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

PROTOCOL NO.: A6301083

PROTOCOL TITLE: 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

Study Centers: A total of 62 centers took part in the study of which 59 enrolled subjects; 8 in United Kingdom (UK), 6 each in Denmark, the Russian Federation, and Sweden, 5 in Poland, 4 each in Greece, Italy, and Ukraine, 3 each in the Czech Republic, Lithuania, and Spain, 2 in Austria, 1 each in Belgium, Canada, Finland, Germany, and Norway.

Study Initiation Date and Final Completion Date: 08 April 2008 to 05 October 2010. The study was terminated prematurely on 13 May 2010.

Phase of Development: Phase 3b

Study Objectives:

Primary Objective: To evaluate the effect of dalteparin compared to placebo on the healing of chronic neuroischaemic foot ulcers in diabetic subjects with peripheral arterial occlusive disease (PAOD) and peripheral neuropathy, as determined by the number of subjects who had ≥50% reduction in ulcer surface area including intact skin healing after a maximum of 6 months of treatment.

Secondary Objectives:

- To evaluate the effect of dalteparin compared to placebo on the number of diabetic subjects with chronic neuroischaemic foot ulcers who had intact skin healing within the 6-month treatment period;

- To evaluate the effect of dalteparin compared to placebo on the number of diabetic subjects with chronic neuroischaemic foot ulcers requiring an amputation within the 6-month treatment period;

- To evaluate the safety and tolerability of dalteparin compared to placebo in treatment of diabetic subjects with neuroischaemic foot ulcers;

- To evaluate the effect of dalteparin compared to placebo on the all-cause mortality of diabetic subjects with chronic neuroischaemic foot ulcers;
- To evaluate the effect of dalteparin compared to placebo on cardiovascular morbidity and mortality of diabetic subjects with chronic neuroischaemic foot ulcers;
- To evaluate the effect of dalteparin compared to placebo on the time to amputation;
- To evaluate the effect of dalteparin compared to placebo on the time to intact skin healing;
- To evaluate the effect of dalteparin compared to placebo on health related quality of life as measured using European Quality of Life (EuroQol)-5 Dimensions (EQ-5D) questionnaire;
- To evaluate the effect of dalteparin compared to placebo on health related quality of life as measured using Short Form (SF)-36 questionnaire;
- To evaluate the effect of dalteparin compared to placebo on the local tissue oxygenation (pO_2) as measured by transcutaneous pO_2;
- To evaluate the effect of dalteparin compared to placebo on reduction of pain associated with the foot ulcer.

METHODS:

Study Design: The study was planned as a 6-month, prospective, randomized, double blind, placebo-controlled, parallel group clinical trial to evaluate the efficacy and safety of dalteparin in the treatment of chronic neuroischaemic foot ulcers in diabetic subjects.

This was a Phase 3b multicenter study. All subjects who had undergone the appropriate informed consent procedure and whose eligibility had been established as per inclusion/exclusion criteria were enrolled and randomized at a 2:1 ratio of dalteparin or placebo, respectively.

Treatment duration was up to a maximum of 6-months or until impaired healing, defined as an increase of >50% in ulcer area or until intact skin healing. All subjects received study treatment over and above the standard of diabetic ulcer care, which included off-loading the ulcer, debridement and treatment of infections and edema.

The trial incorporated an interim analysis for futility. The study did not meet its target number of subjects. Therefore, on 13 May 2010, the decision was made to terminate the study prematurely. As a result of the early termination, only summary statistics are presented.

The schedule of activities during the study is provided in Table 1.

Table 1. Timetable of Study Procedures/Evaluations

Protocol Activity	Visit 1 Screening/ Enrollment Week -1	Visit 2 Randomization/ Baseline Week 0	Visit 3 Week 4 (±5 Days)	Visit 4 Week 8 (±5 Days)	Visit 5 Week 12 (±5 Days)	Visit 6 Week 16 (±5 Days)	Visit 7 Week 20 (±5 Days)	Visit 8 EOT Week 24/Early Termination[a] Visit (±5 Days)	Follow Up
Informed consent	X								
Demography	X								
Vitals	X	X	X	X	X	X	X	X	
Ophthalmological examination[b]	X								
Medical history and physical examination	X								
Height, weight, waist: hip ratio	X								
Inclusion/exclusion criteria	X	X							
Toe/arm BP index	X								
Peripheral neuropathy assessment and NDS score	X								
University of Texas Wound Classification	X								
Registration/randomization		X							
Laboratory tests									
Haematology[c]	X		X		X			X	
Blood chemistry	X				X			X	
Estimated creatinine clearance[d]		X						X	
Prothrombin complex	X								
Anti-factor Xa levels[e]			X[d]	X[d]	X[d]	X[d]	X[d]		
Hb1Ac		X			X			X	
Fibrinogen and D-dimer		X						X	
C-reactive protein	X				X			X	
Urine pregnancy test[f]	X								
Deep ulcer swab for culture[g]	X		X	X	X	X	X		
$TcpO_2$		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[h]	X	X	X	X	X	X	
Amputation assessment			X	X	X	X	X	X	
Safety-adverse events		X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	

