Table (9.1.1.1) 3 - Number (%) of Patients Experiencing Adverse Events During Treatment Period by WHO Organ Class and Preferred Term (When Incidence >2.0% in at Least One Group) - All Treated Patients in Orthopedic Surgery Studies With Post-Operative Randomization

WHO Organ Class Adverse Events (WHO Preferred Term)	Org31540/SR90107A			Enoxaparin
	<2.5 mg (N = 517)	2.5 mg (N = 1645)	>2.5 mg (N = 472)	30 mg bid (N = 1906)
Any event	497 (96.1%)	1278 (77.7%)	457 (96.8%)	1526 (80.1%)
Body as a whole - General disorders				
Total	356 (68.9%)	637 (38.7%)	333 (70.6%)	808 (42.4%)
Fever	250 (48.4%)	362 (22.0%)	231 (48.9%)	484 (25.4%)
Oedema	106 (20.5%)	166 (10.1%)	92 (19.5%)	181 (9.5%)
Wound drainage increased	63 (12.2%)	69 (4.2%)	65 (13.8%)	103 (5.4%)
Oedema peripheral	60 (11.6%)	71 (4.3%)	54 (11.4%)	93 (4.9%)
Pain	54 (10.4%)	48 (2.9%)	63 (13.3%)	82 (4.3%)
Leg pain	19 (3.7%)	35 (2.1%)	14 (3.0%)	34 (1.8%)
Chest pain	16 (3.1%)	31 (1.9%)	8 (1.7%)	36 (1.9%)
Gastro-intestinal system disorders				
Total	341 (66.0%)	503 (30.6%)	334 (70.8%)	653 (34.3%)
Nausea	172 (33.3%)	243 (14.8%)	176 (37.3%)	315 (16.5%)
Constipation	211 (40.8%)	180 (10.9%)	216 (45.8%)	247 (13.0%)
Vomiting	67 (13.0%)	110 (6.7%)	75 (15.9%)	141 (7.4%)
Dyspepsia	39 (7.5%)	65 (4.0%)	53 (11.2%)	83 (4.4%)
Diarrhoea	20 (3.9%)	42 (2.6%)	16 (3.4%)	55 (2.9%)
Abdominal pain	18 (3.5%)	25 (1.5%)	14 (3.0%)	44 (2.3%)
Flatulence	15 (2.9%)	11 (0.7%)	9 (1.9%)	15 (0.8%)
Central and peripheral nervous system disorders				
Total	183 (35.4%)	347 (21.1%)	197 (41.7%)	440 (23.1%)
Dizziness	51 (9.9%)	84 (5.1%)	56 (11.9%)	113 (5.9%)
Urinary retention	41 (7.9%)	85 (5.2%)	56 (11.9%)	91 (4.8%)
Confusion	27 (5.2%)	67 (4.1%)	33 (7.0%)	86 (4.5%)
Headache	35 (6.8%)	45 (2.7%)	34 (7.2%)	69 (3.6%)
Hypertonia	19 (3.7%)	52 (3.2%)	27 (5.7%)	62 (3.3%)
Hypoaesthesia	14 (2.7%)	21 (1.3%)	10 (2.1%)	26 (1.4%)
Urinary incontinence	13 (2.5%)	16 (1.0%)	18 (3.8%)	21 (1.1%)
Red blood cell disorders				
Total	131 (25.3%)	410 (24.9%)	156 (33.1%)	401 (21.0%)
Anaemia	130 (25.1%)	407 (24.7%)	151 (32.0%)	397 (20.8%)
Skin and appendages disorders				
Total	136 (26.3%)	346 (21.0%)	122 (25.8%)	429 (22.5%)
Rash erythematous	59 (11.4%)	91 (5.5%)	41 (8.7%)	112 (5.9%)
Pruritus	35 (6.8%)	91 (5.5%)	33 (7.0%)	113 (5.9%)
Bullous eruption[a]	19 (3.7%)	90 (5.5%)	30 (6.4%)	86 (4.5%)
Rash	25 (4.8%)	65 (4.0%)	13 (2.8%)	87 (4.6%)
Sweating increased	12 (2.3%)	17 (1.0%)	15 (3.2%)	25 (1.3%)
Skin disorder	9 (1.7%)	20 (1.2%)	10 (2.1%)	22 (1.2%)
Platelet, bleeding and clotting disorders				
Total	95 (18.4%)	223 (13.6%)	129 (27.3%)	242 (12.7%)
Purpura	61 (11.8%)	116 (7.1%)	56 (11.9%)	130 (6.8%)
Haematoma	9 (1.7%)	30 (1.8%)	35 (7.4%)	35 (1.8%)
Post-operative haemorrhage	4 (0.8%)	32 (1.9%)	30 (6.4%)	33 (1.7%)

