Study No.: FRX106365

Title: The INPACT Study (Improving with Nadroparin the Prognosis in Advanced Cancer Treatment). A randomized, controlled trial to evaluate the effects of nadroparin on survival and disease progression in patients with advanced malignancies of the lung, pancreas or prostate

Rationale: This study was designed to assess the efficacy of nadroparin compared with no nadroparin on survival and disease progression in subjects with Non-Small-Cell-Lung Carcinoma (NSCLC) stage IIIB, hormone refractory prostate cancer (HRPC), and locally advanced pancreatic cancer (LAPC).

Phase: IIIa

Study Period: 02-May-2006 – 07-Jul-2009

Study Design: This was a multicentre, randomized, open-label study of nadroparin in subjects with either a diagnosis of hormone-refractory prostate cancer within the previous 6 months, with locally advanced pancreatic cancer within 3 months of diagnosis of cancer, or with Non-Small-Cell-Lung Carcinoma (NSCLC) (without clinically significant pleural effusion on chest X-ray) within 3 months of diagnosis of stage IIIB. Subjects were randomized to nadroparin or no nadroparin in addition to standard anticancer treatment. Subjects randomized to nadroparin received therapeutic doses for 2 weeks followed by half therapeutic doses for 4 weeks. Following a 4-week wash-out period, 6 cycles of 2-weeks of therapeutic doses of nadroparin were given, each cycle separated by a 4-week wash-out. A cycle could be skipped, if necessary, and the decision to continue with each cycle depended upon the subject's condition. The minimum duration of study participation was 46 weeks (end of study treatment period).

Centres: 73 Centres in 10 countries

Indication: Thrombosis, venous

Treatment: Nadroparin was supplied in pre-filled syringes containing 3800 IU (0.4 ml nadoparion 9500 anti-factor Xa units/mL) for subjects weighing <50 kilograms (kg), 11400 IU (0.6 ml nadroparin 19000 anti-factor Xa units/mL) for those between 50-70 kg, and 15200 IU(0.8 ml nadroparin 19000 anti-factor Xa units/mL) for those >70 kg. For the 4 week half-therapeutic dose period of the initial treatment cycle, the pre-filled syringes contained 3800 IU (0.4 ml)) for subjects weighing <50 kg, 5700 IU (0.6 ml) for those between 50-70 kg, and 7600 IU (0.8 ml) for those >70 kg. Nadroparin was administered by subcutaneous injection twice daily (12 hours apart) or once daily during the 4 week half-therapeutic dose period for subjects <50 kg or once daily for subjects between 50-70 kg or >70 kg.

Objectives: The primary efficacy objective was to evaluate the effect of subcutaneous nadroparin on death due to all causes in subjects with advanced malignancies of the lung, pancreas, or prostate.

Primary Outcome/Efficacy Variable: The primary efficacy outcome was all-cause death.

Secondary Outcome/Efficacy Variable(s): The secondary efficacy outcome was time to progression.

Statistical Methods: This study planned to include 500 subjects (250 per arm) to give 85% power (type II error 15%) at an overall significance level of 0.05 (two sided type I error = 5%) for an expected relative risk reduction of minimally 20% in the nadroparin arm compared with the no-treatment arm and a death rate of 70% in the controls during the 12-15 month follow-up. The efficacy and safety analyses were performed on the randomized population. Time to events (death, progression, and thromboembolic events) were evaluated by a Cox proportional hazards model with cancer type as covariate. The hazard ratio with 95% confidence intervals and p-values were calculated for nadroparin versus no nadroparin treatment and by cancer type. For all time to events, the number of subjects, events and censored events, the Kaplan-Meier (KM) estimated median time to event and the KM event free survival estimate were described by treatment group for all subjects and by cancer type. KM plots of time to event were presented by treatment group, for all subjects and separately by cancer type.

