Sponsor

Novartis

Generic Drug Name

Certoparin Sodium

Therapeutic Area of Trial

Atrial Fibrillation

Approved Indication

Indicated for the treatment of deep vein thrombosis

Study Number

CMEX839BDE01

Title

An open-label, multi-center trial to evaluate the feasibility and safety of short-term treatment with subcutaneously injected certoparin (8000 U anti-Xa twice daily) in patients with persistent non valvular atrial fibrillation

Phase of Development

Phase III

Study Start/End Dates

22-Apr-2005 to 15-Aug-2006

Study Design/Methodology

This was an open-label, multi-center trial including patients with the diagnosis of persistent non valvular atrial fibrillation (AF) who received 8000 U anti-Xa of certoparin twice daily according to the following scheme:

- Patients with duration of AF for less than 48 hours received the study drug, afterwards electrical cardioversion was performed followed by overlapping oral anticoagulation.
- Patients with a duration of AF for more than 48 hours (or unknown duration) received the study drug followed by transesophageal echocardiography (TEE) to confirm or exclude the occurrence of thrombi within the left atrium:

1. If the occurrence of thrombi was excluded by TEE, electrical cardioversion was performed followed by overlapping oral anticoagulation.
2. If the occurrence of thrombi was confirmed by TEE (or if there was any suspicion of oc-

curring thrombi), overlapping oral anticoagulation was started.

Centres

32 sites in Germany

Publication

Ongoing

Objectives

The primary objective was to document the feasibility and safety of short-term treatment with a fixed, body weight-independent certoparin regimen (8000 U anti-Xa twice daily) in patients with persistent non valvular AF. Special emphasis was laid on the documentation of cerebral-ischemic neurological events (stroke, transient ischemic attacks), venous thromboembolism (DVT, pulmonary embolism), and bleeding complications (classified as minor or major). Events were documented during treatment with study drug as well as within 2 days after end of treatment.

Test Product (s), Dose(s), and Mode(s) of Administration

8000 U anti-Xa certoparin injected subcutaneously twice daily.

Reference Product(s), Dose(s), and Mode(s) of Administration

None

Criteria for Evaluation

Primary variables

Adverse events (AEs), serious adverse events (SAEs), vital signs (body weight and body mass index, temperature, systolic and diastolic blood pressure). Special emphasis was given to the occurrence of following adverse events: ischemic cerebral infarction or transient ischemic attacks, deep vein thrombosis (DVT) or pulmonary embolism, major and minor bleeding complications and thrombocytopenia.

Secondary variables

None

Safety and tolerability

See primary variables above

Pharmacology

None

Other

None

Statistical Methods

This study was designed to provide data about the feasibility and safety of a short-term treatment with certoparin in patients with persistent non valvular AF and indication for electrical cardioversion. The purpose of this trial was not confirmatory, it aimed at describing the experience gained; therefore, no primary endpoint was defined and analysis was performed by descriptive statistics only.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- women or men =18 years
- persistent AF (electrical cardioversion is planned)
- written informed consent

Exclusion criteria

- unsuccessful cardioversion in the past
- any heparin given for more than 48 hours before start of study drug
- unfractionated heparin (UFH) within 48 hours before start of study drug, but it was allowed to give any low-molecular weight hepatin (LMWH) within 48 hours before start of study drug

