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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Fragmin® / Dalteparin sodium

PROTOCOL NO.: A6301086

PROTOCOL TITLE: A 6 Month, Prospective, Open-Label Multiple Center Extension Trial to Evaluate the Long Term Safety and Sustained Efficacy of Fragmin in the Treatment of Chronic Foot Ulcers in Diabetic Patients With Peripheral Arterial Occlusive Disease

Study Centers: A total of 26 centers participated in study including 5 in Sweden, 4 each in Russian Federation and Poland, 3 in Ukraine, 2 in Czech Republic, and 1 each in Austria, Belgium, Canada, Denmark, Germany, Greece, Norway, and the United Kingdom.

Study Initiation and Final Completion Dates: 01 October 2008 to 06 October 2010.

Phase of Development: Phase 3b

Study Objectives:

Primary Objective: To evaluate long-term safety and tolerability of dalteparin in treatment of chronic neuroischemic foot ulcers in diabetic subjects with peripheral arterial occlusive disease (PAOD) and peripheral neuropathy.

Secondary Objectives:

- Evaluating the number of diabetic subjects with chronic neuroischemic foot ulcers who had improved ulcers at Baseline that develop intact skin healing
- Evaluating the number of diabetic subjects with chronic neuroischemic foot ulcers who had unchanged ulcers at Baseline that develop intact skin healing
- Evaluating the number of diabetic subjects with chronic neuroischemic foot ulcers who had unchanged ulcers at Baseline that develop improved ulcers
- Evaluating the effect of dalteparin on the number of diabetic subjects with chronic neuroischemic foot ulcers requiring an amputation
- To evaluate the effect of dalteparin on the time to intact skin healing (this was done using the Baseline Visit of the previous study as the starting point)

- To evaluate the effect of dalteparin on the time to amputation (this was done using the Baseline Visit of the previous study as the starting point)

- To evaluate the cardiovascular morbidity and mortality of diabetic subjects with chronic neuroischemic foot ulcers on dalteparin

- To evaluate the effect of dalteparin on the reduction of pain associated with the foot ulcer

- To evaluate the effect of dalteparin on health related quality of life as measured using the Short Form 36 (SF-36) questionnaire

METHODS

Study Design: This study was designed as a Phase 3b, 6 month, prospective, open-label, multiple center extension study to evaluate the long-term safety and sustained efficacy of dalteparin in the treatment of chronic neuroischemic foot ulcers in diabetic subjects with PAOD and peripheral neuropathy.

Subjects who had completed the previous study (A 6 Month, Prospective, Randomized, Double Blind, Placebo-Controlled, Parallel Group, Multiple Center Trial to Evaluate the Efficacy and Safety of Fragmin in the Treatment of Chronic Neuroischaemic Foot Ulcers in Diabetic Patients [NCT00662831]) and had a positive ulcer treatment response, defined as a reduction in the study ulcer area size from Baseline (ie, ulcer area reduction >0) were offered enrollment into this open-label extension trial. The study ulcer used in this study was the same as that assessed in the previous study. However, subjects whose study ulcer had undergone intact skin healing or whose study ulcer area at Visit 8 (End of Treatment [EOT] Visit) was greater or equal to the baseline ulcer area (ie, ulcer area increase ≥0%) in the previous study were not eligible for this study.

In order to maintain continuity of treatment all eligible subjects were rolled-over into this extension study within a 2-week window period after completing Visit 8 (EOT Visit) of the the previous study. All subjects who met the entry criteria received dalteparin once daily for a maximum duration of 6 months or until intact skin healing. All subjects received study treatment over and above the standard of diabetic ulcer care. There was no control group for this study. The schedule of activities is presented in Table 1.