Study Population:

	Nadroparin	No treatment
Number of Subjects:	244	259
Planned, N	250	250
Randomised, N	244	259
Completed, n (%)	71 (29.1)	75 (29.0)
Total Number Subjects Withdrawn, N (%)	173 (70.9)	184 (71.0)
Withdrawn due to Adverse Events n (%)	142 (82.0)	161 (87.5)
Withdrawn due to Lack of Efficacy n (%)	1 (0.6)	2 (1.1)
Withdrawn for other reasons n (%)	30 (17.3)	21 (11.4)

Demographics	Nadroparin	No treatment
N (ITT)	244	259
Females: Males	47/197	53/206
Mean Age, years (SD)	65.2 (10.0)	65.2 (9.8)
White, n (%)	241 (98.8)	257 (99.3)
Primary Efficacy Results:		
All Cause Deaths (Study Period)	Nadroparin	No treatment
All subjects N	244	259
Deaths	138 (56.6)	160 (61.8)
Causes of death:		
Tumor progression	123 (89.1)	131 (81.9)
Arterial thromoembolic event	0	2 (1.3)
Venous thromboembolic event	1 (0.7)	4 (2.5)
Bleeding	5 (3.6)	5 (3.1)
Other	9 (6.5)	18 (11.3)
HRPC subjects N	100	97
Deaths	43 (43.0)	54 (55.7)
Causes of death:		
Tumor progression	40 (93.0)	44 (81.5)
Arterial thromoembolic event	0	2 (3.7)
Venous thromboembolic event	0	1 (1.9)
Bleeding	2 (4.7)	1 (1.9)
Other	1 (2.3)	6 (11.1)
NSCLC subjects N	81	88
Deaths	46 (56.8)	53 (60.2)
Causes of death:		
Tumor progression	41 (89.1)	43 (81.1)
Venous thromboembolic event	0	2 (3.8)
Bleeding	2 (4.3)	0
Other	3 (6.5)	8 (15.1)
LAPC subjects N	62	72
Deaths	49 (79.0)	53 (73.6)
Causes of death:		
Tumor progression	42 (85.7)	44 (83.0)
Venous thromboembolic event	1 (2.0)	1 (1.9)
Bleeding	1 (2.0)	4 (7.5)
Other	5 (10.2)	4 (7.5)
Kaplan-Meier analysis of time to death (Study Period):		
All subjects N	244	259
Number of events n (%)	138 (56.8)	160 (61.8)
Number of censored events n (%)	106 (43.4)	99 (38.2)
Median time to death (months) [95% CI]	13.1 [11.0, 15.5]	11.9 [10.3, 14.1]
Kaplan-Meier survival estimate (SD)	23.4% (0.042)	21.2% (0.040)
HRPC subjects N	100	97
Number of events n (%)	43 (43.0)	54 (55.7)
Number of censored events n (%)	57 (57.0)	43 (44.3)
Median time to death (months) [95% CI]	20.0 [14.9, NE]	17.5 [12.2, 23.4]
Kaplan-Meier survival estimate (SD)	38.4% (0.070)	29.2% (0.063)
NSCLC subjects N	81	88
Number of events n (%)	46 (56.8)	53 (60.2)
Number of censored events n (%)	35 (43.2)	35 (39.8)
Median time to death (months) [95% CI]	12.1 [9.4, 17.3]	10.3 [8.1, 17.4]
Kaplan-Meier survival estimate (SD)	25.7% (0.063)	20.3% (0.092)
LAPC subjects N	62	72
Number of events n (%)	49 (79.0)	53 (73.6)

