AstraZeneca

SH-TPA-0002

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Exanta™

ACTIVE INGREDIENT: H 376/95 (ximelagatran)

Trial title (number): Tolerability and Safety of the Oral Thrombin Inhibitor H 376/95 (ximelagatran), Compared to Warfarin, as Stroke Prophylaxis in Patients with Atrial Fibrillation. A Dose-Guiding, Feasibility Multicentre Study (SPORTIF II)

Developmental phase: II
First subject recruited:17 May 1999
Last subject completed:12 January 2000
Approval date:18 December 2000

OBJECTIVES

The primary objective was to evaluate tolerability of 3 different doses of H 376/95 (ximelagatran) compared with warfarin during 12 weeks of 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.

Secondary objectives were to study pharmacokinetics of H 376/95 in the patient population, and to test the feasibility of the study design to optimise the design of the large Phase III trial.

METHODS

STUDY DESIGN

This was a multicentre, randomised, parallel group, dose-guiding study to compare the safety and tolerability of the oral thrombin inhibitor H 376/95 (20, 40 or 60 mg bid, given double-blind) with warfarin (aiming for an INR of 2.0 – 3.0) as stroke prophylaxis in patients with nonvalvular AF.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Eligible patients were to be at least 18 years of age; weight 50 – 120 kg; have a history of chronic or intermittent AF verified by at least 2 ECG readings; and were to have at least one of the following risk factors for stroke: history of hypertension, age ≥ 65 years, previous cerebral ischaemic attack (stroke or TIA), previous systemic embolism, left ventricular dysfunction (either LVEF <40% or symptomatic CHF within 3 months), diabetes mellitus or coronary heart disease.

Patients were to be excluded from the study if they had:
- stroke or TIA 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
- pregnancy and lactation
- continuous NSAID treatment
- treatment with fibrinolytic drugs within one week
- contra-indications for warfarin treatment

- conditions associated with increased risk of bleeding (eg history of intracranial bleeding, bleeding gastrointestinal disorder and/or endoscopically verified ulcer disease within the year prior to inclusion in the study, major surgical procedure or trauma 2 weeks prior to inclusion, known haemophilic disorder)
- diastolic blood pressure >100 mmHg or systolic blood pressure >180 mmHg
- renal impairment (calculated creatinine clearance (CrCL) <40 mL · min^{-1})
- known active liver disease or liver insufficiency
- anaemia (Hb <100 g · L^{-1})
- platelet count <100x10^9 · L^{-1}
- planned cardioversion or surgery during the study, or
- history of rheumatic valvular disease.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 376/95 tablets 20 mg. Batch numbers H 1309-02-01-01 & H 1309-02-01-02. Dosage 20, 40 or 60 mg bid. Placebo tablets to H 376/95. Batch number H 1383-02-01-01.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Warfarin tablets, administered according to hospital routines aiming for an INR of 2.0-3.0. Batch numbers: H 0724-04-01-01, H 0724-02-01-04/07/08/09, H 0724-03-01-01, H 1432-01-01-01, H 1433-02-01-01/02/03, H 1441-01-01-01, H 1432-02-01-02, H 1433-03-01-01, H 1433-01-01-01, ZL 8-1, ZM 9-2.

DURATION OF TREATMENT

Twelve weeks.

MAIN VARIABLES:

The primary variable was the number of adverse events (AEs), with special regard to bleeding and thromboembolic events.

EFFICACY

Occurrence of stroke, transient ischaemic attack (TIA) or other thromboembolic events; 12-lead ECG; plasma concentration of the active metabolite melagatran, activated partial thromboplastin time (APTT) and ecarin clotting time (ECT) (H 376/95 patients only); P-prothrombin complex / P-prothrombin time (PTC/PT) (warfarin patients only for calculation of INR).

SAFETY

Adverse events, bleeding events, clinical chemistry, haematology, urinary erythrocytes (U-Hb), faecal haemoglobin (Fe-Hb) and vital signs.

STATISTICAL METHODS

The safety and tolerability of the 3 dose levels of H 376/95 were assessed exploratively, with the warfarin group as a reference. Estimates of proportions within groups, and differences in proportions between groups, with 95% confidence intervals, were given for the occurrences of minor and major bleeding, as well as for new occurrences of stroke. Laboratory variables, blood pressure, heart rate and ECG recordings were assessed using descriptive statistics.
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.

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.

PATIENTS

It was planned in the study protocol that a total of 220 patients would be randomised in equal numbers to receive treatment with one of 3 different dose levels of H 376/95 or warfarin in order to achieve 50 evaluable patients in each treatment group. Of the 257 patients randomised into the study, 254 received treatment, of whom 207 completed treatment. There were 254 evaluable patients. In total, 167 patients proceeded to participate in the long term open-label follow-up study SH-TPA-0004 (Table S1).

Table S1 Summary of patient disposition

	H 376/95 dose			Warfarin	Total
	20 mg bid	40 mg bid	60 mg bid		
No. randomised	66	64	60	67	257
No. received study drug	66	62	59	67	254
Males / Females	43 / 23	42 / 20	32 / 27	37 / 30	154 / 100
Mean age (range)	69.9 (41.0 – 90.0)	69.7 (39.0 – 95.0)	68.4 (49.0 – 93.0)	70.0 (44.0 – 93.0)	69.5 (39.0 – 95.0)
No. completed (%)*	56 (85%)	50 (81%)	47 (80%)	54 (81%)	207 (81%)
No. continued in SH TPA 0004 (%)	48 (73%)	37 (60%)	40 (68%)	42 (63%)	167 (66%)

* % of no. completed / no. received study drug

SUMMARY

EFFICACY RESULTS

No systemic embolic events were detected during the study. One patient who received 60 mg bid H 376/95, and 2 patients who received warfarin experienced a TIA; one patient who received 60 mg bid H 376/95 experienced an ischaemic stroke. One of the 4 patients had a previous history of TIA.