Table 1. Schedule of Activities

Protocol Activity	Visit 1 Screening/ Baseline Week 0	Visit 2 Week 4 (±5 Days)	Visit 3 Week 8 (±5 Days)	Visit 4 Week 12 (±5 Days)	Visit 5 Week 16 (±5 Days)	Visit 6 Week 20 (±5 Days)	Visit 7 EOT Week 24/Early Termination Visit (±5 Days)[a]	Follow-Up
Informed consent	X							
Vitals	X	X	X	X	X	X	X	
Physical examination	X							
Inclusion/exclusion criteria	X							
University of Texas wound classification	X							
Laboratory tests								
Haematology[b]	X[c]	X		X			X	
Blood chemistry	X[c]			X			X	
Estimated creatinine clearance[d]	X[c]						X	
Hb1Ac	X[c]			X			X	
Fibrinogen and D-dimer	X[c]						X	
CRP	X[c]			X			X	
Anti-factor Xa		X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	
Urine pregnancy test[f]	X							
Deep ulcer swab for culture[g]	X	X	X	X	X	X		
Dispense trial medication	X	X	X	X	X	X		
Trial medication return/count		X	X	X	X	X	X	
Assessments								
Ulcer assessment	X[h]	X	X	X	X	X	X	
Amputation assessment	X	X	X	X	X	X	X	
Safety - adverse events	X	X	X	X	X	X	X	X
Cardiovascular morbidity and mortality events	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	
11-point likert pain scale	X[i]						X	
SF-36	X[i]						X	

CRP = C-reactive protein; EOT = End of Treatment; Hb1Ac = glycated haemoglobin; HIT = heparin induced thrombocytopenia; IEC = Independent Ethics Committee; IRB = Institutional Review Board; SF-36 = Short form 36.

Table 1. Schedule of Activities

a. All subjects who had intact skin healing or who had impaired healing as defined by ulcer area increase >50%, or were withdrawn for any other reason had an early discontinuation visit (this took the place of the 4 weekly visit).
b. Haematology was repeated at unscheduled visit in order to comply with local regulations on monitoring subjects on lower molecular weight heparins for HIT type II.
c. Laboratory test only to be performed if the laboratory tests of Visit 8 (EOT Visit) of the previous study were not taken/available or at the clinical discretion of the Investigator.
d. All subjects with an estimated creatinine clearance <30 mL/minute required an unplanned visit on Day 3 or Day 4 of monitoring of anti-factor Xa levels. All subjects with a creatinine clearance of <60 had their anti-factor-Xa monitored at each visit. Subjects were instructed to take the dalteparin injection 3-5 hours prior to their visit.
e. Laboratory tests were performed only on subjects who had an estimated creatinine clearance <60 ml/minute (including subjects with a creatinine clearance <30 mL/minute).
f. Urine pregnancy test was performed on women with childbearing potential. Pregnancy tests were also repeated as per request of IRB/IEC or if required by local regulations.
g. Only if clinically indicated.
h. Ulcer assessment was done at Screening for eligibility.
i. Only performed if not done at visit 8 (EOT Visit) of the previous study.

Number of Subjects (Planned and Analyzed): The number of subjects enrolled was not based on statistical consideration but rather was dependent upon the number of subjects who completed the previous study and met the criteria for inclusion in the study. It was estimated that around 215 subjects would be enrolled in the study. A total of 62 subjects were enrolled and treated in the study.

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged ≥18 years who completed the 6 month study duration of the previous study, with a positive ulcer treatment response, defined as a reduction in the study ulcer area size (ie, ulcer area reduction >0%) at Visit 8 (EOT Visit) from Baseline of the previous study. All ulcers must have had an ulcer staging of 1C, 2C, 1D or 2D according to the University of Texas wound classification system.

Exclusion Criteria: Subjects who were found to be major protocol violators or did not complete the 6 month study period of the previous study; those with intact skin healing (defined as 100% reduction in ulcer surface area with full epithelialisation) or study ulcer area greater or equal to the baseline ulcer area (ie, ulcer area increase ≥0%) at or prior to the EOT Visit of the previous study; an ulcer grading of 0 or 3 or staging of A or B according to the University of Texas wound classification system; a known bleeding disorder or evidence of active bleeding; or who were on dialysis were excluded from the study.

Study Treatment: All subjects received dalteparin 5000 IU (0.2 mL) once daily administered through subcutaneous (SC) injection preferably given in the abdomen, although the thigh and buttocks were also used. Subjects were instructed to sit or lie down and dalteparin was administered by deep SC injection. Dalteparin was injected in a U-shape area around the navel, the upper outer side of the thigh or the upper outer quadrangle of the buttock. The injection site was varied daily. When the area around the navel or thigh was used, a fold of skin was lifted using the thumb and forefinger while giving the injection. The entire length of the needle was inserted at a 45 to 90 degree angle.

