteosynthesis or acute hip replacement due to unilateral fracture of the collum femoris, pertrochanteric or

subtrochanteric fracture. These patients were judged to be candidates for a total of 5 weeks of prophylaxis.

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

Patients randomized to melagatran/ximelagatran received melagatran 3 milligram (mg) given as an subcutaneous (sc) injection 4-8 hours after the end of surgery and twice daily (bid) for up to 2 days after surgery followed by oral ximelagatran 24mg bid, as soon as the patient could take tablets, until post-op day 35 (±3). Placebo enoxaparin was started pre/post-op according to local practice.

Patients randomized to enoxaparin received enoxaparin 40mg sc once daily (od), starting as a pre-op injection od the night before surgery or post-op, according to local practice. Placebo melagatran was started post-op and switched to placebo ximelagatran when the patient could take tablets. The treatment continued with one injection every evening until post-op day 35 (±3).

Duration of treatment

The Investigational Products were administered for 35 (±3) post-op days.

Criteria for evaluation (main variables)

Due to the premature stop of this study, data collection was not completed as planned according to the clinical study protocol. Therefore, it has not been possible to fully evaluate the risk-benefit of melagatran/ximelagatran relative to enoxaparin as specified in the study objectives.

Statistical methods

Since data were not analysed according to the clinical study protocol because of the study stop and withdrawal of melagatran/ximelagatran from the market, the planned statistical methods are not presented here. The data analyses presented in this abbreviated report are described in the statistical analysis plan see Appendix 12.1.9 (Documentation of statistical methods and supporting statistical analyses).

Patient population

Demographics, baseline characteristics and disposition of patients are shown in Table S 1 (elective hip replacement surgery and acute hip fracture surgery patients).

Table S 1 Patient population and disposition

		mel/ximel		enoxaparin		Total	
Population							
N randomized (N planned)		580	(1650)	578	(1650)	1158	(3300)
		n	**(%)**	**n**	**(%)**	**N**	**(%)**
Demographic characteristics							
Sex (n and % of patients)	Male	252	(43.5)	245	(42.4)	497	(42.9)
	Female	328	(56.5)	333	(57.6)	661	(57.1)
Age (years)	Mean (SD)	66.0	(11.5)	64.9	(11.1)	65.4	(11.3)
	Range	24 to 91		21 to 94		21 to 94	
Race (n and % of patients)	Caucasian	580	(100)	576	(99.6)	1156	(99.8)
	Black	0	(0)	1	(0.2)	1	(0.1)
	Oriental	0	(0)	1	(0.2)	1	(0.1)
	Other	0	(0)	0	(0)	0	(0)
Baseline characteristics							
History of DVT/PE	Yes (%)	19	(3.3)	16	(2.8)	35	(3.0)
Current smoker	Yes (%)	86	(14.8)	96	(16.6)	182	(15.7)
Alcohol use	Yes (%)	232	(40.0)	243	(42.0)	475	(41.0)
BMI (kg/m^2)	Mean (SD)	27.3	(4.6)	27.6	(4.7)	27.4	(4.7)
	Range	13.7	44.8	16.3	45.2	13.7	45.2
Calculated CrCl (mL/min)[a]	Mean (SD)	81.6	(27.9)	84.7	(29.3)	83.1	(28.7)
	Range	25.5	179.4	29.1	214.6	25.5	215.6
Disposition							
N (%) of patients who	Completed[b]	308	(53.1)	333	(57.6)	641	(55.3)
	Discontinued before 13 February 2006[c]	70	(12.1)	80	(13.8)	150	(13.0)
	Discontinued 13 February 2006	202	(34.8)	165	(28.6)	367	(31.7)
N analysed for safety[d]		557		562		1119	
N analysed for efficacy (ITT)		556		552		1108	

a Calculated CrCl: [weight (kg) x b x (140-age (years))]/S-creatinine (µmol/L); b=1 23 for women, 1 04 for men

b All patients who completed study treatment until post-op day 35 (±3)

c Including patients discontinuing study treatment prior to first dose of investigational product

d Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing

ITT=Intention to treat; N=Number;

Efficacy and pharmacokinetic results

Due to the premature stop of this study, and consequently fewer events, it was not possible to fully evaluate the risk-benefit of melagatran/ximelagatran relative to enoxaparin as specified in the study objectives. The data do not therefore allow for any firm conclusions regarding any observed differences between melagatran/ximelagatran and enoxaparin. There has been no attempt to evaluate any possible differences between the two surgery populations.

