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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00077805
		Study Code :	XRP4563H_4001
Generic drug name:	enoxaparin	**Date:**	12 September 2007

Title of the study:	An Open-Label, Randomized, Parallel-Group, Multi-Center Study to Evaluate the Efficacy and Safety of Enoxaparin Versus Unfractionated Heparin in the Prevention of Venous Thromboembolism in Patients Following Acute Ischemic Stroke	
Investigator:	David G. Sherman	
Study centers:	177 centers in 15 countries: Australia, Austria, Brazil, Canada, Colombia, Czech Republic, India, Israel, Italy, Korea, Mexico, Poland, South Africa, Turkey, and USA	
Publications (reference):	The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL study): an open-label randomized comparison. David G. Sherman, Gregory W. Albers, Christopher Bladin, Cesare Fieschi, Alberto A. Gabbai, Carlos S. Kase, William O'Riordan, Graham F. Pineo, for the PREVAIL Investigators; Lancet 2007; 369:1347-55	
Study period: Date first patient enrolled: 18 August 2003. Date last patient completed: 01 July 2006.		**Phase of development:** Phase 4
Objectives:	Primary: To demonstrate superiority of enoxaparin 40 mg s.c. qd in the prevention of venous thromboembolism (VTE) compared to unfractionated heparin (UFH) 5000 U s.c. q12 hours given for 10 ± 4 days following acute ischemic stroke. Secondary: • To compare the incidence of VTE between the 2 treatment groups at 30, 60, and 90 days from the time of randomization; • To compare neurologic outcomes between the 2 treatment groups, including incidence of stroke recurrence, rate of stroke progression, and patient functional status, during the 10 ± 4 days of treatment, and after 30, 60, and 90 days from the time of randomization; • To evaluate the safety of using enoxaparin compared to UFH for VTE prevention in patients following acute ischemic stroke.	
Methodology:	Prospective, open-label, randomized (1:1) parallel-group, multicenter study	
Number of patients: **Evaluated:**	Planned: 1760 Randomized: 1762 Treated: 1749 Efficacy (VTE):1335 Safety: 1749 Pharmacokinetics: NA Efficacy for VTE included 666 patients in the enoxaparin group and 669 in the UFH group.	

Diagnosis and criteria for inclusion:	Male or female patients aged 18 years or older with ischemic stroke, any territory, with appropriate neuroradiologic study (head CT-scan or brain MRI), with results consistent with a nonhemorrhagic stroke. Onset of symptoms of qualifying stroke within 48 hours prior to randomization. Significant motor impairment of the leg (NIHSS score ≥2 on item 6) and inability to walk without assistance. Written informed consent.
Investigational product: Dose: Administration:	Enoxaparin 40 mg 40 mg Subcutaneous once a day in 0.4 mL
Duration of treatment: 6 to 14 days	**Duration of observation:** 90 days
Reference therapy: Dose: Administration:	Unfractionated heparin (UFH) 5000 U Subcutaneous in 1 mL every 12 hours
Criteria for evaluation: Efficacy: Safety: Pharmacokinetics:	 <u>Primary efficacy criterion</u>: cumulative occurrrence of VTE events documented by bilateral contrast venography or compression ultrasonography for deep-vein thrombosis (DVT) or by ventilation/perfusion lung scan or thoracic helical CT-scan or pulmonary angiography for pulmonary embolism (PE) during the treatment period (10 ± 4 days). <u>Secondary efficacy criteria</u>: cumulative VTE events at 30-day, 60-day and 90-day periods post-randomization, stroke recurrence, stroke progression, National Institute of Health Stroke Scale (NIHSS) scores during treatment and follow-up periods and Modified Rankin Scale (MRS) scores at 30-day and 90-day follow-up. Adjudicated hemorrhages defined as major hemorrhages (symptomatic and associated with death, transfusion of at least 2 units of blood, ≥30 g/L fall in hemoglobin, required surgical intervention, retroperitoneal, or intraocular) or minor hemorrhages. Treatment emergent adverse events (TEAE), serious adverse events (SAE), all-cause mortality. Laboratory measurement of hemoglobin, hematocrit and platelet count. Not applicable.
Pharmacokinetic sampling times and bioanalytical methods:	Not applicable.
Statistical methods:	Primary efficacy endpoint: VTE events were analyzed in the efficacy population defined as treated patients who had proven VTE or had interpretable bilateral contrast venography or ultrasound during Day 1 to Day 17 period. Event rates were compared between treatment groups using Cochran-Mantel-Haenszel test adjusting for baseline NIHSS strata (<14 or ≥14). Secondary efficacy endpoint: Stroke recurrence and stroke progression were assessed on randomized and treated patients. The unadjusted analyses were done using Chi-square test or Fisher's exact test. Times to event were analyzed by the Kaplan-Meier method and 2-sided Log-rank test.