Efficacy and Safety Endpoints:

Efficacy Endpoints:

- Number of subjects who have intact skin healing
- Number of subjects with improved ulcer healing
- Number of subjects who underwent amputation (major and minor)
- Number of subjects who underwent major amputation
- Number of subjects who underwent minor amputation
- Time to healing
- Time to amputation

- Number of major cardiovascular disease events (MCVE), defined as any one of the following:
    - Death due to vascular cause
    - Non-fatal myocardial infarction (MI) excluding procedures related to MI
    - Coronary revascularization procedures not related to MI
    - Hospitalization for unstable angina
    - Non-fatal stroke
- The 11-point Likert scale
- SF-36

Safety Endpoints:

- The number of all hemorrhages (major and minor)
- The number of major hemorrhages
- The number of minor hemorrhages
- The number of clinically relevant minor hemorrhages
- The number of minor trivial hemorrhages
- Incidence, severity, and relatedness to treatment of all reported and treatment emergent adverse events (TEAEs) and withdrawals from the trial due to adverse events (AEs)

Safety Evaluations: The safety evaluations included the assessment of major and minor hemorrhages, serious adverse events (SAEs), laboratory evaluations (hematology; blood biochemistry; C-reactive protein; estimated creatinine clearance; hemoglobin A1c; anti-factor Xa levels; urine pregnancy test; deep ulcer swab for microbiology, culture and sensitivity), physical examination, peripheral neuropathy assessment; cardiovascular morbidity and mortality, vital signs, and AEs.

Statistical Methods: The intent-to-treat (ITT) population was defined as all subjects enrolled into the study.

The safety population included all subjects who took at least 1 dose of study drug.

The primary efficacy analysis was intended to investigate the sustained efficacy of dalteparin. The responder rate of subjects who had intact skin healing after a maximum of an additional 6 months of treatment was summarized for binary data. This analysis was carried out using the ITT population. Only the summary statistics evaluations were performed.

All secondary endpoints were analyzed using the ITT population. The proportion of subjects who had major amputations and minor amputations were analyzed separately using the same analysis as specified for the primary endpoint. The individual domains, total utility score and visual analog scale was summarized at each visit. The change from Baseline to the EOT in the 11-point Likert scale was summarized between treatment groups. Scores at each visit were summarized. The change from Baseline at Week 24 in each domain of the Short-Form Health Survey Score (SF-36) questionnaire was presented.

RESULTS

Subject Disposition and Demography: A total of 62 subjects were screened and assigned to study treatment (Table 2). A total of 32 subjects discontinued the study prematurely.

Table 2 Disposition of Subjects

Variable	Dalteparin Number (%) of Subjects
Screened	62
Assigned to study treatment	62
Treated	62
Completed	30 (48.4)
Discontinued	32 (51.6)
Relation to study drug not defined	28 (45.2)
Insufficient clinical response	5 (8.1)
No longer willing to participate in study	1 (1.6)
Other	16 (25.8)
Protocol violation	6 (9.7)
Not related to study drug	4 (6.5)
Adverse event	4 (6.5)
Analyzed for safety	
Adverse events	62 (100.0)
Laboratory data	62 (100.0)

Discontinuations occurring outside the lag period were attributed to the last study treatment received.

Subject demographics for the entire population are summarized in Table 3. Forty six males and 16 females were assigned to study drug. Most of the subjects were White.

Table 3. Demographic Characteristics

Variable	Dalteparin		
	Male	Female	Total
Number (%) of subjects	46	16	62
Age (years)			
18-44	2 (4.3)	0	2 (3.2)
45-64	22 (47.8)	6 (37.5)	28 (45.2)
≥65	22 (47.8)	10 (62.5)	32 (51.6)
Mean	64.2	68.3	65.2
SD	11.4	9.4	11.0
Range	28-84	52-83	28-84
Race			
White	45 (97.8)	16 (100.0)	61 (98.4)
Asian	1 (2.2)	0	1 (1.6)
Weight (kg)			
Mean	94.5	87.0	92.6
SD	19.9	15.3	19.0
Range	60.0-139.0	57.0-111.0	57.0-139.0
Height (cm)			
Mean	176.2	162.5	172.7
SD	7.4	6.8	9.4
Range	162.0-195.0	144.0-173.0	144.0-195.0

SD = standard deviation.