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EQ-5D		X						X	
SF-36		X						X	
11-point Likert pain scale		X						X	

BP = blood pressure; EOT = end-of-treatment; EQ-5D = European Quality of Life-5 Dimensions; Hb1Ac = glycated hemoglobin; HIT = heparin induced thrombocytopaenia; IEC = Institutional Ethics Committee; IRB = Institutional Review Board; NDS: Neuropathy Disability Score; SF-36 = Short Form-36; $TcpO_2$ = transcutaneous local tissue oxygenation (pO_2).

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. An ophthalmological exam was done at screening to exclude subjects with proliferative diabetic retinopathy that in the Investigators opinion resulted in an increased risk of hemorrhage if treated with dalteparin.
c. Hematology was repeated at an unscheduled visit in order to comply with local regulations on monitoring patients on lower molecular weight heparins for HIT type 2.
d. All subjects with an estimated creatinine clearance of <30 mL/minute required an unplanned visit on Day 3 or 4 of treatment for 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 their dalteparin injection 3-5 hours prior to the visit.
e. Laboratory test 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 only to be performed on women with childbearing potential. Pregnancy tests may also be repeated as per request of IRB/IEC or if required by local regulations.
g. Only if clinically indicated.
h. Ulcer assessment was done at both screening and baseline for eligibility, the baseline ulcer assessment was used if assessments differed between these visits.

Number of Subjects (Planned and Analyzed): A sample size of 645 subjects was the planned enrollment. A total of 321 subjects were screened to entry into the study and 276 subjects were randomized, of which 184 were randomized to dalteparin and 92 subjects were randomized to receive placebo.

Of 276 subjects, 66 were randomized in the Russian Federation, 65 in Ukraine, 24 in the Czech Republic, 21 in the UK, 20 in Poland, 19 in Sweden, 10 in Denmark, 8 each in Italy and Spain, 7 in Canada, 6 each in Greece and Lithuania, 5 each in Austria and Germany, 3 in Norway, 2 in Belgium, and 1 in Finland.

Diagnosis and Main Criteria for Inclusion: Male or female subjects aged 18 years or older who were diagnosed with type 1 or type 2 diabetes, with PAOD and a neuropathy disability score of >3 were enrolled in the study. Exclusion criteria included: subjects who had undergone vascular reconstruction or angioplasty <1 month prior to randomization; subjects with an ulcer grading of 0 or 3 and staging of A, B or D according to the University of Texas Wound Classification system; and subjects with a known bleeding disorder or evidence of active bleeding.

Study Treatment: All subjects were randomized to 1 of the 2 treatment groups: dalteparin (0.2 mL or 5000 IU/daily subcutaneously [SC]) or placebo (0.2 mL normal saline daily SC). Subjects were treated for a maximum duration of 24 weeks.

Dalteparin/placebo was administered through SC injection preferably given in the abdomen, although the thigh and buttocks could also be used. The injection site was varied daily. When the area around the navel or thigh was used, using the thumb and forefinger, a fold of skin was lifted up while giving the injection. It was suggested that the dalteparin/placebo injections be administered in the morning in all subjects with creatinine clearance <60 mL/minute to facilitate the right timing of anti-factor Xa testing, which ideally occurred 4-6 hours post-administration.

Dalteparin/placebo was not to be injected intravenously/intramuscularly.

Dalteparin and placebo were supplied by the Sponsor. Saline placebo, identical in appearance and volume to the active dalteparin sodium, was provided in pre-filled syringes. Dalteparin/placebo syringes were for single daily use.

Efficacy and Safety Endpoints:

Efficacy Endpoints:

Primary Endpoint: Number of subjects with ≥50% reduction in ulcer surface area including intact skin healing.

Secondary Endpoints:

- Number of subjects who had intact skin healing;
- Number of subjects who underwent amputation (major and minor);

- Number of subjects who underwent major amputation;
- Number of subjects who underwent minor amputation;
- Number of subjects with ≥50% reduction in ulcer surface area excluding intact skin healing;
- Number of deaths;
- Number of major cardiovascular disease events (MCVE), defined as any 1 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;
- Time to healing;
- Time to amputation;
- EQ-5D;
- SF-36;
- 11-point Likert pain scale;
- Transcutaneous pO_2;

Safety Endpoints:

- The number of all hemorrhages (this includes minor and major);
- 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 AEs.

