Sponsor

Novartis

Generic Drug Name

Certoparin

Therapeutic Area of Trial

Prophylaxis of thromboembolic events in acutely ill medical patients

Approved Indication

According to the German SPC:

- Primary prophylaxis of deep vein thrombosis (DVT) in peri- or postoperative patients with medium or high risk of DVT and in patients with acute ischemic stroke.

- Therapy of an acute DVT.

Study Number

CMEX839BDE03

Title

A randomized, double-blind, multi-center comparison of the efficacy and safety of certoparin (3000 U anti-Xa o.d.) with unfractionated heparin (5000 IU t.i.d.) in the prophylaxis of thromboembolic events in acutely ill medical patients

Phase of Development

Phase III

Study Start/End Dates

27 Jan 2007 to 22 Jun 2009

Study Design/Methodology

This study was a randomized, double blind, parallel-group, active controlled, prospective multicenter trial. Three-thousand-two-hundred acutely ill, hospitalized medical patients 70 years of age or older were planned for enrollment into the study. Patients were randomized to one of two treatment groups for routine thromboprophylaxis, either certoparin 3000 U anti-Xa once daily or UFH 5000 IU three times daily.

The planned treatment period was a minimum of eight days and up to a maximum of 20 days. Whether DVT occurred during this period was assessed by compression ultrasound (CUS) at visit 2 (end of treatment).

Centres

148 centers in Germany
24 centers in Romania

Objectives

Primary objective(s)

The primary objective of this study was to confirm that certoparin is non-inferior in preventing the composite primary endpoint consisting of proximal DVT, symptomatic non-fatal pulmonary embolism (PE) and VTE related death during treatment when compared to UFH in acutely ill medical patients.

Secondary objective(s)

The secondary objectives were to evaluate the efficacy of certoparin compared to UFH in preventing the individual components of the primary endpoint and other clinically important endpoints during treatment when compared to UFH in the study population. These endpoints were:

- proximal and distal DVT (combined and separately)
- symptomatic DVT
- symptomatic non-fatal PE
- combination of proximal DVT, non-fatal PE and death from all causes including PE
- VTE related death
- death from all causes
- documented symptomatic VTE (PE and/or DVTs, during follow up period).

Pharmacology

None.

Other

None.

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

Investigational drug

- Active agent: Certoparin-sodium (Novartis Pharma GmbH, Nürnberg, Germany)
- Formulation: solution for subcutaneous injection,
- Unit dose: 3000 U anti Xa of Certoparin in 0,3 ml
- Packaging: prefilled syringes.

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

- Active agent: unfractionated heparin
- Formulation: solution for subcutaneous injection
- Unit dose: 5000 IU of UFH in 0,3 ml
- Packaging: prefilled syringes

Criteria for Evaluation

Primary variables

The incidenceof thromboembolic events (rate of proximal DVT, symptomatic non-fatal PE or VTE related death) during treatment.
The objective findings of the ultrasonographic examination and clinical endpoints were adjudicated by a Central Endpoint Adjudication Committee.

Secondary variables

The incidence of thromboembolic event:

-proximal and distal DVT (combined and separately),

-symptomatic DVT,

-symptomatic non-fatal PE,

-combination of proximal DVT, non fatal PE and death from all causes including PE

-VTE related death,

-death from all causes,

-documented symptomatic VTE (PE and/or DVTs, during follow up period)

Safety and tolerability

Safety endpoints occurring during the treatment period are:

-minor and major bleedings,

-HIT II

Pharmacology

None.

Other

None

Statistical Methods

The primary analysis aimed to demonstrate the non-inferiority of LMWH (Test, T) compared to UFH (Reference, R). Non-inferiority was defined both on an absolute (i.e. difference) as well as

on a relative (i.e. odds ratio) scale. Non-inferiority of T was claimed only, if it could be demonstrated on both scales.
An odds ratio of 1.8 and an absolute delta of 3.45 % were defined based on an expected incidence of the primary endpoint in the control group of 4.7 %. 1600 patients per group have been calculated to reach a power > 90%.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Hospitalized medical patients 70 years of age or older
2. Acute medical illness with significant decrease in mobility expected for at least 4 days (patient bedridden or only able to walk short distances)
3. written informed consent