- current oral anticoagulation
- after electrical cardioversion overlapping oral anticoagulation was not planned
- indication for medical cardioversion
- subclinical hyperthyroidism
- acute clinical signs of venous thromboembolism
- platelet count <100000/µL
- body weight <60 kg
- known hypersensitivity to certoparin or heparin
- history of or current heparin-induced thrombocytopenia of type II
- bleeding or active peptic ulceration within the last 4 weeks
- recent (within the last 3 months) or active bleeding (e.g. gastrointestinal, urogenital or other abnormal bleeding) or persisting increased risk of bleeding after surgery
- history of, or current clinically relevant coagulopathy with hemophilia or any clinical condition with an enhanced risk of bleeding during therapy with heparin (e.g. clotting factor deficiency, consumptive coagulopathy, severe thrombocytopenia)
- acute (or suspicion of) stroke, intracranial bleeding or cerebral aneurysm
- recent (i.e. within the last 14 days) operation or injuries on central nervous system
- indication for spinal/peridural/epidural anesthesia or spinal puncture
- vascular retinopathy, hemorrhage into the vitreous body or other intraocular bleeding
- scheduled operation or lysis therapy
- endocarditis lenta
- severe uncontrolled hypertension (systolic blood pressure >200 mmHg or diastolic blood pressure >120 mmHg or both)
- known severe hepatic or renal insufficiency or serum creatinine >2 mg/dL
- abortus imminens
- history of malignancy of any organ system, treated or untreated, within the past five years, whether or not evidence of local recurrence or metastases exists, are excluded, with the exception of localized basal cell carcinoma of the skin
- predicted life expectancy less than 3 months
- drug or alcohol abuse
- known pregnancy or breastfeeding or women of childbearing potential without reliable contraception
- participation in another investigative drug study within the last 30 days.

Number of Subjects

	Certoparin Sodium
Planned N	200
Treated n	200
Completed n (%)	134 (67)
Discontinued n (%)	66 (33)
Discontinued due to adverse events n (%)	18 (9)

Demographic and Background Characteristics

	n	%
Total number of patients	200	100.0
Gender		
Male	140	70.0
Female	60	30.0
Race		
Caucasian	197	98.5
Asian/Oriental	3	1.5
Age		
Mean age (years) ± SD	65.7± 11.8	
Range	33.0 - 88.5	
Duration of atrial fibrillation		
	37	18.5
≥ 24h	163	81.5

Primary Objective Result(s)

Number (%) of patients with most frequent AEs (5% or more for any body system class); multiple response

	n	%
Total number of patients	200	100.0
Number of patients with AEs	104	52.0
AE Body System/preferred term		
Cardiac disorders	53	26.5
Mitral valve incompetence	17	8.5
Atrial fibrillation	14	7.0
Investigations	33	16.5
Hepatic enzyme increased	19	9.5
Psychiatric disorders	20	10.0
Sleep disorders	15	7.5
Gastrointestinal disorders	18	9.0
Respiratory, thoracic and mediastinal disorders	12	6.0

Number (%) of AEs and maximum severity

	n	%
Total number of patients	200	
Total number of AEs	242	100.0
Severity		
Missing	1	0.4
Mild	183	75.6
Moderate	50	20.7
Severe	8	3.3

Number (%) of patients with significant AEs

	n	%
Total number of patients	200	100.0
Number of patients with AEs	104	52.0
Serious or significant events		
SAEs	25	12.5
Deaths	2	1.0
Patients with SAEs with suspected drug relationship	3	1.5
Discontinuation due to SAEs	10	5.0
Patients with AEs with suspected drug relation	23	11.5
Study discontinuation due to AEs	19	9.5
Dose adjustment or study-drug interruption required due to AE	1	0.5

Patients with AEs requiring concomitant medication/non-drug therapy	60	30.0

Number (%) of patients with most frequent SAEs (1% or more for any body system class); multiple response

	n	%
Total number of patients	200	100.0
Number of patients with SAEs	25	12.5
AE Body System/preferred term		
Cardiac disorders	18	9.0
Atrial fibrillation	10	5.0
Investigations	3	1.5
Gastrointestinal disorders	2	1.0
Respiratory, thoracic and mediastinal disorders	2	1.0
Dyspnoea	2	1.0
Vascular disorders	2	1.0

Number (%) of patients with ischemic cerebral infarction or transient ischemic attacks, deep vein thrombosis (DVT) or pulmonary embolism, major and minor bleeding complications and thrombocytopenia (fall of platelet counts below 100000/µL or fall of platelet counts below 50% of baseline value) during treatment and up to two days after last study drug intake

	n	%
Cerebral ischemia	1	0.5
Bleeding	8	4.0
Major	3	1.5
Minor	5	2.5
Death*	-	-
DVT/pulmonary embolism	-	-
Thrombocytopenia	1	0.5