Number of censored events n (%)	13 (21.0)	19 (26.4)
Median time to death (months) [95% CI]	8.0 [6.7, 11.7]	10.4 [8.4, 13.0]
Kaplan-Meier survival estimate (SD)	0.0% (0.000)	11.1% (0.050)
Cox proportional hazards analysis of time to death adjusted on cancer type (Study Period)	HR [95% CI]	p-value
Overall		
Nadroparin/no nadroparin	0.935 [0.745, 1.175]	0.565
NSCLC/HRPC	1.492 [1.125, 1.977]	<0.001
LAPC/HRPC	2.249 [1.695, 2.984]	
HRPC subjects		
Nadroparin/no nadroparin	0.789 [0.528, 1.177]	0.246
NSCLC subjects		
Nadroparin/no nadroparin	0.897 [0.604, 1.331]	0.588
LAPC subjects		
Nadroparin/no nadroparin	1.135 [0.767, 1.679]	0.527
All Cause Deaths (Treatment Period) n (%)	Nadroparin	No treatment
Deaths	95 (38.9)	113 (43.6)
Causes of death:		
Tumor progression	81 (85.3)	88 (77.9)
Arterial thromoembolic event	0	1 (0.9)
Venous thromboembolic event	1 (1.1)	4 (3.5)
Bleeding	4 (4.2)	5 (4.4)
Other	9 (9.5)	15 (13.3)
Kaplan-Meier analysis of time to death (Treatment Period):	Nadroparin	No treatment
Number of subjects n	244	259
Number of events n (%)	95 (38.9)	113 (43.6)
Number of censored events n (%)	149 (61.1)	146 (56.4)
Median time to death (months) [95% CI]	12.1 [10.7, NE]	11.4 [10.3, NE]
Kaplan-Meier survival estimate (SD)	34.6% (0.144)	21.0% (0.156)
Cox proportional hazards analysis of time to death adjusted on cancer type (Treatment Period)	HR [95% CI]	p-value
Nadroparin/no nadroparin	0.890 [0.677, 1.170]	0.404
NSCLC/HRPC	1.498 [1.068, 2.099]	<0.001
LAPC/HRPC	2.000 [1.425, 2.808]	
Secondary Outcome Variables:		
First tumor progression (Study Period) n (%)	Nadroparin	No treatment
Overall	192 (78.7)	198 (76.4)
HRPC subjects	86 (86.0)	86 (88.7)
NSCLC subjects	56 (69.1)	56 (63.6)
LAPC subjects	50 (80.6)	55 (76.4)
Kaplan-Meier analysis of time to first tumor progression (Study Period):		
Number of subjects overall n	244	259
Number of events n (%)	192 (78.7)	198 (76.4)
Number of censored events n (%)	52 (21.3)	61 (23.6)
Median time to death (months) [95% CI]	5.0 [4.0, 5.7]	5.8 [5.1, 6.5]
Kaplan-Meier survival estimate (SD)	6.3% (0.022)	8.7%, (0.026)
Number of HRPC subjects n	100	97
Number of events n (%)	86 (86.0)	86 (88.7)
Number of censored events n (%)	14 (14.0)	11 (11.3)
Median time to death (months) [95% CI]	3.4 [2.4, 4.0]	4.4 [3.3, 5.3]
Kaplan-Meier survival estimate (SD)	0.0% (0.000)	4.7% (0.023)
Number of NSCLC subjects n	81	88
Number of events n (%)	56 (69.1)	56 (63.6)
Number of censored events n (%)	25 (30.9)	32 (36.4)