Exclusion criteria

1. immobilization longer than 3 days prior to randomization
2. prior major surgery, trauma or invasive procedure within the last 4 weeks including any injuries or operation of central nervous system
3. expected major surgical or invasive procedure within 3 weeks following randomization (e.g. thoracic surgery; but permitted are: e.g. uncomplicated angiography, gastroscopy)
4. patients with severe sepsis or need for ventilatory support (permitted are CPAP, oxygen via mask etc.)
5. LMWH/heparin administration longer than 48 hours in the 5 days prior to randomization
6. immobilization due to cast or fracture
7. indication for anticoagulatory or thrombolytic therapy
8. life expectancy < 6 months or illness with very high acute mortality ($\geq$ 30%)
9. acute symptomatic DVT / PE
10. known hypersensitivity to any of the study drugs or drugs with similar chemical structures
11. Acute or history of heparin induced thrombocytopenia type II (HIT II)
12. hemorrhagic diathesis, deficiency of coagulation factors, severe thrombocytopenia
13. acute or history of non-hemorrhagic stroke (< 3 months); hemorrhagic stroke or intracranial bleeding (< 12 months)
14. acute or ongoing intracranial disease, e.g. cerebral aneurysm
15. high risk of gastrointestinal bleeding
16. spinal or epidural anesthesia, lumbar punction within the last 12 hours
17. uncontrolled hypertension, RRdiast. > 105 mmHg
18. severe liver disease
19. severe renal dysfunction (estimated GFR < 30 ml/min, Cockcroft-Gault or MDRD formula)
20. acute endocarditis
21. known active retinopathy, intravitreal or other intraocular bleeding
22. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer
23. Subjects unlikely to comply with the requirements of the protocol.

Number of Subjects

	Certoparin	**UFH**
Planned N	1600	1600
Randomised n	1626	1618
Intent-to-treat population (ITT) n (%)*	1624 (99,9%)	1615 (99,8%)
Completed n (%)	1418 (87,2%)	1384 (85,5%)
Withdrawn n (%)	206 (12,7%)	231 (14,3%)
Withdrawn due to adverse events n (%)	50 (3,1%)	69 (4,3%)

Withdrawn due to lack of efficacy n (%)	0	0
Withdrawn for other reasons including death n (%)	156 (9,6 %)	162 (10 %)

*The intention to treat (ITT) population consisted of all patients as randomized who received at least one dose of study drug. According to this definition, the ITT population is identical to the Safety Population.

The Safety Population consisted of all patients who received at least one dose of study drug. Patients were analyzed according to the treatment received.

Demographic and Background Characteristics

			Safety Population		
			Total	**UFH**	**Certoparin**
Variable		**Statistic**	**(N=3239)**	**(N=1615)**	**(N=1624)**
Age, yrs		Mean (SD)	78.8 (6.3)	78.7 (6.3)	79.0 (6.2)
	<80 years	n (%)	1874 (57.9)	939 (58.1)	935 (57.6)
	≥80 years	n (%)	1365 (42.1)	676 (41.9)	689 (42.4)
Sex	Male	n (%)	1324 (40.9)	655 (40.6)	669 (41.2)
	Female	n (%)	1915 (59.1)	960 (59.4)	955 (58.8)
Weight,kg		Mean (SD)	72.1 (15.7)	71.9 (15.3)	72.3 (16.2)
Race	Caucasian	n (%)	3205 (99.0)	1597 (98.9)	1608 (99.0)
	Black	n (%)	1 (0.0)	1 (0.1)	0 (0.0)
	Oriental	n (%)	17 (0.5)	5 (0.3)	12 (0.7)
	Other	n (%)	16 (0.5)	12 (0.7)	4 (0.2)

Primary Objective Result(s)

Number (%) of patients with proximal DVT, symptomatic non-fatal PE or VTE related death (ITT population)

Certo-parin (N=1372)	UFH (N=1371)	Difference				Odds Ratio			
n¹ (%*)	n¹ (%*)	%	95 % CI	p|Diff = 0	p|Diff > 3.4534 %	OR	95 % CI	p|OR=1	p|OR>1.8
54 (3.94)	62 (4.52)	-0.59	[-2.09; 0.92]	0.4454	<0.0001	0.87	[0.60; 1.26]	0.4458	0.0001

* Rate based on evaluable patients (all treated patients and evaluable for the specific endpoint)
¹ with event
P | Diff=0 and P | OR=1 are the two-sided unshifted p-values (superiority)
P | Diff>3.4534% and P | OR>1.8 are the one-sided shifted p-values (non-inferiority)