* 2 patients died during the 4 week follow-up period

Secondary Objective Result(s)

None

Safety Results

Number of patients with adverse events by system organ class

	n	%
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2	1.0
CARDIAC DISORDERS	53	26.5
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1	0.5
EAR AND LABYRINTH DISORDERS	3	1.5
ENDOCRINE DISORDERS	3	1.5
EYE DISORDERS	1	0.5
GASTROINTESTINAL DISORDERS	18	9.0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5	2.5
HEPATOBILIARY DISORDERS	4	2.0
IMMUNE SYSTEM DISORDERS	1	0.5
INFECTIONS AND INFESTATIONS	7	3.5
INVESTIGATIONS	33	16.5
METABOLISM AND NUTRITION DISORDERS	7	3.5
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	5	2.5
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYP	3	1.5
NERVOUS SYSTEM DISORDERS	9	4.5
PSYCHIATRIC DISORDERS	20	10.0
RENAL AND URINARY DISORDERS	1	0.5
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	12	6.0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2	1.0
VASCULAR DISORDERS	9	4.5

10 most frequent adverse events by preferred term

	n	%
HEPATIC ENZYME INCREASED	19	9.5
MITRAL VALVE INCOMPETENCE	17	8.5
SLEEP DISORDER	15	7.5
ATRIAL FIBRILLATION	14	7.0
CONSTIPATION	7	3.5
HEADACHE	7	3.5
AORTIC VALVE INCOMPETENCE	6	3.0
TRICUSPID VALVE INCOMPETENCE	6	3.0
INSOMNIA	4	2.0
ANGINA PECTORIS	3	1.5
ATRIOVENTRICULAR BLOCK FIRST DEGREE	3	1.5
BRADYCARDIA	3	1.5

CARDIAC FAILURE	3	1.5
CORONARY ARTERY DISEASE	3	1.5
PALPITATIONS	3	1.5
HEPATIC STEATOSIS	3	1.5
BLOOD UREA INCREASED	3	1.5
HYPOKALAEMIA	3	1.5
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	3	1.5
EPISTAXIS	3	1.5
HYPERTENSION	3	1.5

All serious adverse events *

	n	%
ANAEMIA	1	0.5
ACUTE CORONARY SYNDROME	1	0.5
ANGINA PECTORIS	1	0.5
ANGINA UNSTABLE	1	0.5
ATRIAL FIBRILLATION	10	5.0
ATRIAL FLUTTER	1	0.5
ATRIOVENTRICULAR BLOCK COMPLETE	1	0.5
BRADYARRHYTHMIA	1	0.5
BRADYCARDIA	1	0.5
CORONARY ARTERY DISEASE	1	0.5
PALPITATIONS	1	0.5
SICK SINUS SYNDROME	1	0.5
TORSADE DE POINTES	1	0.5
VENTRICULAR TACHYCARDIA	1	0.5
ABDOMINAL HAEMATOMA	1	0.5
GASTROINTESTINAL HAEMORRHAGE	1	0.5
MALAISE	1	0.5
CATHETERISATION CARDIAC	1	0.5
ELECTROCARDIOGRAM T WAVE INVERSION	1	0.5
HEPATIC ENZYME INCREASED	1	0.5
PAIN IN JAW	1	0.5
PLASMACYTOMA	1	0.5
APHASIA	1	0.5
CEREBRAL INFARCTION	1	0.5
DYSPNOEA	2	1.0
HAEMORRHAGE	1	0.5
HYPERTENSIVE CRISIS	1	0.5

* 2 patients died during the 4 week follow-up period One patient died of severe cardiac arrhythmia. The other patient died of unclear reason with suspicion of cardiac or cerebral ischemia

Other Relevant Findings

None

Date of Clinical Trial Report

07 August 2007

Date Inclusion on Novartis Clinical Trial Results Database

11 October 2007

Date of Latest Update

26 September 2007