Out of 1158 patients in the ITT population, only 743 patients had a mandatory compression ultrasound (CUS) examination or reported symptoms of DVT/PE prior to the premature stop of the study. These patients are considered evaluable with respect to efficacy.

Altogether 7 VTE events were adjudicated as major VTE events (including fatal PE, non-fatal PE, symptomatic DVT, asymptomatic proximal DVT, VTE-related death and deaths for which a VTE related cause could not be excluded).

Two of 340 (0.59 %) elective hip replacement surgery patients randomized to melagatran/ximelagatran had a major VTE event, and 4 of 312 (1.28%) randomized to enoxaparin elective hip replacement surgery patients had a major VTE event. There was one major VTE event after acute hip fracture surgery, in a patient randomized to melagatran/ximelagatran.

Safety results

Any conclusions from comparisons between treatment regimens concerning the total number of AEs have to be cautiously interpreted as the premature stop of the study caused differences in length of the observation periods for melagatran/ximelagatran and enoxaparin patients. Furthermore, the differences in demographic and baseline characteristics between the two treatment groups consisting of acute hip fracture surgery patients also make a comparison difficult within this group of patients. The melagatran/ximelagatran group consisted of more females, the patients tended to be older, and tended to have lower creatinine clearance (CrCl). These imbalances may have had implications for the safety results when comparing the two groups.

The most important safety finding in this study was the observation of increases in ALAT (≥2xULN) that developed, in part A of the study, after the end of treatment with melagatran/ximelagatran. These ALAT elevations, seen in 11 melagatran/ximelagatran and 0 enoxaparin patients, were first observed at the follow-up visit 3 weeks after end of treatment (on post-op day 56 (±3)). Such a pattern had not been previously observed in connection with ximelagatran treatment. One of these patients developed signs and symptoms of serious liver injury and had a maximum ALAT of 46.6xULN and a maximum bilirubin value of 17.2xULN. The findings led to termination of treatment with investigational product in the whole study for all patients.

28 of 481 (5.8%) elective hip replacement surgery patients randomized to melagatran/ximelagatran had at least one SAE, compared to 24 of 488 (4.9%) enoxaparin patients during the treatment and/or follow-up periods. 15 (3.1%) elective hip replacement

surgery patients discontinued melagatran/ximelagatran treatment due to an AE, compared with 24 (4.9%) in the enoxaparin group.

Among the acute hip fracture surgery patients, 18 of 76 (23.7%) melagatran/ximelagatran and 7 of 74 (9.5%) enoxaparin patients had at least one SAE during the treatment and/or follow-up periods. There were a total of 9 deaths in the acute hip fracture patient group, 8 in the melagatran/ximelagatran and 1 in the enoxaparin treatment group. Three of the melagatran/ximelagatran patients died while on active treatment and 2 died during the follow-up period in part A of the study. Three melagatran/ximelagatran patients died during part B of the study (after post-op day 56 (±3) follow-up visit). The enoxaparin patient died while on treatment. There were 6 (7.9 %) and 1 (1.4 %) treatment discontinuations due to AE from the melagatran/ximelagatran and enoxaparin treatment groups, respectively. The imbalance in baseline characteristics in combination with imbalance in follow-up time between acute hip fracture treatment groups make interpretation of possibly different AE patterns difficult.

There were no clinically important differences in the frequency of blood transfusions and volume of blood transfused between the treatment groups.

The findings in laboratory variables (except ALAT) and vital signs did not raise any safety concerns.

Summaries of the AEs (adverse events) in this study are shown in Table S 2 (elective hip replacement surgery) and Table S 3 (acute hip fracture surgery). The most common AEs, listed by preferred term, are listed in Table S 4 and Table S 5.

Table S 2 Elective hip replacement surgery: Number (%) of patients who had an AE in any category during the treatment and follow-up period until post-op day 56 (±3) (safety population)

Category	mel/ximel (n=481) Onset any time (n)	(%)	mel/ximel (n=461) Onset in Follow-up (n)	(%)	enoxa (n=488) Onset any time (n)	(%)	enoxa (n=329) Onset in Follow-up (n)	(%)
Any AE	271	(56.3%)	47	(10.2%)	260	(53.3%)	23	(7%)
Any SAE	28	(5.8%)	13	(2.8%)	24	(4.9%)	3	(0.9%)
Any Fatal SAE	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Any Non-fatal SAE	28	(5.8%)	13	(2.8%)	24	(4.9%)	3	(0.9%)
Discont. of IP due to AE	15	(3.1%)	0	(0%)	24	(4.9%)	0	(0%)
Causally related to IP as judged by inv.	41	(8.5%)	2	(0.4%)	35	(7.2%)	1	(0.3%)