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

Major hemorrhages were defined as fatal bleeding, clinically overt bleeding causing a fall in hemoglobin ≥20 g/L (2 g/dL), clinically overt bleeding leading to transfusion of ≥2 units of whole blood or red cells, or symptomatic bleeding in areas of special concern (such as intracranial, retroperitoneal, intraocular, intraspinal, pericardial, intramuscular with compartmental syndrome, or intraarticular). Minor hemorrhages were defined as bleeding that did not meet the definition of major bleeding and were divided into 2 groups: clinically relevant minor (non-major) bleeding and trivial bleeding.

Laboratory tests, physical examination, vital signs, AE assessments were performed at specified times during the study (Table 1).

Statistical Methods: The study did not meet its target number of subjects. Therefore, the study was terminated prematurely. As a result of the early termination, only summary statistics were presented.

All summaries were performed in the intent to treat (ITT) analysis set, defined as all subjects who were randomized. All safety analyses were reported on the safety set defined as all subjects who took at least 1 dose of study drug.

Analysis of Primary Efficacy Endpoint: The number and percent of subjects with a ≥50% reduction in ulcer surface area including intact skin healing was calculated by treatment group and strata.

Analysis of Secondary Efficacy Endpoints: Summaries (number and percent of subjects) were provided for the following secondary endpoints: ≥50% reduction in ulcer surface area excluding intact skin healing, intact skin healing during the treatment period, amputations (major and minor) during the treatment period, and individual EQ-5D domain scores.

Summaries (mean, standard deviation, inter-quartile range, and range) were provided for the following secondary endpoints: EQ-5D utility and Visual Analogue Scale scores, Likert scale, and individual SF-36 items.

Analysis of Safety Endpoints: Safety analyses were descriptive in nature. Standard safety tables were produced as per Sponsor data standards. Alongside the standard safety tables, the following non-standard tables were also produced: the number of all (minor and major) hemorrhages, the number of major hemorrhages, the number of minor hemorrhages, the number of clinically relevant minor hemorrhages, and the number of minor trivial hemorrhages.

For each of these tables, the numbers and percentages of subjects were presented by treatment group. The number and percent of deaths and of major cardiovascular events (as assessed by the Investigator) were summarized by treatment group.

RESULTS:

Subject Disposition and Demography: A summary of subject disposition is presented in Table 2.

Table 2. Disposition of Subjects

	Dalteparin	Placebo
	Number (%) of subjects	**Number (%) of subjects**
Screened=321		
Assigned to study treatment	184	92
Treated	184	92
Completed	78 (42.4)	33 (35.9)
Discontinued	106 (57.6)	59 (64.1)
Subject died	4 (2.2)	1 (1.1)
Relation to study drug not defined	79 (42.9)	42 (45.7)
Insufficient clinical response	6 (3.3)	6 (6.5)
Lost to follow up	1 (0.5)	0
No longer willing to participate in study	2 (1.1)	1 (1.1)
Other	62 (33.7)	31 (33.7)
Discontinued due to intact skin healing	48 (26.1)	24 (26.1)
Discontinued due to ulcer healed	6 (3.3)	3 (3.3)
Protocol violation	8 (4.3)	4 (4.3)
Related to study drug	4 (2.2)	2 (2.2)
Adverse event	4 (2.2)	2 (2.2)
Not related to study drug	19 (10.3)	14 (15.2)
Adverse event	19 (10.3)	14 (15.2)
Analyzed for safety		
Adverse events	184 (100.0)	92 (100.0)
Laboratory data	174 (94.6)	89 (96.7)

The summary of demographic characteristics is provided in Table 3.

Table 3. Demographic Characteristics

	Dalteparin			Placebo		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Number (%) of subjects	121	63	184	62	30	92
Age (years)						
<18	0	0	0	0	0	0
18-44	4 (3.3)	1 (1.6)	5 (2.7)	3 (4.8)	2 (6.7)	5 (5.4)
45-64	72 (59.5)	21 (33.3)	93 (50.5)	24 (38.7)	12 (40.0)	36 (39.1)
≥65	45 (37.2)	41 (65.1)	86 (46.7)	35 (56.5)	16 (53.3)	51 (55.4)
Mean	62.9	68.4	64.8	64.6	64.9	64.7
Standard deviation	10.5	8.9	10.3	10.7	11.6	10.9
Range	35-89	44-85	35-89	28-88	35-83	28-88
Race						
White	118 (97.5)	63 (100.0)	181 (98.4)	62 (100.0)	29 (96.7)	91 (98.9)
Black	1 (0.8)	0	1 (0.5)	0	0	0
Asian	1 (0.8)	0	1 (0.5)	0	1 (3.3)	1 (1.1)
Other	1 (0.8)	0	1 (0.5)	0	0	0
Weight (kg):						
Mean	91.4	80.2	87.5	90.1	81.3	87.2
Standard deviation	18.0	15.7	18.0	17.9	13.7	17.1
Range	54.0-136.0	52.0-130.0	52.0-136.0	49.0-139.0	53.1-111.0	49.0-139.0
Height (cm):						
Mean	175.2	161.6	170.5	175.1	162.7	171.1
Standard deviation	7.3	6.0	9.4	8.2	6.5	9.7
Range	158.0-196.0	145.0-176.0	145.0-196.0	155.0-200.0	144.0-170.0	144.0-200.0

All the subjects had a primary diagnoses for diabetic foot. The mean duration since onset was 1.1 years in the dalteparin arm and 0.7 year in the placebo arm.