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Table (9.1.1.1) 3 - Number (%) of Patients Experiencing Adverse Events During Treatment Period by WHO Organ Class and Preferred Term (When Incidence >2.0% in at Least One Group) - All Treated Patients in Orthopedic Surgery Studies With Post-Operative Randomization (continued)

WHO Organ Class Adverse Events (WHO Preferred Term)	Org31540/SR90107A <2.5 mg (N = 517)	 2.5 mg (N = 1645)	 >2.5 mg (N = 472)	Enoxaparin 30 mg bid (N = 1906)
Respiratory system disorders				
Total	82 (15.9%)	160 (9.7%)	81 (17.2%)	203 (10.7%)
Dyspnoea	19 (3.7%)	31 (1.9%)	17 (3.6%)	39 (2.0%)
Hypoxia	12 (2.3%)	21 (1.3%)	22 (4.7%)	31 (1.6%)
Coughing	10 (1.9%)	27 (1.6%)	11 (2.3%)	29 (1.5%)
Pharyngitis	11 (2.1%)	17 (1.0%)	9 (1.9%)	25 (1.3%)
Psychiatric disorders				
Total	109 (21.1%)	143 (8.7%)	100 (21.2%)	166 (8.7%)
Insomnia	69 (13.3%)	54 (3.3%)	62 (13.1%)	81 (4.2%)
Anxiety	27 (5.2%)	31 (1.9%)	23 (4.9%)	31 (1.6%)
Urinary system disorders				
Total	76 (14.7%)	141 (8.6%)	70 (14.8%)	141 (7.4%)
Micturition disorder	43 (8.3%)	34 (2.1%)	38 (8.1%)	41 (2.2%)
Urinary tract infection	21 (4.1%)	53 (3.2%)	17 (3.6%)	53 (2.8%)
Metabolic and nutritional disorders				
Total	49 (9.5%)	142 (8.6%)	51 (10.8%)	180 (9.4%)
Hypokalaemia	22 (4.3%)	89 (5.4%)	26 (5.5%)	118 (6.2%)
Hyponatraemia	5 (1.0%)	19 (1.2%)	16 (3.4%)	20 (1.0%)
Secondary terms				
Total	126 (24.4%)	62 (3.8%)	111 (23.5%)	91 (4.8%)
Post-operative pain	100 (19.3%)	14 (0.9%)	80 (16.9%)	21 (1.1%)
Surgical site reaction	9 (1.7%)	10 (0.6%)	17 (3.6%)	25 (1.3%)
Extravasation	13 (2.5%)	1 (0.1%)	8 (1.7%)	12 (0.6%)
Musculo-skeletal system disorders				
Total	65 (12.6%)	67 (4.1%)	64 (13.6%)	100 (5.2%)
Arthralgia	43 (8.3%)	25 (1.5%)	28 (5.9%)	38 (2.0%)
Back pain	10 (1.9%)	10 (0.6%)	17 (3.6%)	31 (1.6%)
Cardiovascular disorders, general				
Total	47 (9.1%)	101 (6.1%)	36 (7.6%)	97 (5.1%)
Hypotension	22 (4.3%)	53 (3.2%)	15 (3.2%)	48 (2.5%)
Hypertension	11 (2.1%)	29 (1.8%)	11 (2.3%)	27 (1.4%)
Heart rate and rhythm disorders				
Total	32 (6.2%)	54 (3.3%)	31 (6.6%)	83 (4.4%)
Tachycardia	23 (4.4%)	33 (2.0%)	21 (4.4%)	49 (2.6%)
Liver and biliary system disorders				
Total	6 (1.2%)	44 (2.7%)	7 (1.5%)	88 (4.6%)
SGOT increased	1 (0.2%)	18 (1.1%)	0 (0.0%)	41 (2.2%)
Resistance mechanism disorders				
Total	16 (3.1%)	62 (3.8%)	11 (2.3%)	38 (2.0%)
Autonomic nervous system disorders				
Total	10 (1.9%)	30 (1.8%)	11 (2.3%)	41 (2.2%)
Application site disorders				
Total	2 (0.4%)	23 (1.4%)	4 (0.8%)	11 (0.6%)
Vision disorders				
Total	5 (1.0%)	14 (0.9%)	2 (0.4%)	11 (0.6%)