Median time to death (months) [95% CI]	7.7 [5.3, 9.3]	6.4 [5.6, 8.9]
Kaplan-Meier survival estimate (SD)	14.8% (0.048)	23.6% (0.054)
Number of LAPC subjects n	62	72
Number of events n (%)	50 (80.6)	55 (76.4)
Number of censored events n (%)	12 (19.4)	17 (23.6)
Median time to death (months) [95% CI]	5.7 [3.5, 7.0]	6.7 [5.1, 9.0]
Kaplan-Meier survival estimate (SD)	6.0% (0.044)	3.3% (0.031)
Cox proportional hazards analysis of time to first tumor progression adjusted on cancer type (Study Period)	HR [95% CI]	
Nadroparin/no nadroparin	1.090 [0.893, 1.330]	
NSCLC/HRPC	0.435 [0.341, 0.554]	
LAPC/HRPC	0.599 [0.469, 0.764]	
Aterial or venous thromboembolic events (Study Period)	Nadroparin	No treatment
Overall subjects		
At least one arterial or venous thromboembolic event	18 (7.4)	22 (8.5)
At least one deep vein thrombosis (DVT)	13 (72.2)	8 (36.4)
At least one pulmonary embolism (PE)	3 (16.7)	7 (31.8)
At least one ST-segment elevation myocardial infarction (STEMI)	0	1 (4.5)
At least one non ST-segment elevation myocardial infarction (NSTEMI)	1 (5.6)	3 (13.6)
At least one unstable angina (UA)	18 (100)	22 (100)
At least one ischemic stroke	2 (11.1)	2 (9.1)
At least one Central nervous system (CNS) systemic embolism	0	4 (18.2)
HRPC subjects		
At least one arterial or venous thromboembolic event	8 (8.0)	8 (8.2)
At least one DVT	4 (50.0)	3 (37.5)
At least one PE	2 (25.0)	3 (37.5)
At least one STEMI	0	0
At least one NSTEMI	0	1 (12.5)
At least one UA	0	0
At least one ischemic stroke	2 (25.0)	2 (25.0)
At least one CNS systemic embolism	0	0
NSCLC subjects		
At least one arterial or venous thromboembolic event	2 (2.5)	5 (7.5)
At least one DVT	1 (50.0)	1 (20.0)
At least one PE	0	2 (40.0)
At least one STEMI	0	0
At least one NSTEMI	1 (50.0)	0
At least one UA	0	0
At least one ischemic stroke	0	0
At least one CNS systemic embolism	0	2 (40.0)
LAPC subjects		
At least one arterial or venous thromboembolic event	8 (12.9)	9 (12.5)
At least one DVT	8 (100)	4 (44.4)
At least one PE	1 (12.5)	2 (22.2)
At least one STEMI	0	1 (11.1)
At least one NSTEMI	0	2 (22.2)
At least one UA	0	0
At least one ischemic stroke	0	0
At least one CNS systemic embolism	0	2 (22.2)
Kaplan-Meier analysis of time to first arterial or venous thromboembolic event (Study Period):		
Number of subjects overall n	244	259
Number of events n (%)	18 (7.4)	23 (8.9)
Number of censored events n (%)	226 (92.6)	236 (91.1)
Median time to death (months) [95% CI]	NE [NE, NE]	NE [NE, NE]

Kaplan-Meier survival estimate (SD)	83.0% (0.075)	82.9% (0.038)
Number of HRPC subjects n	100	97
Number of events n (%)	8 (8.0)	8 (8.2)
Number of censored events n (%)	92 (92.0)	89 (91.8)
Median time to death (months) [95% CI]	NE [NE, NE]	NE [NE, NE]
Kaplan-Meier survival estimate (SD)	80.4% (0.100)	84.3% (0.057)
Number of NSCLC subjects n	81	88
Number of events n (%)	2 (2.5)	6 (6.8)
Number of censored events n (%)	79 (97.5)	82 (93.2)
Median time to death (months) [95% CI]	NE [NE, NE]	NE [NE, NE]
Kaplan-Meier survival estimate (SD)	96.8% (0.022)	88.9% (0.051)
Number of LAPC subjects n	62	72
Number of events n (%)	8 (12.9)	9 (12.5)
Number of censored events n (%)	54 (87.1)	63 (87.5)
Median time to death (months) [95% CI]	NE [NE, NE]	NE [NE, NE]
Kaplan-Meier survival estimate (SD)	83.6% (0.055)	71.2% (0.103)
Cox proportional hazards analysis of time to first arterial or venous thromboembolic event adjusted on cancer type (Study Period)	HR	
Nadroparin/no nadroparin	0.838 [0.452, 1.554]	
NSCLC/HRPC	0.681 [0.290, 1.597]	
LAPC/HRPC	2.069 [1.032, 4.148]	
Change from baseline in Karnofsky performance status (Treatment period) Mean (SD)	Nadroparin	No treatment
Screening	87.6 (10.7)	88.0 (10.4)
Week 6	86.2 (13.5)	85.4 (13.4)
Week 6 change from baseline	-1.7 (8.6)	-3.2 (9.9)
Week 10	85.1 (13.6)	84.5 (14.1)
Week 10 change from baseline	-3.0 (10.0)	-4.1 (10.8)
Week 16	84.1 (14.2)	83.2 (15.3)
Week 16 change from baseline	-4.7 (11.4)	-5.8 (11.8)
Week 22	83.9 (14.2)	82.6 (15.4)
Week 22 change from baseline	-5.7 (12.2)	-7.1 (13.2)
Week 28	82.7 (17.4)	81.7 (16.4)
Week 28 change from baseline	-7.6 (15.6)	-8.0 (14.9)
Week 34	82.7 (16.2)	79.8 (18.4)
Week 34 change from baseline	-7.7 (14.6)	-9.7 (16.8)
Week 40	81.9 (18.3)	81.1 (17.2)
Week 40 change from baseline	-8.6 (16.5)	-9.1 (16.0)
Week 46	81.0 (17.9)	80.1 (18.6)
Week 46 change from baseline	-9.8 (16.6)	-10.7 (18.1)
Adverse events (AEs) and serious AEs (SAEs) were collected between randomization until 2 days after the last dose of study treatment or until 2 days after the last treatment period visit in subjects not treated with nadroparin.		
	Nadroparin	No treatment
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects with any AE(s), n(%)	174 (71.3)	197 (76.1)
Nausea	24 (9.8)	23 (8.9)
Anaemia	23 (9.4)	32 (12.4)
Asthenia	23 (9.4)	23 (8.9)
Anorexia	20 (8.2)	23 (8.9)
Back pain	18 (7.4)	11 (4.2)
Abdominal pain	17 (7.0)	11 (4.2)
Fatigue	16 (6.6)	19 (7.3)
Diarrhoea	15 (6.1)	18 (6.9)
Oedema peripheral	15 (6.1)	10 (3.9)
Pyrexia	14 (5.7)	16 (6.2)