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 There were no AEs defined as OAEs

Table S 3 Acute hip fracture surgery: Number (%) of patients who had an AE in any category during treatment and follow-up period until post-op day 56 (±3) (safety population)

Category	mel/ximel (n=76) Onset any time (n)	(%)	mel/ximel (n=70) Onset in Follow Up (n)	(%)	enoxa (n=74) Onset any time (n)	(%)	enoxa (n=48) Onset in Follow up (n)	(%)
Any AE	49	(64.5%)	17	(24.3%)	39	(52.7%)	6	(12.5%)
Any SAE	18	(23.7%)	8	(11.5%)	7	(9.5%)	0	(0%)
Any Fatal SAE	5	(6.6%)	2	(2.9%)	1	(1.4%)	0	(0%)
Any Non-fatal SAE	13	(17.1%)	6	(8.6%)	6	(8.1%)	0	(0%)
Discont. of IP due to AE	6	(7.9%)	0	(0%)	1	(1.4%)	0	(0%)
Causally related to IP as judged by inv.	7	(9.2%)	2	(2.9%)	1	(1.4%)	0	(0%)

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 There were no AEs defined as OAEs

Table S 4 Elective hip replacement surgery: Number (%) of patients reporting an adverse event. Safety Population. Most common Events[a]. Sorted by decreasing frequency in the total population (not shown)

Preferred Term	mel/ximel (n=481) Onset any time n	(%)	mel/ximel (n=461) Onset in Follow Up n	(%)	enoxa (n=488) Onset any time n	(%)	enoxa (n=329) Onset in Follow Up n	(%)
NAUSEA	48	10	1	0.2	38	7.8	0	0
VOMITING	20	4.2	0	0	20	4.1	0	0
DIARRHOEA	16	3.3	0	0	16	3.3	0	0
URINARY TRACT INFECTION	19	4	4	0.9	13	2.7	2	0.6
INSOMNIA	11	2.3	0	0	19	3.9	1	0.3
PRURITUS	12	2.5	1	0.2	17	3.5	0	0
PYREXIA	12	2.5	0	0	15	3.1	0	0
HYPOTENSION	14	2.9	1	0.2	12	2.5	0	0
ANAEMIA	12	2.5	1	0.2	12	2.5	0	0
POSTOPERATIVE CONSTIPATION	13	2.7	0	0	10	2	0	0
DIZZINESS	14	2.9	2	0.4	8	1.6	1	0.3
OEDEMA PERIPHERAL	17	3.5	0	0	5	1	1	0.3
HAEMATOMA	8	1.7	0	0	13	2.7	0	0
ANAEMIA	12	2.5	1	0.2	8	1.6	1	0.3
NASOPHARYNGITIS	13	2.7	8	1.7	7	1.4	3	0.9

a A cut off at 2% in the safety population was used

Table S 5 Acute hip fracture surgery: Number (%) of patients reporting an adverse event. Safety Population. Most common Events[a]. Sorted by decreasing frequency in the total population (not shown)

Preferred Term	mel/ximel (n=76) Onset any time n	(%)	mel/ximel (n=70) Onset in Follow Up n	(%)	enoxa (n=74) Onset any time n	(%)	enoxa (n=48) Onset in Follow Up n	(%)
URINARY TRACT INFECTION	8	10.5	3	4.3	8	10.8	2	4.2
ANAEMIA	6	7.9	0	0	8	10.8	0	0
DIARRHOEA	2	2.6	1	1.4	6	8.1	0	0
PNEUMONIA	7	9.2	3	4.3	1	1.4	0	0
CONSTIPATION	3	3.9	1	1.4	3	4.1	0	0
DECUBITUS ULCER	2	2.6	0	0	4	5.4	0	0
COUGH	3	3.9	1	1.4	2	2.7	0	0
NAUSEA	2	2.6	0	0	3	4.1	0	0
VOMITING	3	3.9	0	0	2	2.7	0	0
CONFUSIONAL STATE	4	5.3	0	0	0	0	0	0
DIZZINESS	0	0	0	0	4	5.4	0	0
HYPERTENSION	1	1.3	1	1.4	3	4.1	0	0

a A cut off at 2% in the safety population was used

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Date of the report

31 October 2006