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Table (9.1.1.1) 3 - Number (%) of Patients Experiencing Adverse Events During Treatment Period by WHO Organ Class and Preferred Term (When Incidence >2.0% in at Least One Group) - All Treated Patients in Orthopedic Surgery Studies With Post-Operative Randomization (continued)

WHO Organ Class Adverse Events (WHO Preferred Term)	Org31540/SR90107A			Enoxaparin
	<2.5 mg (N = 517)	2.5 mg (N = 1645)	>2.5 mg (N = 472)	30 mg bid (N = 1906)
Myo endo pericardial and valve disorders				
Total	6 (1.2%)	5 (0.3%)	3 (0.6%)	12 (0.6%)
Vascular (extracardiac) disorders				
Total	6 (1.2%)	5 (0.3%)	2 (0.4%)	8 (0.4%)
White cell and reticulo-endothelial system disorders				
Total	3 (0.6%)	3 (0.2%)	2 (0.4%)	4 (0.2%)
Hearing and vestibular disorders				
Total	3 (0.6%)	2 (0.1%)	0 (0.0%)	2 (0.1%)
Reproductive disorders, male				
Total	3 (0.6%)	1 (0.1%)	0 (0.0%)	2 (0.1%)
Endocrine disorders				
Total	0 (0.0%)	1 (0.1%)	0 (0.0%)	3 (0.2%)
Special senses other, disorders				
Total	0 (0.0%)	2 (0.1%)	1 (0.2%)	1 (0.1%)
Foetal disorders				
Total	1 (0.2%)	0 (0.0%)	1 (0.2%)	1 (0.1%)
Reproductive disorders, female				
Total	0 (0.0%)	1 (0.1%)	1 (0.2%)	1 (0.1%)
Neoplasm				
Total	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)

PGM: [redacted] OUT: output/OS91121_T2b (24JAN01 - 20:20)
NOTE: includes studies DR12643, EFC2442, 095-001 and 095-002
SGOT = serum glutamate oxaloacetate transaminase
* Localized blister coded as bullous eruption
Ref.: Appendix 2.5.1.12

Sponsor's table volume 3.238 pp.108-110

The sponsor analyzed fondaparinux dose-concentration and AEs and noted that with increasing fondaparinux dose there was:

1) an increased incidence of hematoma ($p < 0.0001$)
2) an increased incidence of post-operative hemorrhage ($p < 0.0001$)
3) an increased incidence of anemia ($p < 0.004$)
4) an increased incidence of constipation ($p < 0.02$)
5) an increased incidence of urinary retention ($p < 0.04$)
6) an increased incidence of hyperglycemia ($p < 0.05$)
7) an increased incidence of atrial fibrillation ($p < 0.02$).

Drug-Demographic Interactions

The sponsor's next two tables show the relationship between drug-demographic and AEs for the preoperative and post-operative randomization trials.

Reviewer's Comment: Both tables show that with increasing age, worsening renal function, or weight less than 50 kg, there was a general trend toward an increased adverse event rate.