Efficacy Results:

The primary endpoint, the number of subjects with ≥50% reduction in ulcer surface area including intact skin healing after a maximum of 6-months of treatment, was evaluated at 4 stratums using toe BP(>30 mm Hg, ≤30 mm Hg) and the University of Texas Wound Classification (1C/2C) as covariates. The results were provided for all the 4 stratums. The number of subjects for the primary efficacy parameter is presented in Table 4.

Table 4. Summary of Efficacy Endpoints by Stratum (ITT)

Endpoint		Dalteparin			Placebo		
				Responder Rate			Responder Rate
	Stratum	N	N*	n (%)	N	N*	n (%)
≥50% reduction in ulcer surface[a]	1	97	92	68 (70.1)	49	49	31 (63.3)
	2	39	37	23 (59)	19	19	14 (73.7)
	3	29	28	21 (72.4)	14	13	10 (71.4)
	4	19	19	9 (47.4)	10	9	6 (60)
≥50% reduction in ulcer surface area excluding skin intact healing[a]	1	97	92	33 (34)	49	49	15 (30.6)
	2	39	37	8 (20.5)	19	19	10 (52.6)
	3	29	28	13 (44.8)	14	13	6 (42.9)
	4	19	19	8 (42.1)	10	9	2 (20)
Subjects with intact skin healing[a]	1	97	92	35 (36.1)	49	49	16 (32.7)
	2	39	37	15 (38.5)	19	19	4 (21.1)
	3	29	28	8 (27.6)	14	13	4 (28.6)
	4	19	19	1 (5.3)	10	9	4 (40)
Subjects with lower limb amputations[b]	1	97	93	3 (3.2)	49	49	1 (2.0)
	2	39	39	2 (5.1)	19	19	1 (5.3)
	3	29	29	1 (3.4)	14	13	0
	4	19	19	2 (10.5)	10	9	0

Stratum 1- toe pressure >30 mm Hg and University of Texas Grade and Stage 1C.
Stratum 2- toe pressure ≤30 mm Hg and University of Texas Grade and Stage 1C.
Stratum 3- toe pressure >30 mm Hg and University of Texas Grade and Stage 2C.
Stratum 4- toe pressure ≤30 mm Hg and University of Texas Grade and Stage 2C.
N is the number of subjects in the ITT population for the given treatment arm.
N* is the number of subjects with a non-missing response.
n is the number of subjects who were responders.
ITT= intent-to-treat population.
a. All percentages use N in the denominator.
b. All percentages use N* in the denominator.

Secondary Efficacy Endpoints Results:

Number of Subjects With Intact Skin Healing: The stratum wise results are presented in Table 4.

Number of Subjects With ≥50% Reduction in Ulcer Surface Area Excluding Intact Skin Healing: The stratum wise results are presented in Table 4.

Number of Subjects Who Underwent Amputation (Major and Minor, Major, and Minor): The results for lower limb amputations are presented in Table 5.

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

	Dalteparin	Placebo
	n (%)	n (%)
Number of subjects	184	92
Evaluable for lower limb amputations	180 (97.8)	90 (97.8)
Number of lower limb amputations	9 (4.9)	2 (2.2)
Subjects with lower limb amputations	8 (4.3)	2 (2.2)
Subjects with major lower limb Amputations	2 (1.1)	1 (1.1)
Subjects with minor lower limb amputations	7 (3.8)	1 (1.1)

n is the number of subjects who were responders.

European Quality of Life-5 Dimensions Questionnaire: The EQ-5D score results are presented in Table 6.

Table 6. Summary of EQ-5D VAS Score by Visit

	Dalteparin		Placebo	
	Baseline	**EOT**	**Baseline**	**EOT**
N	182	157	91	76
Mean	60.2	63.3	55.3	60.7
Standard deviation	18.68	18.76	19.72	18.02
Interquartile range	49.00-75.00	50.00-80.00	40.00-71.00	50.00-78.50
Minimum, Maximum	19.00, 95.00	1.00, 100.00	16.00, 100.00	18.00, 95.00

EOT = end-of-treatment; EQ-5D = European Quality of Life-5 Dimensions; N = number of evaluated subjects; VAS = Visual Analogue Scale.