Secondary Objective Result(s)

Incidence of proximal DVT, symptomatic non-fatal PE and death from any cause during core study (ITT population)

	Certoparin N; n (%)[1]	UFH N; n (%)[1]	Difference 95% CI [%]	Odds ratio 95% CL
Proximal DVT	1371; 49 (3,57)	1370; 59 (4,31)	-0,73 (-2,19; 0,72)	0,82 (0,56; 1,21)
Distal DVT	1224; 86 (7,03)	1253; 109 (8,70)	-1,67 (-3,79; 0,44)	0,79 (0,59; 1,06)
Proximal or distal DVT	1228; 109 (8,88)	1259; 130 (10,33)	-1,45 (-3,76; 0,86)	0,85 (0,65; 1,11)
Symptomatic DVT	1549; 4 (0,26)	1518; 5 (0,33)	-0,07 (-0,45; 0,31)	0,78 (0,21; 2,92)
Symptomatic non-fatal PE	1555; 7 (0,45)	1529; 3 (0,20)	0,25 (-0,15; 0,65)	2,30 (0,59; 8,91)
VTE related death	1571; 0 (0,00)	1544; 1 (0,06)	-0,06 (-0,19; 0,06)	
Death from any cause	1571; 20 (1,27)	1544; 21 (1,36)	-0,09 (-0,89; 0,71)	0,94 (0,50; 1,73)
Proximal DVT, non-fatal PE and death from any cause including PE	1392; 74 (5,32)	1390; 82 (5,90)	-0,58 (-2,29; 1,16)	0,90 (0,65; 1,24)

[1] N indicates no. of evaluable patients for the respective endpoint and n indicates no. of patients with event

DVT: deep vein thrombosis; ITT: intention to treat; PE: pulmonary embolism; VTE: venous thromboembolism

	Certoparin (N=1392)	UFH (N=1390)	Difference			Odds Ratio		
	n[1] (%)	n[1] (%)	%	95 % CI	p|Diff=0	OR	95 % CI	p|OR=1
	74 (5.32)	82 (5.90)	-0.58	[-2.29 , 1.13]	0.5038	0.9	[0.65 , 1.24]	0.5040

* Rate based on evaluable patients (all treated patients and evaluable for the specific endpoint)

[1] with event

P | Diff=0 and P | OR=1 are the two-sided unshifted p-values (superiority)

AEs of Special Interest, occurring during treatment (Safety population)

	Total (N=3239) n (%)	Certoparin (N=1624) n (%)	UFH (N=1615) n (%)
Any bleedings	126 (3.89)	52 (3.20)	74 (4.58)
Major bleedings	17 (0.52)	7 (0.43)	10 (0.62)
Minor bleedings	110 (3.39)	45 (2.77)	65 (4.02)
HIT II[1]	3 (0.09)	1 (0.06)	2 (0.12)

- n indicates no. of patients with event and N indicates no. of evaluable patients for the respective endpoint
- Major bleeding: fatal bleeding, critical bleeding in area or organ (such as intracranial, intraspinal, retroperitoneal, intrapericardial), overt bleeding with decrease in hemoglobin > 20 g/l or requiring > 2 units of RBC

Minor bleeding: non-major bleeding

- [1]HITII: heparin induced thrombocytopenia type II. In each group one case adjudicated as unclear.