Vomiting	12 (4.9)	23 (8.9)
Dyspnoea	10 (4.1)	20 (7.7)
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]		
	Nadroparin	No treatment
	n (%) [related]	n (%) [related]
Subjects with SAEs, n (%)	71 (29.1)	88 (34.0)
Anaemia	2 (0.8) [1]	5 (1.9) [0]
Cardiac failure	3 (1.2) [0]	1 (0.4) [0]
Diarrhoea	3 (1.2) [0]	2 (0.8) [0]
Vomiting	0 [0]	5 (1.9) [0]
General physical health deterioration	2 (0.8) [0]	3 (1.2) [0]
Oedema peripheral	4 (1.6) [0]	0 [0]
Pyrexia	3 (1.2) [0]	5 (1.9) [0]
Jaundice	0 [0]	3 (1.2) [0]
Bronchitis	0 [0]	3 (1.2) [0]
Pneumonia	6 (2.5) [0]	8 (3.1) [0]
Sepsis	1 (0.4) [0]	5 (1.9) [0]
Urinary tract infection	0 [0]	3 (1.2) [0]
Dehydration	2 (0.8) [0]	4 (1.5) [0]
Back pain	3 (1.2) [0]	0 [0]
Neoplasm progression	4 (1.6) [0]	2 (0.8) [0]
Chronic obstructive pulmonary disease	0 [0]	4 (1.5) [0]
Pulmonary embolism	1 (0.4) [0]	4 (1.5) [0]
Deep vein thrombosis	5 (2.0) [0]	2 (0.8) [0]
Disseminated intravascular coagulation	1 (0.4) [0]	0 [0]
Febrile neutropenia	0 [0]	4 (1.5) [0]
Leukopenia	0 [0]	1 (0.4) [0]
Neutropenia	1 (0.4) [0]	1 (0.4) [0]
Pancytopenia	0 [0]	1 (0.4) [0]
Thrombocytopenia	1 (0.4) [0]	0 [0]
Acute myocardial infarction	0 [0]	1 (0.4) [0]
Angina pectoris	2 (0.8) [0]	0 [0]
Atrial fibrillation	1 (0.4) [0]	0 [0]
Atrial flutter	0 [0]	1 (0.4) [0]
Cardiac tamponade	0 [0]	1 (0.4) [0]
Cardiopulmonary failure	0 [0]	2 (0.8) [0]
Hypertensive cardiomyopathy	1 (0.4) [0]	0 [0]
Myocardial infarction	0 [0]	2 (0.8) [0]
Pericardial effusion	0 [0]	2 (0.8) [0]
Supraventricular tachyarrhythmia	1 (0.4) [0]	1 (0.4) [0]
Ascites	1 (0.4) [0]	0 [0]
Colitis	0 [0]	1 (0.4) [0]
Duodenal perforation	1 (0.4) [0]	0 [0]
Duodenal stenosis	1 (0.4) [0]	0 [0]
Faecaloma	0 [0]	1 (0.4) [0]
Gastric haemorrhage	0 [0]	1 (0.4) [0]
Gastrointestinal haemorrhage	0 [0]	2 (0.8) [0]
Haematemesis	0 [0]	2 (0.8) [0]
Haemorrhagic erosive gastritis	1 (0.4) [0]	0 [0]
Ileus	2 (0.8) [0]	2 (0.8) [0]
Intestinal obstruction	0 [0]	1 (0.4) [0]
Melaena	1 (0.4) [0]	1 (0.4) [0]
Nausea	0 [0]	2 (0.8) [0]
Oesophageal varices haemorrhage	0 [0]	1 (0.4) [0]