Efficacy Results:

Number of Subjects Who Have Intact Skin Healing: Nineteen (19) subjects showed intact skin healing after an additional 6 months of treatment. The response rate was 30.6%. The responder rate for the primary efficacy endpoint is shown in Table 4.

Table 4. Summary of Efficacy Endpoints (ITT)

Endpoint	Dalteparin		
	N	N*	Responder Rate n (%)
≥50% Reduction in ulcer surface area including intact skin healing[a]	62	60	44 (71.0)
≥50% Reduction in ulcer surface area excluding intact skin healing[a]	62	60	25 (40.3)
Subjects with intact skin healing[a]	62	60	19 (30.6)
Subjects with lower limb amputations[b]	62	62	1 (1.6)

N was the number of subjects in the intention to treat population for the given treatment arm.
N* was the number of subjects with a non-missing response.
n was the number of subjects who were responders.
ITT = intent-to-treat.
a. All percentages use N in the denominator.
b. All percentages use N* in the denominator.

Number of Subjects With Improved Ulcer Healing: There were 25 (40.3%) responders with ≥50% reduction in ulcer surface area excluding intact skin healing (Table 4).

Number of Subjects Who Underwent Amputation (Major and Minor) Amputations: There was 1 (1.6%) responder with lower limb (major) amputation (Table 5). There were no minor amputations.

Table 5. Incidence and Severity of Lower Limb Amputations (Safety Population)

Number of Subjects	Dalteparin n (%)
Evaluable for lower limb amputations	62
Number of lower limb amputations	1 (1.6)
Subjects with lower limb amputations	1 (1.6)
Subjects with major lower limb amputations	1 (1.6)
Subjects with minor lower limb amputations	0

n = number of subjects with pre specified criteria.

Time to Healing: This secondary efficacy endpoint was not evaluated for this study.

Time to Amputation: This secondary efficacy endpoint was not evaluated for this study.

Number of Major Cardiovascular Event: One MCVE was observed and it was of non-fatal nature.

The 11-point Likert scale: The mean (±SD) 11-point Likert scale score was 2.4 (±2.14) at Baseline and 2.2 (±2.14) at EOT Visit (Table 6).

Table 6. Summary of 11-Point Likert Scale by Visit

Variable	Dalteparin	
	Baseline	EOT
N	59	57
Mean	2.4	2.2
SD	2.14	2.14
IQR	0.00-3.00	0.00-4.00
Min, Max	0.00, 8.00	0.00, 8.00

EOT = End of Treatment; IQR = Interquartile Range; Max= maximum; Min = minimum; N = number of subjects; SD = standard deviation.

Short Form-36: The mean SF-36 scores corresponding to physical functioning, role limitations due to physical health problems, bodily pain, visibility, social functioning, and role limitations were almost similar from Baseline to EOT Visit. A slight decrease in the score was observed for general health. The detailed scores have been presented in Table 7.

Table 7. Summary of SF-36 Score by Visit

	Dalteparin							
	Physical Functioning		**Role-Physical**		**Bodily Pain**		**General Health**	
	Baseline	**EOT**	**Baseline**	**EOT**	**Baseline**	**EOT**	**Baseline**	**EOT**
N	43	57	43	57	43	57	43	57
Mean	34.7	34.8	36.5	35.1	45.1	45.5	44.1	42.9
SD	11.68	11.21	10.66	10.99	9.56	11.26	4.50	4.57
IQR	25.47-46.51	25.47-44.41	29.91-42.16	27.47-42.16	37.18-51.13	37.18-53.67	41.02-48.17	40.06-45.78
Min, Max	14.94, 54.93	14.94, 57.03	17.67, 56.85	17.67, 56.85	19.86, 62.12	19.86, 62.12	32.91, 50.55	31.48, 55.32
	Visibility		**Social Functioning**		**Role-Emotional**		**Mental Health**	
N	43	57	43	56	43	57	43	57
Mean	48.1	48.7	34.3	35.1	36.6	36.3	42.1	42.2
SD	5.67	6.25	7.58	4.47	13.81	14.91	6.42	7.12
IQR	42.72-52.09	45.85-52.09	29.58-35.03	35.03-37.76	24.78-48.10	24.78-48.10	38.74-47.19	38.74-47.19
Min, Max	36.48, 58.33	33.36, 64.58	13.22, 51.40	24.13, 45.94	9.23, 55.88	9.23, 55.88	27.48, 52.82	21.85, 55.64
	Physical (PCS)		**Mental (MCS)**					
N	43	56	43	56				
Mean	40.1	39.4	41.4	41.9				
SD	7.74	8.96	7.17	7.85				
IQR	35.03-45.48	33.40-47.29	35.71-49.05	36.03-48.28				
Min, Max	21.93,54.05	18.81,58.32	26.40,53.59	23.75,59.47				