Table (9.1.1.1) 5 - Number (%) of Patients Experiencing Adverse Events During the Treatment Period by Baseline Covariate - All Treated Patients in Orthopedic Surgery Studies With Pre-Operative Randomization

	Org31540/SR90107A			Enoxaparin	Nadroparin*
Covariate	<2.5 mg (N = 77)	2.5 mg (N = 1971)	>2.5 mg (N = 141)	40 mg od (N = 2050)	(N = 45)
Gender					
Male	18/30 (60.0%)	380/680 (55.9%)	28/58 (48.3%)	398/735 (54.1%)	8/17 (47.1%)
Female	26/47 (55.3%)	701/1291 (54.3%)	49/83 (59.0%)	724/1315 (55.1%)	13/28 (46.4%)
Age (years)					
<65	18/32 (56.3%)	322/604 (53.3%)	35/60 (58.3%)	331/604 (54.8%)	7/15 (46.7%)
[65-75[	14/27 (51.9%)	299/556 (53.8%)	22/54 (40.7%)	327/619 (52.8%)	10/21 (47.6%)
≥75	12/18 (66.7%)	459/807 (56.9%)	20/27 (74.1%)	463/824 (56.2%)	4/9 (44.4%)
Weight (kg)					
<50	1/1 (100.0%)	65/109 (59.6%)	0/0	85/132 (64.4%)	0/0
[50-100[	42/74 (56.8%)	947/1739 (54.5%)	76/139 (54.7%)	973/1783 (54.6%)	21/45 (46.7%)
≥100	1/2 (50.0%)	44/86 (51.2%)	1/2 (50.0%)	42/87 (48.3%)	0/0
Creatinine clearance (mL/min)					
<30	1/1 (100.0%)	47/72 (65.3%)	0/0	44/75 (58.7%)	0/0
[30-50[	6/12 (50.0%)	216/386 (56.0%)	13/24 (54.2%)	251/441 (56.9%)	4/8 (50.0%)
[50-80[	25/43 (58.1%)	436/788 (55.3%)	41/70 (58.6%)	434/789 (55.0%)	12/19 (63.2%)
≥80	6/12 (50.0%)	337/647 (52.1%)	21/44 (47.7%)	351/664 (52.9%)	5/18 (27.8%)
Race					
Caucasian	44/77 (57.1%)	1068/1954 (54.7%)	41/75 (54.7%)	1108/2033 (54.5%)	0/0
Black	0/0	6/8 (75.0%)	0/0	6/7 (85.7%)	0/0
Asian/Oriental	0/0	5/5 (100.0%)	0/2 (0.0%)	4/6 (66.7%)	0/0
Other	0/0	2/3 (66.7%)	0/0	3/3 (100.0%)	0/0

PGM: [redacted] OUT: output/OS91115 (25JAN01 - 10:07)

NOTE: includes studies ACT1840, ACT2545, 63118 and EFC2698

* 100 CIU/kg od pre-operatively and until Day 3 then 150 CIU/kg od for the last 3 days (study ACT1840)

Ref.: Appendix 2.5.1.30

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Table (9.1.1.1) 6 - Number (%) of Patients Experiencing Adverse Events During the Treatment Period by Baseline Covariate - All Treated Patients in Orthopedic Surgery Studies With Post-Operative Randomization

Covariate	Org31540/SR90107A <2.5 mg (N = 517)	Org31540/SR90107A 2.5 mg (N = 1645)	Org31540/SR90107A >2.5 mg (N = 472)	Enoxaparin 30 mg bid (N = 1906))
Gender				
Gender Male	251/259 (96.9%)	583/760 (76.7%)	211/217 (97.2%)	700/882 (79.4%)
Female	246/258 (95.3%)	695/885 (78.5%)	246/255 (96.5%)	826/1024 (80.7%)
Age (years)				
<65	185/195 (94.9%)	495/658 (75.2%)	166/173 (96.0%)	601/760 (79.1%)
[65-75[	187/193 (96.9%)	434/561 (77.4%)	185/191 (96.9%)	568/709 (80.1%)
≥75	125/129 (96.9%)	349/426 (81.9%)	106/108 (98.1%)	357/437 (81.7%)
Weight (kg)				
<50	8/8 (100.0%)	17/21 (81.0%)	8/8 (100.0%)	21/34 (61.8%)
[50-100[	416/432 (96.3%)	1012/1310 (77.3%)	369/383 (96.3%)	1251/1541 (81.2%)
≥100	70/73 (95.9%)	248/313 (79.2%)	77/78 (98.7%)	252/328 (76.8%)
Creatinine clearance (mL/min)				
<30	3/3 (100.0%)	10/11 (90.9%)	0/1 (0.0%)	9/12 (75.0%)
[30-50[	49/51 (96.1%)	101/121 (83.5%)	48/48 (100.0%)	116/145 (80.0%)
[50-80[	190/194 (97.9%)	407/502 (81.1%)	158/163 (96.9%)	531/658 (80.7%)
≥80	199/209 (95.2%)	704/932 (75.5%)	192/199 (96.5%)	792/992 (79.8%)
Race				
Caucasian	450/465 (96.8%)	1178/1524 (77.3%)	416/429 (97.0%)	1392/1742 (79.9%)
Black	36/38 (94.7%)	70/84 (83.3%)	30/31 (96.8%)	91/110 (82.7%)
Asian/Oriental	1/1 (100.0%)	4/6 (66.7%)	0/0	7/7 (100.0%)
Other	10/13 (76.9%)	26/31 (83.9%)	11/12 (91.7%)	36/47 (76.6%)