Short Form-36: The SF-36 scores and subscales results are shown in Table 7. The SF-36 scores were calculated corresponding to each of the 8 health concepts.

Table 7. Summary of SF-36 Score by Visit

	Dalteparin		Placebo	
Physical functioning	**Baseline**	**EOT**	**Baseline**	**EOT**
N	183	156	90	76
Mean	34.7	37.1	32.5	35.5
Standard deviation	12.06	11.71	10.96	11.39
Interquartile range	25.47-44.41	27.57-46.51	23.36-42.30	25.47-44.41
Minimum, Maximum	14.94, 57.03	14.94, 57.03	14.94, 57.03	14.94, 57.03
Role-Physical	**Baseline**	**EOT**	**Baseline**	**EOT**
N	183	155	90	76
Mean	35.4	39.3	35.2	37.5
Standard deviation	11.22	11.25	11.41	11.31
Interquartile range	27.47-42.16	32.36-47.06	27.47-42.16	27.47-47.06
Minimum, Maximum	17.67, 56.85	17.67, 56.85	17.67, 56.85	17.67, 56.85
Bodily Pain	**Baseline**	**EOT**	**Baseline**	**EOT**
N	184	156	90	76
Mean	42.3	47.5	40.3	45.0
Standard deviation	11.19	10.30	11.52	10.73
Interquartile range	33.38-51.13	37.18-55.36	32.96-46.06	37.18-51.13
Minimum, Maximum	19.86, 62.12	24.93, 62.12	19.86, 62.12	19.86, 62.12
General Health	**Baseline**	**EOT**	**Baseline**	**EOT**
N	183	156	90	76
Mean	42.3	42.5	42.6	42.8
Standard deviation	5.52	5.10	5.10	5.15
Interquartile range	38.63-45.78	40.06-45.78	40.06-45.78	40.06-47.21
Minimum, Maximum	23.38 ,63.90	21.00, 55.32	28.15, 55.32	23.38, 52.93
Visibility	**Baseline**	**EOT**	**Baseline**	**EOT**
N	183	156	90	76
Mean	48.3	48.2	48.7	48.8
Standard deviation	5.63	5.58	5.02	5.15
Interquartile range	45.85-52.09	45.85-52.09	45.85-52.09	45.85-52.09
Minimum, Maximum	30.24, 70.82	33.36, 61.46	36.48, 61.46	36.48, 58.33
Social Functioning	**Baseline**	**EOT**	**Baseline**	**EOT**
N	181	152	90	73
Mean	33.0	33.3	33.1	32.3
Standard deviation	6.49	6.13	6.90	5.83
Interquartile range	29.58-35.03	29.58-35.03	29.58-35.03	29.58-35.03
Minimum, Maximum	13.22, 45.94	13.22, 51.40	13.22, 45.94	13.22, 45.94
Role-Emotional	**Baseline**	**EOT**	**Baseline**	**EOT**
N	182	155	90	76
Mean	39.1	41.2	38.3	38.8
Standard deviation	13.48	13.44	13.49	13.48
Interquartile range	32.56-51.99	32.56-55.88	32.56-48.10	30.61-50.05
Minimum, Maximum	9.23, 55.88	9.23, 55.88	9.23, 55.88	9.23, 55.88
Mental Health	**Baseline**	**EOT**	**Baseline**	**EOT**
N	183	156	90	76
Mean	41.9	41.9	41.3	42.0
Standard deviation	6.57	6.20	6.72	6.80
Interquartile range	38.74-47.19	38.74-47.19	38.74-47.19	35.93-47.19
Minimum, Maximum	19.03, 61.27	19.03, 55.64	21.85, 55.64	27.48, 64.09

EOT= end-of-treatment; N = number of evaluated subjects; SF-36 = Short Form-36.

11-Point Likert Pain Scale: The 11-point Likert scale score results are presented in Table 8.

Table 8. Summary of 11-Point Likert Scale by Visit

	Dalteparin		Placebo	
	Baseline	**EOT**	**Baseline**	**EOT**
N	183	155	89	75
Mean	4.2	2.1	4.5	2.5
Standard deviation	2.76	2.27	2.83	2.54
Interquartile range	2.00-6.00	0.00-4.00	2.00-7.00	0.00-4.00
Minimum, Maximum	0.00, 10.00	0.00, 8.00	0.00, 10.00	0.00, 10.00

EOT= end-of-treatment; N = number of evaluated subjects.

Transcutaneous Local Tissue Oxygenation: The transcutaneous pO_2 scores are presented in Table 9.

Table 9. Summary of Transcutaneous pO_2 by Visit

	Dalteparin		Placebo	
	Baseline	**EOT**	**Baseline**	**EOT**
N	47	32	26	19
Mean	31.8	38.8	36.0	39.7
Standard deviation	21.29	19.58	17.11	16.18
Interquartile range	16.00-42.00	27.00-47.50	21.00-47.00	35.00-53.00
Minimum, Maximum	1.00, 98.00	1.00, 94.00	8.00, 67.00	9.00, 68.00

EOT = end-of-treatment; N = number of evaluated subjects; pO_2 = local tissue oxygenation.