EOT = end of treatment; IQR = interquartile range; Max = maximum; MCS = mental component summary; Min = minimum; N = total number of subjects; PCS = physical component summary; SD = standard deviation; SF-36 = Short form 36.

Safety Results:

The treatment-emergent non serious AEs are presented in Table 8.

Table 8. Treatment-Emergent Non Serious Adverse Events (All Causalities)

System Organ Class and MedDRA Preferred Term	Dalteparin n (%)
Number (%) of subjects:	
Evaluable for AEs	62
With AEs	26 (41.9)
Blood and lymphatic system disorders	1 (1.6)
Anaemia	1 (1.6)
Cardiac disorders	2 (3.2)
Atrial fibrillation	1 (1.6)
Cardiac failure	2 (3.2)
Ear and labyrinth disorders	1 (1.6)
Vertigo	1 (1.6)
Endocrine disorders	1 (1.6)
Hypothyroidism	1 (1.6)
Eye disorders	1 (1.6)
Panophthalmitis	1 (1.6)
Gastrointestinal disorders	4 (6.5)
Abdominal pain	1 (1.6)
Diarrhoea	2 (3.2)
Haemorrhoidal haemorrhage	1 (1.6)
Nausea	2 (3.2)
General disorders and administration site conditions	2 (3.2)
Oedema peripheral	1 (1.6)
Ulcer haemorrhage	1 (1.6)
Infections and infestations	12 (19.4)
Cystitis	1 (1.6)
Diabetic foot infection	3 (4.8)
Erysipelas	2 (3.2)
Folliculitis	1 (1.6)
Infected skin ulcer	1 (1.6)
Nasopharyngitis	4 (6.5)
Orchitis	1 (1.6)
Pneumonia	1 (1.6)
Respiratory tract infection	1 (1.6)
Tooth infection	1 (1.6)
Urinary tract infection	1 (1.6)
Wound infection	1 (1.6)
Injury, poisoning and procedural complications	4 (6.5)
Chest injury	1 (1.6)
Contusion	2 (3.2)
Wound	1 (1.6)
Investigations	1 (1.6)
Body temperature increased	1 (1.6)
Metabolism and nutrition disorders	1 (1.6)
Hypertriglyceridaemia	1 (1.6)
Musculoskeletal and connective tissue disorders	3 (4.8)
Back pain	2 (3.2)
Musculoskeletal pain	1 (1.6)
Osteitis	1 (1.6)

Table 8. Treatment-Emergent Non Serious Adverse Events (All Causalities)

System Organ Class and MedDRA Preferred Term	Dalteparin n (%)
Psychiatric disorders	1 (1.6)
Sleep disorder	1 (1.6)
Renal and urinary disorders	1 (1.6)
Urinary retention	1 (1.6)
Respiratory, thoracic and mediastinal disorders	1 (1.6)
Dyspnoea	1 (1.6)
Skin and subcutaneous tissue disorders	9 (14.5)
Decubitus ulcer	1 (1.6)
Diabetic ulcer	2 (3.2)
Dry gangrene	1 (1.6)
Skin discolouration	1 (1.6)
Skin ulcer	4 (6.5)
Urticaria	1 (1.6)
Surgical and medical procedures	1 (1.6)
Tooth extraction	1 (1.6)
Vascular disorders	3 (4.8)
Circulatory collapse	1 (1.6)
Hypertensive crisis	1 (1.6)
Intra-abdominal haematoma	1 (1.6)

Subjects were only counted once per treatment for each row.
Included data up to 30 days after last dose of study drug.
MedDRA (version 13.1) coding dictionary applied.
AE = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with AEs.

