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Sponsor/company:	**sanofi-aventis**	**Clinicaltrials.gov Identifier:**	**NCT00265993**
		Study Code:	**XRP4563A_4001**
Generic drug name:	**enoxaparin**	**Date:**	**29-JAN-2010**

Title of the study:	The efficacy of once daily enoxaparin treatment in acute venous thromboembolic disease: an open-label, single arm, multi-center, phase IV clinical trial (XRP4563A/4001)		
Investigator(s):	Prof Dr Mehmet KURDOĞLU ISTANBUL UNIVERSITY, FACULTY OF MEDICINE, EMERGENCY SURGERY UNIT 34390 ÇAPA – ISTANBUL		
Study center(s):	Fourteen active centers from Turkey		
Publications (reference):	None		
Study period: Date first patient enrolled: 24 December 2004 Date last patient completed: 07 January 2009		Phase of development: IV	
Objectives:	<u>Primary:</u> Evaluation the efficacy of once daily enoxaparin treatment in acute venous thromboembolic disease <u>Secondary:</u> Evaluation the safety profile of once daily enoxaparin treatment in acute venous thromboembolic disease		
Methodology:	Open-label, single arm, multi-center, phase IV clinical trial		
Number of patients:	Planned: 250	Randomized: 251	Treated: 246
Evaluated:	246	Safety: 246	
	5 Cases were not included in the final statistical analysis due to treatment with LMWH other then investigational products		
Diagnosis and criteria for inclusion:	Male or female patients aged ≥18 with symptomatic lower extremity deep vein thrombosis diagnosed with Doppler ultrasonography (USG), whether accompanied by verified symptomatic pulmonary emboli or not, and carrying temporary risk.		

Investigational product: Dose: Administration:	Enoxaparin 1.5 mg/kg once daily subcutaneously
Duration of treatment: Enoxaparin treatment was maintained until INR value reaches >2 after initiation of oral anticoagulant (warfarin) treatment.	Duration of observation: 18 months
Reference therapy:	NA
Criteria for evaluation:	
Efficacy:	Frequency of deep vein thrombosis (as per definition, recurrence of DVT is defined as re-occlusion of any vein during treatment or follow-up period) verified through Doppler USG or of occurrence of pulmonary emboli cases verified through multisliced contrast spiral computed tomography or pulmonary perfusion scintigraphy or of post thrombophlebitic syndrome within 3 and 18 months as of the start of treatment.
Safety:	Primary: ▪ Frequency of hemorrhage (minor and major hemorrhages) during the period in which the study drug was applied. Secondary: ▪ Frequency of hemorrhage during the 3 months' period of follow up with oral anticoagulant ▪ Laboratory findings beyond the normal limits during the treatment and follow up periods. ▪ Standard adverse event reporting.
Statistical methods:	The efficacy and safety parameters were summarized by using descriptive statistics (mean, ratio, median, standard deviation, confidence intervals). The analyses of the changes observed during the treatment period as compared with pretreatment period and various subgroups analysis were conducted through parametric or non-parametric tests depending on the character of the data (t-test, Fischer's exact test, MacNemar). Limit of statistical significance has been determined as $P < 0.05$.