Summary:

A total of 884 patients (mean age of 65.9 years) were randomized to enoxaparin and 878 (mean age of 66.1 years) were randomized to UFH.

Efficacy results:

The incidence of adjudicated venous thromboembolic events up to Day 10 ± 4 is summarized in the following table:

Endpoint	Enoxaparin (N = 666)		UFH (N = 669)		Relative risk	p-value
	n/N	(%)	n/N	(%)	[95% CI][a]	
VTE[b]	68/666	(10.2)	121/669	(18.1)	0.57 [0.44; 0.76]	0.0001
DVT[b]	67/666	(10.1)	118/669	(17.6)	0.58 [0.44; 0.77]	0.0001
PE	1/666	(0.2)	6/669	(0.9)	0.17 [0.02; 1.39]	0.0590
Symptomatic VTE	2/666	(0.3)	7/669	(1.0)	0.29 [0.06; 1.38]	0.0959
Symptomatic PE	1/666	(0.2)	3/669	(0.4)	0.33 [0.03; 3.21]	0.3189
Symptomatic DVT	1/666	(0.2)	4/669	(0.6)	0.25 [0.03; 2.24]	0.1807
Asymptomatic DVT	66/666	(9.9)	114/669	(17.0)	0.58 [0.44; 0.77]	0.0001
Proximal DVT	30/666	(4.5)	64/669	(9.6)	0.47 [0.31; 0.72]	0.0003
Distal DVT	44/666	(6.6)	85/669	(12.7)	0.52 [0.37; 0.74]	0.0002
Proximal and distal DVT[c]	7/666	(1.1)	31/669	(4.6)	0.23 [0.10; 0.51]	<0.0001
Fatal VTE/PE	1/666	(0.2)	2/669	(0.3)	0.50 [0.05; 5.53]	0.5660

UFH = unfractionated heparin; CI = confidence interval; VTE = venous thromboembolism; DVT = deep-vein thrombosis; PE = pulmonary embolism

[a] enoxaparin/UFH

[b] adjusted for NIHSS stratification

[c] events are already counted in the proximal DVT and distal DVT

PEs override DVTs in the frequency counts.

The relative risk of VTE occurrence up to Day 10 ± 4 days was significantly lower in the enoxaparin group compared to the UFH group for adjudicated VTE, adjudicated DVT, asymptomatic DVT, proximal and distal DVT. For adjudicated PE, the relative risk in favor of enoxaparin was of borderline significance.

The reduction in VTE risk was consistent in patients with a NIHSS score ≥14 or <14.

Summary: (continued)

Efficacy results:

The occurrence of stroke recurrence up to Day 90 is summarized in the following table:

Time	Enoxaparin[a] (N = 877) n (%)	UFH[a] (N = 872) n (%)	All[a] (N = 1749) n (%)	Hazard ratio enoxaparin versus UFH[b]	[95% CI]	p-value
Day 14	3 (0.4)	3 (0.4)	6 (0.4)	0.978	[0.197; 4.844]	0.978
Day 30	7 (0.9)	5 (0.6)	12 (0.7)	1.379	[0.438; 4.347]	0.583
Day 60	9 (1.1)	9 (1.2)	18 (1.1)	0.997	[0.396; 2.512]	0.994
Day 90	12 (1.5)	13 (1.7)	25 (1.6)	0.913	[0.416; 2.000]	0.819

[a] events from randomization through the defined follow -up period

[b] hazard ratio calculated using the Cox proportional hazards model, adjusted by NIHSS stratification. Percents are hazard rates

UFH = unfractionated heparin; CI = confidence interval; NIHSS = National Institute of Health Stroke Scale

There was no statistically significant difference between the 2 treatment groups for stroke recurrence.

The occurrence of stroke progression up to Day 90 is summarized in the following table:

Time	Enoxaparin[a] (N = 877) n (%)	UFH[a] (N = 872) n (%)	All[a] (N = 1749) n (%)	Hazard ratio enoxaparin versus UFH[b]	[95% CI]	p-value
Day 14	43 (5.0)	39 (4.6)	82 (4.8)	1.144	[0.741; 1.765]	0.543
Day 30	45 (5.3)	40 (4.7)	85 (5.0)	1.168	[0.763; 1.788]	0.476
Day 60	45 (5.3)	42 (5.0)	87 (5.1)	1.112	[0.730; 1.693]	0.622
Day 90	45 (5.3)	42 (5.0)	87 (5.1)	1.112	[0.730; 1.693]	0.622

[a] events from randomization through the defined follow -up period

[b] hazard ratio calculated using the Cox proportional hazards model, adjusted by NIHSS stratification. Percents are hazard rates

UFH = unfractionated heparin; CI = confidence interval; NIHSS = National Institute of Health Stroke Scale

There was no statistically significant difference between the 2 treatment groups for stroke progression.