Three (3) treatment-related AEs (contusion, hypertensive crisis, and intra-abdominal hematoma) were observed in the study. All the treatment-related AEs were moderate in severity.

Serious Adverse Events: A total of 11 subjects experienced SAEs during the study (Table 9). None were considered treatment-related.

Table 9. Treatment-Emergent Serious Adverse Events (All Causalities)

System Organ Class and MedDRA Preferred Term	Dalteparin n (%)
Number (%) of subjects:	
Evaluable for AEs	62
With AEs	11 (17.7)
Blood and lymphatic system disorders	1 (1.6)
Anaemia	1 (1.6)
Cardiac disorders	2 (3.2)
Cardiac failure	1 (1.6)
Cardiac failure acute	1 (1.6)
Myocardial infarction	1 (1.6)
Infections and infestations	8 (12.9)
Cellulitis	2 (3.2)
Erysipelas	1 (1.6)
Gangrene	1 (1.6)
Infected skin ulcer	1 (1.6)
Pneumonia	2 (3.2)
Urinary tract infection	1 (1.6)
Injury, poisoning and procedural complications	1 (1.6)
Fall	1 (1.6)
Femoral neck fracture	1 (1.6)
Metabolism and nutrition disorders	1 (1.6)
Hypoglycaemia	1 (1.6)
Musculoskeletal and connective tissue disorders	1 (1.6)
Pain in extremity	1 (1.6)
Nervous system disorders	1 (1.6)
Carpal tunnel syndrome	1 (1.6)

Subjects were only counted once per treatment for each row.
Included data up to 30 days after last dose of study drug.
MedDRA (version 13.1) coding dictionary applied.
AE = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with AEs.

Discontinuation: There were 4 cases of permanent withdrawals due to AE in the study. Three (3) of the subject discontinuations were attributed to a severe AE (infected skin ulcer, gangrene, and cellulitis). One withdrawal was attributed to a moderate AE (fibrin d dimer increased). All the AEs except for fibrin d dimer increased were considered as treatment-emergent. Two (infected skin ulcer and gangrene) of them were considered as resolved while 2 (fibrin d dimmer increased and cellulitis) remained unresolved at the time the database was finalized.

There were 3 subjects who temporarily discontinued from the study. These discontinuations were attributed one subject each to mild (tooth extraction), moderate (contusion & intra-abdominal hematoma) and severe (cardiac failure acute, myocardial infarction & pneumonia) AEs. All the AEs were classified as treatment-emergent and were considered as resolved. There were no cases of dose reduction in the study.

Deaths: No event of death was recorded in the study.

Hemorrhages: Two minor hemorrhages were reported, one was classified as hemorrhage with clinically relevant minor bleeding, while the other was a trivial bleeding (Table 10).

Table 10. Incidence and Severity of Haemorrhages (Safety Population)

Variable	Dalteparin n (%)
Number of subjects	62
Evaluable for haemorrhages	62 (100)
Subjects with haemorrhages	2 (3.2)
Subjects with major haemorrhages	0
Subjects with minor haemorrhages	2 (3.2)
Subjects with clinically relevant minor bleeding	1 (1.6)
Subjects with trivial bleeding	1 (1.6)

Minor hemorrhages were defined as bleeding that did not meet the definition for major bleeding and were divided into 2 groups: 1. Clinically relevant minor bleeding; 2. Trivial bleeding.
n = number of subjects with hemorrhages.

Vital Signs, ECG, Physical Findings, and Other Observations: One instance of clinical significant laboratory abnormalities was reported during the study. In 1 subject, abnormal values were reported for albumin, C-reactive proteins, D-Dimer level, and platelet count on Day 0. While there was a decrease in albumin level, an increase was reported for the other values. These abnormal values were attributed to a pneumonia attack experienced by the subject. While abnormal albumin was resolved, it was unresolved with respect to other parameters. The severity of this AE was assessed to be moderate. An increase in the body temperature was seen in another subject on Day 3 of study. However, it was resolved later and no action was taken with respect to treatment.

CONCLUSIONS:

- No conclusions could be drawn regarding efficacy. Regarding safety dalteparin was well tolerated, with no unexpected safety findings.