Time to Healing and Time to Amputation: These end points were not evaluated for this study.

Safety Results: A summary of the number of subjects with TEAEs, by treatment arm is presented in Table 10.

Table 10. Treatment-Emergent Adverse Events (All-Causalities)

Number (%) of Subjects	Dalteparin		Placebo	
	n	**%**	**n**	**%**
Subjects evaluable for adverse events	184		92	
Number of adverse events	208		93	
Subjects with adverse events	91	49.5	45	48.9
Subjects with serious adverse events	33	17.9	18	19.6
Subjects with severe adverse events	24	13.0	10	10.9
Subjects discontinued due to adverse events	25	13.6	18	19.6
Subjects with dose reduced or temporary discontinuation due to adverse events	6	3.3	2	2.2

Includes data up to 30 days after last dose of study drug.
Except for the number of adverse events subjects were counted only once per treatment in each row.
Serious adverse events - according to the Investigator's assessment.
AE = adverse event; n = number of evaluable subjects; SAE = serious adverse event.

All-Causality Treatment-Emergent Adverse Events: The all-causality TEAEs reported in ≥2% of subjects in any of the treatment group are presented in Table 11. The most common AE was skin ulcer, with 15 incidents across treatment arms.

Table 11. Treatment-Emergent Adverse Events Reported in ≥2% of Subjects in any of the Treatment Group by System Organ Class and Preferred Term (All-Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA (v13.1) Preferred Term	Dalteparin n (%)	Placebo n (%)
Number of subjects evaluable for adverse events	184	92
Number of subjects with adverse events	76 (41.3)	36 (39.1)
General disorders and administration site conditions	16 (8.7)	11 (12.0)
Injection site haematoma	7 (3.8)	0
Oedema peripheral	1 (0.5)	3 (3.3)
Ulcer	3 (1.6)	4 (4.3)
Infections and infestations	35 (19.0)	19 (20.7)
Diabetic foot infection	4 (2.2)	2 (2.2)
Erysipelas	4 (2.2)	0
Infected skin ulcer	6 (3.3)	5 (5.4)
Infection	4 (2.2)	0
Localised infection	3 (1.6)	3 (3.3)
Urinary tract infection	1 (0.5)	2 (2.2)
Wound infection	3 (1.6)	2 (2.2)
Injury, poisoning and procedural complications	14 (7.6)	5 (5.4)
Contusion	2 (1.1)	2 (2.2)
Investigations	7 (3.8)	3 (3.3)
Fibrin D dimer increased	1 (0.5)	2 (2.2)
Musculoskeletal and connective tissue disorders	11 (6.0)	3 (3.3)
Pain in extremity	5 (2.7)	2 (2.2)
Skin and subcutaneous tissue disorders	14 (7.6)	6 (6.5)
Skin ulcer	12 (6.5)	3 (3.3)

Subjects were only counted once per treatment for each row.
Includes data up to 30 days after last dose of study drug.
MedDRA (v13.1) coding dictionary applied.
MedDRA (v13.1) = Medical Dictionary for Regulatory Activities (version 13.1); n = number of subjects with adverse events.

Treatment-Related Adverse Events: A summary of the incidence of AEs considered to be treatment-related is presented in Table 12. The most commonly occurring treatment-related AE was injection site haematoma.

Table 12. Treatment-Emergent Adverse Events by Body System (Treatment-Related)