Warfarin was administered aiming for an INR of 2.0 – 3.0. Only 34% of patients had an INR of 2.0 – 3.0 at the start of the study, but this figure increased to 57% after 3 months of treatment, showing an anticoagulant effect in line with well-controlled warfarin administration.

Mean plasma melagatran concentrations, evaluated after 12 weeks of treatment (Visit 7), at 3 - 5 h post-dose were: 0.25, 0.60 and 0.88 $\mu mol \cdot L^{-1}$ for the 20 mg, 40 mg and 60 mg bid H 376/95 treatment groups, respectively. After dose-normalisation the plasma concentrations were similar for the 3 dose groups, suggesting that there were no dose-dependent changes in the pharmacokinetics of melagatran.

The pharmacokinetics of melagatran after oral administration of H 376/95, estimated by the population modelling approach in all 153 patients that completed the study, was well described by a one-compartment model with a first-order absorption rate constant. Total clearance was estimated to be 19.1 $L \cdot h^{-1}$ at a median creatinine clearance of 67 $mL \cdot min^{-1}$, and was positively correlated to renal function assessed by calculated creatinine clearance. Volume of distribution was estimated to be 125 L at a median body weight of 83 kg, and was positively correlated to body weight. Residual inter-patient variability, not accounted for by the covariates, was 35% for clearance and 32% for volume of distribution. The terminal half-life, derived from the final population estimates of clearance and volume, was 4.6 h. The plasma concentrations of melagatran in the present patient population were higher than expected from previous pharmacokinetic studies in healthy volunteers (young & elderly), and in orthopaedic surgery patients. Clearance and volume of distribution were lower, while the half-life was similar to

previous estimates from orthopaedic surgery patients, which may suggest that the bioavailability of melagatran is higher in atrial fibrillation patients.

The coagulation time variables ECT and APTT both increased with increasing dose of H 376/95. For each dose group, the prolongations in ECT and APTT were consistent over time for the measurements performed during the 12-week treatment period. ECT was linearly correlated to the plasma concentration of melagatran (R^2 = 0.85). A non-linear concentration-effect relationship was observed for APTT, with a linear function fitted for the square root of melagatran plasma concentrations (R^2 = 0.46).

SAFETY RESULTS

In general the study drugs were well tolerated with 16 (8.6%) patients discontinuing H 376/95 and 6 (9.0%) discontinuing warfarin because of AEs Elevated liver enzymes, although asymptomatic, were more common in the H 376/95 groups than in the warfarin group. It cannot be excluded that an increase in liver enzymes is an adverse drug reaction caused by H 376/95. These findings will be investigated further in ongoing and planned long-term studies. Bleeding events are expected AEs with all anticoagulants. Bleeding events tended to be less common in the H 376/95 groups than in the warfarin group. Other AEs were those that commonly occur in an elderly population with chronic AF, and were probably not related to the study drugs.

No major bleeds were reported by patients who received H 376/95, and one major bleed was experienced by a patient in the warfarin group. Five (2%) patients experienced multiple minor bleeds, 7 (3%) patients experienced minor bleeds, and 10 (4%) patients experienced other unspecified bleeding. In total, 23 patients experienced bleeding events actively asked for during the study: 4, 5, 7 and 7 patients in the 20 mg, 40 mg, 60 mg bid H 376/95 and warfarin treatment groups, respectively. The bleeding profile for the 60 mg bid H 376/95 and warfarin treatment groups was comparable, whilst bleeds were somewhat less frequent in the 20 mg and 40 mg bid H 376/95 treatment groups. However the majority of patients (91%) did not experience any bleeding events. There was no correlation between the patients who experienced bleeding and age, CrCL or ASA use.

CrCL had a cut-off point at 40 $mL \cdot min^{-1}$ as an entry criterion as melagatran is excreted up to 80% via the kidneys. There were no notable differences in S-CrCL between the H 376/95 dose groups or compared with the warfarin group. In total, 22 patients had a positive test for Fe-Hb (6, 4, 7 and 5 patients in the 20 mg, 40 mg, 60 mg bid H 376/95 and warfarin treatment groups, respectively), and 22 patients had a positive test for U-Hb, at one or multiple visits during the study (5, 5, 4 and 8 patients in the 20 mg, 40 mg, 60 mg bid H 376/95 and warfarin treatment groups, respectively). There were no notable changes in other laboratory variables measured, except liver function tests.

References:

Petersen P, Grind M, Adler J. Ximelagatran versus warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. SPORTIF II: a dose-guiding, tolerability, and safety study. Journal of the American College of Cardiology 2003;41(9):1445-51.

Grind M, Hamren B, Baathe S, Wollbratt M, Eriksson UG. Pharmacokinetics of the oral direct thrombin inhibitor ximelagatran in patients with non-valvular atrial fibrillation receiving long-term treatment: a population analysis by nonlinear mixed effect modelling. Clin Pharmacol Ther 2002; 71 (2): P31 MPI-99.

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.