Rectal haemorrhage	2 (0.8) [1]	1 (0.4) [0]
Reflux oesophagitis	1 (0.4) [0]	0 [0]
Subileus	1 (0.4) [0]	0 [0]
Upper gastrointestinal haemorrhage	1 (0.4) [0]	0 [0]
Asthenia	1 (0.4) [0]	0 [0]
Death	1 (0.4) [0]	1 (0.4) [0]
Disease progression	0 [0]	2 (0.8) [0]
Euthanasia	0 [0]	1 (0.4) [0]
Generalised oedema	0 [0]	1 (0.4) [0]
Malaise	1 (0.4) [0]	0 [0]
Pain	1 (0.4) [0]	0 [0]
Bile duct obstruction	1 (0.4) [0]	0 [0]
Bile duct stenosis	1 (0.4) [0]	0 [0]
Cholangitis	2 (0.8) [0]	1 (0.4) [0]
Cholestasis	0 [0]	1 (0.4) [0]
Jaundice cholestatic	1 (0.4) [0]	1 (0.4) [0]
Anaphylactic reaction	0 [0]	1 (0.4) [0]
Drug hypersensitivity	0 [0]	1 (0.4) [0]
Appendicitis	0 [0]	1 (0.4) [0]
Catheter related infection	1 (0.4) [0]	0 [0]
Cellulitis	0 [0]	1 (0.4) [0]
Erysipelas	1 (0.4) [0]	0 [0]
Lobar pneumonia	0 [0]	1 (0.4) [0]
Lung infection	0 [0]	1 (0.4) [0]
Neutropenic sepsis	0 [0]	1 (0.4) [0]
Pyelonephritis	1 (0.4) [0]	0 [0]
Septic shock	0 [0]	1 (0.4) [0]
Tracheobronchitis	1 (0.4) [0]	0 [0]
Urosepsis	0 [0]	2 (0.8) [0]
Alcohol poisoning	0 [0]	1 (0.4) [0]
Device failure	0 [0]	1 (0.4) [0]
Femur fracture	2 (0.8) [0]	0 [0]
Hip fracture	0 [0]	1 (0.4) [0]
Medical device complication	0 [0]	1 (0.4) [0]
Radiation pneumonitis	1 (0.4) [0]	1 (0.4) [0]
Stent occlusion	2 (0.8) [0]	0 [0]
Subdural haematoma	1 (0.4) [1]	1 (0.4) [0]
Wound dehiscence	0 [0]	1 (0.4) [0]
Respiratory rate decreased	0 [0]	1 (0.4) [0]
Anorexia	0 [0]	1 (0.4) [0]
Diabetes mellitus inadequate control	0 [0]	1 (0.4) [0]
Hyperglycaemia	1 (0.4) [0]	0 [0]
Musculoskeletal chest pain	1 (0.4) [0]	0 [0]
Pathological fracture	1 (0.4) [0]	0 [0]
Mesothelioma	1 (0.4) [0]	0 [0]
Neoplasm malignant	0 [0]	1 (0.4) [0]
Cerebral haemorrhage	1 (0.4) [0]	0 [0]
Cerebral venous thrombosis	0 [0]	1 (0.4) [0]
Cerebrovascular accident	0 [0]	1 (0.4) [0]
Convulsion	1 (0.4) [0]	0 [0]
Dizziness	0 [0]	1 (0.4) [0]
Ischaemic stroke	0 [0]	1 (0.4) [0]
Lacunar infarction	1 (0.4) [0]	0 [0]
Paraparesis	0 [0]	1 (0.4) [0]
Somnolence	0 [0]	1 (0.4) [0]