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA (v13.1) Preferred Term	Dalteparin (N=184) n (%)	Placebo (N=92) n (%)
Total preferred term events	31	7
Blood and lymphatic system disorders	2 (1.1)	1 (1.1)
Anaemia	0	1 (1.1)
Monocytopenia	0	1 (1.1)
Normochromic normocytic anaemia	1 (0.5)	0
Pancytopenia	1 (0.5)	0
Cardiac disorders	1 (0.5)	0
Atrial fibrillation	1 (0.5)	0
Eye disorders	4 (2.2)	1 (1.1)
Eye haemorrhage	1 (0.5)	0
Retinal haemorrhage	3 (1.6)	1 (1.1)
Gastrointestinal disorders	1 (0.5)	0
Diarrhoea	1 (0.5)	0
General disorders and administration site conditions	7 (3.8)	1 (1.1)
Asthenia	1 (0.5)	0
Injection site haematoma	4 (2.2)	0
Injection site pain	1 (0.5)	0
Oedema	0	1 (1.1)
Ulcer	1 (0.5)	0
Injury, poisoning and procedural complications	2 (1.1)	0
Contusion	1 (0.5)	0
Subcutaneous haematoma	1 (0.5)	0
Investigations	2 (1.1)	1 (1.1)
Fibrin D dimer increased	1 (0.5)	1 (1.1)
Haemoglobin decreased	1 (0.5)	0
Metabolism and nutrition disorders	2 (1.1)	0
Diabetic foot	1 (0.5)	0
Hyperuricaemia	1 (0.5)	0
Musculoskeletal and connective tissue disorders	1 (0.5)	0
Musculoskeletal chest pain	1 (0.5)	0
Psychiatric disorders	1 (0.5)	0
Sleep disorder	1 (0.5)	0
Reproductive system and breast disorders	1 (0.5)	0
Genital haemorrhage	1 (0.5)	0
Respiratory, thoracic and mediastinal disorders	1 (0.5)	1 (1.1)
Epistaxis	1 (0.5)	1 (1.1)
Skin and subcutaneous tissue disorders	3 (1.6)	0
Pruritus generalised	1 (0.5)	0
Skin ulcer	2 (1.1)	0
Skin ulcer haemorrhage	1 (0.5)	0
Vascular disorders	2 (1.1)	1 (1.1)
Flushing	0	1 (1.1)
Haematoma	1 (0.5)	0
Haemorrhage	1 (0.5)	0

Adverse events and serious adverse events are not separated out.
Subjects were counted only once per treatment in each row.
Includes data up to 30 days after last dose of study drug.
MedDRA (v13.1) = Medical Dictionary for Regulatory Authorities (version 13.1); N = number of subjects in each treatment group; n = number of subjects with adverse events.

All-Causality Serious Adverse Events: There were 36 cases of SAEs (46 events) reported in the dalteparin sodium arm, and 20 SAE cases (27 events) reported in the placebo arm. Table 13 presents all-causality SAEs reported during the study.

Table 13. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All-Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA (v13.1) Preferred Term	Dalteparin n (%)	Placebo n (%)
Number of subjects evaluable for adverse events	184	92
Number of subjects with adverse events	33 (17.9)	18 (19.6)
Cardiac disorders	6 (3.3)	5 (5.4)
Acute myocardial infarction	0	1 (1.1)
Cardiac failure	2 (1.1)	2 (2.2)
Cardiac failure congestive	1 (0.5)	0
Myocardial infarction	2 (1.1)	1 (1.1)
Myocardial ischaemia	1 (0.5)	0
Trifascicular block	0	1 (1.1)
Eye disorders	3 (1.6)	0
Retinal haemorrhage	3 (1.6)	0
Gastrointestinal disorders	2 (1.1)	1 (1.1)
Ascites	1 (0.5)	0
Colonic stenosis	1 (0.5)	0
Pancreatitis acute	0	1 (1.1)
General disorders and administration site conditions	2 (1.1)	3 (3.3)
Condition aggravated	0	1 (1.1)
Oedema peripheral	1 (0.5)	1 (1.1)
Ulcer	1 (0.5)	1 (1.1)
Hepatobiliary disorders	0	1 (1.1)
Cholelithiasis	0	1 (1.1)
Infections and infestations	15 (8.2)	9 (9.8)
Arteriosclerotic gangrene	1 (0.5)	0
Cellulitis	5 (2.7)	1 (1.1)
Erysipelas	1 (0.5)	3 (3.3)
Gangrene	4 (2.2)	0
Infected skin ulcer	3 (1.6)	1 (1.1)
Infection	1 (0.5)	0
Influenza	0	1 (1.1)
Localised infection	1 (0.5)	2 (2.2)
Osteomyelitis	1 (0.5)	0
Pneumonia	2 (1.1)	1 (1.1)
Urinary tract infection	0	2 (2.2)
Metabolism and nutrition disorders	4 (2.2)	1 (1.1)
Diabetes mellitus	1 (0.5)	0
Diabetic foot	2 (1.1)	0
Diabetic ketoacidosis	0	1 (1.1)
Hyperuricaemia	1 (0.5)	0
Musculoskeletal and connective tissue disorders	1 (0.5)	1 (1.1)
Back pain	1 (0.5)	0
Pain in extremity	0	1 (1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5)	0
Lung neoplasm malignant	1 (0.5)	0
Nervous system disorders	1 (0.5)	0
Cerebrovascular accident	1 (0.5)	0
Renal and urinary disorders	2 (1.1)	0
Renal failure acute	1 (0.5)	0
Strangury	1 (0.5)	0
Respiratory, thoracic and mediastinal disorders	2 (1.1)	0
Acute respiratory failure	1 (0.5)	0
Chronic obstructive pulmonary disease	1 (0.5)	0
Skin and subcutaneous tissue disorders	0	2 (2.2)
Diabetic ulcer	0	1 (1.1)
Skin necrosis	0	1 (1.1)
Vascular disorders	1 (0.5)	0

Table 13. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All-Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA (v13.1) Preferred Term	Dalteparin n (%)	Placebo n (%)
Venous thrombosis	1 (0.5)	0

Subjects were only counted once per treatment for each row.
Includes data up to 30 days after last dose of study drug.
MedDRA (v13.1) coding dictionary applied.
MedDRA (v13.1) = Medical Dictionary for Regulatory Authorities (version 13.1); n = number of subjects with adverse events.