Safety Results

Adverse Events by System Organ Class

Number of Patients with AEs with suspected drug relation during treatment

System organ class **Preferred term**	**Certoparin** **(N=1624)**	**UFH** **(N=1615)**
	n (%)	**n (%)**
All System Organ Classes	**34 (2.1)**	**59 (3.7)**
Blood and lymphatic disorders	**1(0.1)**	**4 (0.2)**
Heparin-induced thrombocytopenia	0 (0.0)	2 (0.1)
Thrombocytopenia	1 (0.1)	2 (0.1)
Cardiac disorders	**0 (0.0)**	**1 (0.1)**
Mitral valve incompetence	0 (0.0)	1 (0.1)
Eye disorders	**1 (0.1)**	**0 (0.0)**
Conjunctival haemorrhage	1 (0.1)	0 (0.0)
Gastrointestinal disorders	**7 (0.4)**	**4 (0.2)**
Abdominal pain	2 (0.1)	1 (0.1)
Abdominal wall haematoma	1 (0.1)	0 (0.0)
Diarrhoea haemorrhagic	1 (0.1)	0 (0.0)
Gastric ulcer	0 (0.0)	1 (0.1)
Haematemesis	0 (0.0)	1 (0.1)
Nausea	1 (0.1)	1 (0.1)
Rectal haemorrhage	2 (0.1)	0 (0.0)
Small intestinal haemorrhage	1 (0.1)	0 (0.0)
Vomiting	1 (0.1)	0 (0.0)
General disorders and administration site conditions	**3 (0.3)**	**10 (0.6)**
Application site pain	1 (0.1)	0 (0.0)
Injection site haematoma	1 (0.1)	1 (0.1)
Injection site haemorrhage	1 (0.1)	5 (0.3)
Injection site pain	0 (0.0)	1 (0.1)
Puncture site haemorrhage	0 (0.0)	1 (0.1)
Puncture site pain	0 (0.0)	1 (0.1)
Vessel puncture site haematoma	0 (0.0)	1 (0.1)
Immune system disorders	**0 (0.0)**	**2 (0.1)**
Hypersensitivity	0 (0.0)	2 (0.1)
Infections and infestations	**1 (0.1)**	**1 (0.1)**
Gastroenteritis	0 (0.0)	1 (0.1)
Pneumonia	1 (0.1)	0 (0.0)
Injury, poisoning and procedural complications	**0 (0.0)**	**6 (0.4)**

Post procedural haemorrhage	0 (0.0)	1 (0.1)	
Subcutaneous haematoma	0 (0.0)	5 (0.3)	
Investigations	**1 (0.1)**	**1 (0.1)**	
Blood creatine increased	0 (0.0)	1 (0.6)	
Platelet count decreased	1 (0.1)	0 (0.0)	
Musculoskeletal and connective tissue disorders	**1 (0.1)**	**0 (0.0)**	
Pain in extremity	1 (0.1)	0 (0.0)	
Nervous system disorders	**0 (0.0)**	**2 (0.1)**	
Cerebrovascular accident	0 (0.0)	1 (0.1)	
Dizziness	0 (0.0)	1 (0.1)	
Psychiatric disorders	**1 (0.1)**	**0 (0.0)**	
Insomnia	1 (0.1)	0 (0.0)	
Renal and urinal disorders	**2 (0.1)**	**2 (0.1)**	
Haematuria	1 (0.1)	2 (0.1)	
Haemorrhage urinary tract	1 (0.1)	0 (0.0)	
Respiratory, thoratic and mediastinal disorders	**4 (0.2)**	**2 (0.1)**	
Epistaxis	3 (0.2)	2 (0.1)	
Pulmonary embolism	1 (0.1)	0 (0.0)	
Skin and subcutaneous tissue disorders	**7 (0.4)**	**10 (0.6)**	
Dermatitis allergic	0 (0.0)	3 (0.2)	
Ecchymosis	3 (0.2)	1 (0.1)	
Eczema	0 (0.0)	1 (0.1)	
Erythema	0 (0.0)	1 (0.1)	
Haemorrhage subcutaneous	0 (0.0)	1 (0.1)	
Pruritus	1 (0.1)	1 (0.1)	
Rash	4 (0.2)	0 (0.0)	
Subcutaneous nodule	0 (0.0)	2 (0.1)	
Urticaria	0 (0.0)	1 (0.1)	
Surgical and medical procedures	**1 (0.1)**	**0 (0.0)**	
Colon polypectomy	1 (0.1)	0 (0.0)	
Vascular disorders	**8 (0.5)**	**19 (1.2)**	
Arterial thrombosis limb	0 (0.0)	1 (0.1)	
Deep vein thrombosis	2 (0.1)	2 (0.1)	
Embolism	1 (0.1)	0 (0.0)	
Haematoma	2 (0.1)	13 (0.8)	
Hypertension	1 (0.1)	0 (0.0)	
Thrombophlebitis superficial	0 (0.0)	1 (0.1)	
Thrombosis	0 (0.0)	2 (0.1)	
Venous thrombosis	2 (0.1)	0 (0.0)	