SUMMARY Efficacy results:	TROMBOTEK study intended to provide a long-term follow-up data for DVT patients who seek medical care for Acute Venous Thromboembolism. The study protocol required initiation of treatment with enoxaparin at a fixed dose (1.5 mg/kg/day) after enrollment, and ambulatory treatment was planned with oral anticoagulants (warfarin sodium, 5mg/day).After enrollment and during initial treatment period, patients were evaluated during Day 10 and Day 30. After Day 30 visit, patients were seen and evaluated at every 3 months, for the long term follow-up period. On physical evaluation, ambulatory treatment significantly reduced leg pain, edema, tenderness, increase in local leg temperature and edema with godet formation. Calf and mid thigh circumferences decreased significantly, immediately after initiation of treatment. Besides positive outcomes in physical evaluation criteria, duplex ultrasound examinations showed significant decrease in the number of occluded veins with treatment. For common iliac vein, the number of occluded veins decreased from enrollment through Visit 4 (P=0.000) however showed a slight and non-significant decrease until Visit 6 and Visit 7. Similar results were shown for external iliac, common femoral, superficial femoral, popliteal and tibioperoneal veins. Despite significant decrease in occluded veins in overall, there were 11 recurrences of venous thrombus (4.47 %) as shown by ultrasound examination of lower extremity veins. All recurrences occurred after 12th month visit (two cases during 12th month visit), mostly presenting during the last visit of the study (18th month visit). In five cases thrombus occurred at right common femoral vein, others occurred at common iliac, external iliac and superficial femoral veins of the left side. During these occurrences the patients were not receiving any form of treatment. However, there were three cases of thrombus recurrences which were not specified by duplex ultrasound examination but only with clinical symptoms and verified via physical examination. In two cases these patients were on coumadine treatment only and recurrences occurred between Day 10 and Day 30. In the other case patient was not receiving any treatment and recurrence was revealed only at 6 month. There was only one case of pulmonary embolism (0.41%) which was diagnosed by means of pulmonary perfusion scintigraphy during the visit at 30 days and this patient was receiving oral anticoagulant during the incident. Additionally, there were two cases of thrombus occurrences one as right transverse sinus and the other as right retinal artery/vein occlusion, both of which were recorded as adverse events and during the last visit (at 18 months). These patients were not receiving any treatment at the time of recurrences. INR increased during the first 10 days of treatment, significantly at 5-7 days. This increase remained flat at a certain level after Day 15, however dropping below to the levels that was achieved within the first 10 days of treatment. Mean INR evaluation was 2.27 at 90 days. Evaluation of D-Dimer also revealed that DVT, almost always is related with very high levels of D-Dimer, which decreased significantly with treatment. This study was planned as a long term follow-up (18 months) of patients with DVT, together with the ambulatory treatment option. Patients were also evaluated for post-thrombophlebitic syndrome (CEAP), during the last 3 visits (Month 6, 12 and 18). Swelling was the most frequent patient complaint during the last 3 visits, with a tendency to increase to 42.6 % of all patients during the last visit (p=0.248). Additionally, evaluation for post-thrombophlebitic syndrome outcomes revealed one case of active ulcer occurrence, during the 18 month visit (0.7 %).

Efficacy results (cont.)	Physical examination revealed a high percentage of patients with difference in leg circumferences (49.4 % during Visit 5 and 52.0% during visit 7, p= 0,3912 and 0.4414), however, there were no ulcerations at Visit 5 and 6 and only one ulceration case at Visit 7. As a conclusion, acute venous thromboembolic disease treatment with enoxaparin by subcutaneous route at a dose of 1.5 mg/kg once daily and oral anticoagulant treatment (warfarin sodium 5 mg/day) for a minimum of 3 months showed that this combination is an effective treatment in reducing thrombus formation/ organization at all levels of lower extremity venous system. Long term follow-up results also revealed that ambulatory treatment of acute venous thromboembolic disease is an effective and cost-effective option.
<u>Safety results:</u>	During the study .628 adverse events were recorded and 51 of them were classified as Serious Adverse Events. Sixty four adverse events (10.19%) were noted as related to study drugs (enoxaparin and/or warfarin). Only one serious adverse event was noted as related to study drugs. Serious adverse events were hospitalization due to various medical conditions (33.3%), co-morbidities resulting in death (23.5%), thrombosis related events (11.7%) various surgical operations resulting in hospitalizations (7.8%) and hemorrhage events (7.9%). Sixty five 'haemorrhage events' occurred in 52 patients. Hemorrhages were classified as major and minor hemorrhages (Major bleeding is defined as any hemorrhage which resulted in a 3 g/dL or greater fall in hemoglobin, or retroperitoneal bleeding or required a transfusion of at least 2 units of Packed Red Blood Cells). Five events of haemorrhage, observed in 5 patients, were interpreted as major and serious (SAE). These events included subdural hematoma, hemoptysis, epistaxis, increased menorrhagia and intra-abdominal haemorrhage. These events completely resolved and four cases were interpreted as not related to study drugs. In all five cases patients were on warfarin treatment at the time of the occurrence of bleeding. There were 60 cases of minor bleedings. In 24 of these minor bleeding cases (40%) patients were enoxaparine and warfarin combination treatment.
Date of report:	24 December 2009