Treatment-Related Serious Adverse Events: Three SAEs in the dalteparin arm (retinal hemorrhage in two cases and gouty arthritis) were treatment-related. Gouty arthritis in 1 subject, although assessed as related by the Investigator, was judged not treatment-related by the Sponsor. No SAE was considered treatment-related in the placebo arm.

Severity of Adverse Events: Most of the TEAEs were mild in severity (108 in the dalteparin arm and 50 in the placebo arm). There were 71 cases of moderate AEs in the dalteparin arm and 32 cases in the placebo arm. Twenty-nine cases of severe AEs occurred in the dalteparin arm whereas 11 were observed in the placebo arm. The severe AE mostly occurring in the dalteparin arm was gangrene (n=4) in the dalteparin arm and cardiac failure (n=2) in the placebo arm.

Among the treatment-related AEs, 3 severe AEs occurred in the dalteparin arm during the study, and none was reported in the placebo arm. There were 11 cases of moderate AEs in the dalteparin arm and 3 cases in the placebo arm. Most of the treatment-related AEs were mild in severity (17 in the dalteparin arm and 4 in the placebo arm).

Permanent Discontinuations due to Adverse Events: There were 23 (12.5%) subjects in the dalteparin arm and 16 (17.4%) subjects in the placebo arm reporting permanent withdrawal from the study. In the dalteparin arm, 19 subjects were permanently withdrawn due to SAEs. Three other withdrawals were reported due to moderate AEs and 1 due to severe AE. In the placebo arm 11 subjects were permanently withdrawn due to AEs classified as SAEs. Of the remaining withdrawals in placebo arm 3 were attributed to moderate AEs and 2 to mild AEs. Four (2.17%) treatment-related discontinuations due to AEs were observed in the dalteparin arm and 2 (2.17%) in the placebo arm.

Dose Reductions or Temporary Discontinuations due to Adverse Events: There were 8 cases of temporary discontinuations in the study (6 [3.2%] in the dalteparin arm and 2 [2.17%] in the placebo arm). In the dalteparin arm, 3 of the discontinuations were due to SAEs; 2 were due to moderate AEs and 1 mild AE. In the placebo arm, the 2 temporary discontinuations were as a result of SAEs.

All the AEs were classified as treatment-emergent and were resolved. Of all the temporary withdrawals due to SAEs, 3 (1.63%) in the dalteparin arm were assessed as treatment-related. In the placebo arm, none of the temporary withdrawals due to SAEs was considered treatment-related.

There was no case of dose reduction in the study.

Number of Deaths and Deaths due to Vascular Cause: There were 7 SAEs with fatal outcome (4 in the dalteparin arm and 3 in the placebo arm).

Deaths in the dalteparin arm were due to cardiac failure in 1 subject, acute respiratory failure and lung neoplasm malignant in 1 subject, myocardial infarction in 1 subject and myocardial ischaemia in 1 subject.

In the placebo arm, deaths were reported due to cardiac failure and pneumonia in 1 subject, localised infection in 1 subject and cardiac failure in 1 subject. All deaths occurred during the treatment period.

No AE with outcome death was deemed related to treatment.

Number of Major Cardiovascular Disease Events: Seven (3.8%) MCVEs were reported in the dalteparin arm and 4 (4.34%) in the placebo arm.

Number of all Hemorrhages, Major, and Minor Hemorrhages: There were 10 (5.4%) hemorrhages in the dalteparin arm and 2 (2.2%) hemorrhages in the placebo arm. Of the major hemorhages, 2 (1.1%) were in the dalteparin arm and none occurred in the placebo arm. Seven (3.8%) minor hemorhages were observed in the dalteparin arm and 2 (2.2%) in the placebo arm. Also, 5 (2.7%) hemorhages were classified as clinically relevant major bleeding in the dalteparin arm and 2 (1.1%) were classified as trivial bleeding. In the placebo arm, there were 1 (1.1%) each of clinically relevant major and trivial bleeding. All the hemorrhages were attributed to the study drug.

Vital Signs, Physical Examination, and Laboratory Findings: In the dalteparin, arm low BP was observed in 1 subject, which was considered to be treatment-emergent. In the placebo arm reduced heart rate was observed in 1 subject which was also classified as treatment-emergent and resolved later.

None of the laboratory test abnormalities meeting criteria for potential clinical concern suggested a concern for dalteparin in this study.

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