10 Most Frequently Reported AEs Overall by Preferred Term n (%) during core study

	Certoparin (N = 1624)	UFH (N = 1615)
Constipation	138 (8.5)	121 (7.5)
Insomnia	113 (7.0)	131 (8.1)
Deep venous thrombosis	113 (7.0)	131 (8.1)
Nausea	97 (6.0)	78 (4.8)
Hypokalaemia	95 (5.8)	80 (5.0)
Diarrhoea	63 (3.9)	55 (3.4)
Headache	50 (3.1)	52 (3.2)
Vomiting	44 (2.7)	33 (2.0)
Urinary tract infection	31 (1.9)	40 (2.5)
Vertigo	38 (2.3)	26 (1.6)

AEs occurring after start of study drug only.
AE: adverse event

Serious Adverse Events and Deaths

Number of Patients with SAEs during treatment and follow up

	During core study		During Follow up	
	Certo-parin (N=1624)	UFH (N=1615)	Certo-parin (N=1624)	UFH (N=1615)
	n (%)	n (%)	n (%)	n (%)
All System Organ Classes	93 (5.7)	107 (6.6)	110 (6.8)	115 (7.1)
Blood and lymphatic system disorders	2 (0.1)	1 (0.1)	0 (0.0)	3 (0.2)
Cardiac disorders	18 (1.1)	23 (1.4)	26 (1.6)	28 (1.7)
Endocrine disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Gastrointestinal disorders	9 (0.6)	9 (0.6)	8 (0.5)	15 (0.9)
General disorders and administration site disorders	7 (0.4)	2 (0.1)	9 (0.6)	8 (0.5)
Hepatobiliary disorders	3 (0.2)	1 (0.1)	5 (0.3)	2 (0.2)
Infections and infestations	16 (1.0)	20 (1.2)	27 (1.7)	25 (1.5)
Injury, poisoning and procedural complications	2 (0.1)	8 (0.5)	3 (0.2)	7 (0.4)
Investigations	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Metabolism and nutrition disorders	2 (0.1)	0 (0.0)	2 (0.1)	2 (0.1)
Neoplasms benign, malignant and unspecified	14 (0.9)	23 (1.4)	10 (0.6)	22 (1.4)
Nervous system disorders	6 (0.4)	8 (0.5)	8 (0.5)	8 (0.5)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Renal and urinary disorders	6 (0.4)	4 (0.2)	7 (0.4)	8 (0.5)
Reproductive system and breast disorder	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

Respiratory, thoracic and mediastinal disorders	21 (1.3)	13 (0.8)	14 (0.9)	23 (1.4)
Skin and subcutaneous tissue disorders	0 (0.0)	2 (0.1)	0 (0.0)	1 (0.1)
Surgical and medical procedures	2 (0.1)	1 (0.1)	3 (0.2)	0 (0.0)
Vascular disorders	10 (0.6)	17 (1.1)	6 (0.4)	11 (0.7)

Number of Patients with Significant Adverse Events during Treatment and Follow up

	During core study		**During Follow up**	
	Certoparin (N=1624)	**UFH (N=1615)**	**Certoparin (N=1624)**	**UFH (N=1615)**
No. (%) of patients with AE(s)	**985 (60.7)**	**1004 (62.2)**	**119 (7.6)**	**242 (7.5)**
Number (%) of patients with serious or other significant events	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Adverse Events				
with suspected drug relation	34 (2.1)	59 (3.7)	0 (0.0)	6 (0.2)
leading to dose adjustment or temporary interruption	8 (0.5)	12 (0.7)	0 (0.0)	0 (0.0)
leading to permanent discontinuation	55 (3.4)	73 (4.5)	1 (0.1)	1 (0.1)
requiring concomitant medication/non-drug therapy	700 (43.1)	697 (43.2)	45 (2.8)	62 (3.8)
Serious Adverse Events (SAEs)	93 (5.7)	107 (6.6)	110 (6.8)	115 (7.1)
Deaths	20 (1.2)	21 (1.3)	66 (4.1)	72 (4.5)
SAEs with suspected drug relation	5 (0.3)	6 (0.4)	0 (0.0)	6 (0.4)
SAEs leading to permanent discontinuation	34 (2.1)	32 (2.0)	1 (0.1)	1 (0.1)

AEs occurring after start of study drug only.
AE: adverse event; SAE: serious adverse event

Date of Clinical Trial Report

7 Sept 2009

Date Inclusion on Novartis Clinical Trial Results Database

21 June 2010

Date of Latest Update

14 June 2010