Summary: (continued)

Safety results:

The incidence of TEAEs, TESAEs and deaths is summarized in the following table:

	Enoxaparin (N = 877)	UFH (N = 872)	All patients (N = 1749)
	n (%)	n (%)	n (%)
Patients with at least 1 TEAE	432 (49.3)	439 (50.3)	871 (49.8)
Patients with at least 1 possibly-related TEAE	11 (1.3)	23 (2.6)	34 (1.9)
Patients with at least 1 TESAE	77 (8.8)	87 (10.0)	164 (9.4)
Patients with at least 1 possibly-related TESAE	3 (0.3)	5 (0.6)	8 (0.5)
Permanent discontinuation due to TEAE	29 (3.3)	29 (3.3)	58 (3.3)
Deaths during treatment (D1-D14)	48 (5.5)	45 (5.2)	93 (5.3)
Deaths from D1 to D90	100 (11.4%)	103 (11.8)	203 (11.6)

UFH = unfractionated heparin; TEAE = treatment-emergent adverse event; SAE = serious adverse event; TESAE = treatment emergent SAE

The incidence of TEAEs, treatment emergent SAEs (TESAEs) and their overall profile were similar in the 2 treatment groups, and possibly-related TEAEs were unfrequent.

Thrombocytopenia was reported as a TEAE in 1 patient (0.1%) in the enoxaparin group and in 2 patients (0.2%) in the UFH group. Only one was a SAE in UFH group, and the case reported in the enoxaparin group was considered as related to study drug.

Nervous system disorders, cardiac disorders, respiratory disorders and infections were the most frequently reported classes of TESAEs. These TESAEs were considered as possibly related to study drug only in a low number of cases (0.5% overall).

The total number of deaths over the whole observation period of 90 days was similar (100 and 103, respectively) in the 2 treatment groups as was the time of occurrence with respect to randomization.

Summary: (continued)

Safety results:

The causes of death as reported by the investigator during treatment and during follow-up (D1 – D90) are summarized in the following table:

	Enoxaparin (N = 877)	UFH (N = 872)	All patients (N = 1749)
	n/N (%)	n/N (%)	n/N (%)
Deaths during treatment	48/877 (5.5)	45/872 (5.2)	93/1749 (5.3)
Fatal VTE	0/877 (0.0)	2/872 (0.2)	2/1749 (0.1)
Hemorrhage	5/877 (0.6)	2/872 (0.2)	7/1749 (0.4)
Stroke	17/877 (1.9)	10/872 (1.1)	27/1749 (1.5)
Other	26/877 (3.0)	31/872 (3.6)	57/1749 (3.3)
Total deaths at follow-up	100/877 (11.4)	103/872 (11.8)	203/1749 (11.6)
Fatal VTE	0/877 (0.0)	7/872 (0.8)	7/1749 (0.4)
Hemorrhage	7/877 (0.8)	3/872 (0.3)	10/1749 (0.6)
Stroke	26/877 (3.0)	20/872 (2.3)	46/1749 (2.6)
Other	67/877 (7.6)	73/872 (8.4)	140/1749 (8.0)

UFH = unfractionated heparin; VTE = venous thromboembolism

Adjudicated bleeding events are summarized in the following table:

	Enoxaparin (N = 877)	UFH (N = 872)	Relative risk	p-value
	n (%)	n (%)	[95% CI]	
Total hemorrhages[a]	69 (7.9)	70 (8.0)	0.98 [0.71; 1.35]	0.902
Intracranial hemorrhages	20 (2.3)	22 (2.5)	0.90[0.50; 1.64]	0.741
Clinically significant intracranial hemorrhages	4 (0.5)	6 (0.7)	0.66 [0.19; 2.34]	0.547
Intracranial hemorrhages leading to death	3 (0.3)	4 (0.5)	0.75 [0.17; 3.32]	0.725
Asymptomatic intracranial hemorrhages	14 (1.6)	15 (1.7)	0.93 [0.45 1.91]	0.839
Major extracranial hemorrhages	7 (0.8)	0 (0.0)	Not applicable	0.015
Major extracranial + clinically significant intracranial hemorrhages	11 (1.3)	6 (0.7)	1.82 [0.68; 4.91]	0.228
Minor hemorrhage	42 (4.8)	48 (5.5)	0.87 [0.58; 1.30]	0.498

[a] Patients may have experienced more than 1 bleeding event.

UFH = unfractionated heparin; CI = confidence interval

Summary: (continued)	
Safety results:	The total incidence of adjudicated hemorrhages, 7.9% in the enoxaparin group and 8.0% in the UFH group, was not significantly different between the 2 treatment groups. Major extracranial hemorrhages were only reported in the enoxaparin group (7 patients: 0.8%), however, the incidence of major extracranial and clinically significant intracranial hemorrhages combined was not significantly different between the 2 treatment groups.
Pharmacokinetic results:	Not applicable.
Date of report:	28 August 2007