Syncope	1 (0.4) [0]	1 (0.4) [0]
Transfer ischaemic attack	1 (0.4) [0]	0 [0]
Completed suicide	0 [0]	1 (0.4) [0]
Depression	1 (0.4) [0]	0 [0]
Suicide attempt	1 (0.4) [0]	0 [0]
Haematuria	0 [0]	1 (0.4) [0]
Hydronephrosis	0 [0]	1 (0.4) [0]
Nephropathy	0 [0]	1 (0.4) [0]
Renal disorder	0 [0]	1 (0.4) [0]
Renal failure	1 (0.4) [0]	2 (0.8) [0]
Renal failure acute	0 [0]	1 (0.4) [0]
Urinary retention	1 (0.4) [0]	0 [0]
Urinary tract obstruction	0 [0]	1 (0.4) [0]
Acute respiratory distress syndrome	1 (0.4) [0]	1 (0.4) [0]
Acute respiratory failure	0 [0]	2 (0.8) [0]
Dyspnoea	0 [0]	2 (0.8) [0]
Epistaxis	1 (0.4) [1]	0 [0]
Haemoptysis	2 (0.8) [0]	1 (0.4) [0]
Hydrothorax	1 (0.4) [0]	0 [0]
Hypoxia	0 [0]	1 (0.4) [0]
Interstitial lung disease	1 (0.4) [0]	0 [0]
Laryngeal necrosis	1 (0.4) [0]	0 [0]
Lung disorder	2 (0.8) [0]	0 [0]
Pharyngeal haemorrhage	1 (0.4) [0]	0 [0]
Pleural effusion	0 [0]	1 (0.4) [0]
Pleurisy	1 (0.4) [0]	0 [0]
Pneumonitis	0 [0]	1 (0.4) [0]
Respiratory failure	2 (0.8) [0]	2 (0.8) [0]
Pemphigus	1 (0.4) [0]	0 [0]
Arterial occlusive disease	0 [0]	1 (0.4) [0]
Arterial thrombosis	0 [0]	1 (0.4) [0]
Extremity necrosis	0 [0]	1 (0.4) [0]
Haemorrhage	1 (0.4) [0]	0 [0]
Shock	1 (0.4) [0]	0 [0]
Subclavian vein thrombosis	0 [0]	1 (0.4) [0]
Vena cava thrombosis	1 (0.4) [0]	0 [0]
Venous thrombosis	0 [0]	1 (0.4) [0]
Cardiovascular insufficiency	1 (0.4) [0]	1 (0.4) [0]

Conclusion: There were fewer deaths in subjects treated with nadroparin compared with untreated subjects. The predominant cause of death was from tumor progression. Nadroparin treatment did not prolong the survival of subjects with HRPC, NSCLC or LAPC. The incidence of AEs and SAEs were similar between the treatment groups. There were no drug-related SAEs reported in the untreated control group. The most frequently reported AEs in the nadroparin group were nausea, anaemia, and asthenia compared with anaemia, nausea, asthenia, and vomiting in untreated subjects.

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