PGM: [redacted] OUT: output/OS91115 (25JAN01 - 10:07)
NOTE: includes studies DRI2643, EFC2442, 095-001 and 095-002
Ref.: Appendix 2.5.1.31

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Deaths and Serious Adverse Events

The sponsor's table below shows the death rate during the treatment period for all orthopedic studies.

Reviewer's Comment: There was no statistically significant difference in death rate between fondaparinux 2.5 mg and enoxaparin during the treatment period. Similar results were observed for the study period (up to Day 49).

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Table (9.2.1.1) 1 - Summary of Cause of Death During Treatment Period by Adjudication Criterion and According to the Study Type - All Treated Patients in Orthopedic Surgery Studies

	Org31540/SR90107A			Enoxaparin
Studies with pre-operative randomization[a]				
Cause of death	**<2.5 mg (N = 77)**	**2.5 mg (N = 1971)**	**>2.5 mg (N = 141)**	**40 mg od (N = 2050)**
Number of death	0 (0.0%)	11 (0.6%)	0 (0.0%)	18 (0.9%)
Fatal PE	0 (0.0%)	2 (0.1%)	0 (0.0%)	2 (0.1%)
hemorrhagic death	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Death not associated with VTE or bleeding	0 (0.0%)	9 (0.5%)	0 (0.0%)	15 (0.7%)
Studies with post-operative randomization[b]				
Cause of death	**<2.5 mg (N=517)**	**2.5 mg (N=1645)**	**>2.5 mg (N=472)**	**30 mg bid (N=1906)**
Number of death	0 (0.0%)	4 (0.2%)	0 (0.0%)	3 (0.2%)
Fatal PE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Hemorrhagic death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death not associated with VTE or bleeding	0 (0.0%)	4 (0.2%)	0 (0.0%)	2 (0.1%)

PGM: [redacted] OUT: output/OS931110_V2 (24JAN01 - 21:16)

NOTE: nadroparin column (study ACT1840) is not displayed because no deaths were reported in this treatment group

NA = not applicable; PE = pulmonary embolism; VTE = venous thromboembolic event

[a] Includes studies ACT1840, ACT2545, 63118 and EFC2698

[b] Includes studies DR12643, EFC2442, 095-001 and 095-002

Ref.: Appendices 2.5.3.11 and 2.5.3.12

Sponsor's Table volume 3.238 p.137 of 320

The sponsor's next two tables show the serious adverse event rates for the preoperative and post-operative randomization studies during the treatment period.

Reviewer's Comment: There was no statistically significant difference for SAEs between the fondaparinux 2.5 mg and enoxaparin treatment groups. Platelet, bleeding, and clotting disorders were the most frequent adverse event category during the treatment period. Surgical site reaction was the most frequent adverse event during the entire study period (up to Day 49) for the fondaparinux patients.

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Table (9.2.2.1) 1 - Number (%) of Patients Experiencing Serious Adverse Events During Treatment Period by WHO Organ Class and Preferred Term - All Treated Patients in Orthopedic Surgery Studies With Pre-Operative Randomization

WHO Organ Class Serious Adverse Events (WHO Preferred Term)	Org31540/SR90107A <2.5 mg (N = 77)	 2.5 mg (N = 1971)	 >2.5 mg (N = 141)	Enoxaparin 40 mg od (N = 2050)
Any event	3 (3.9%)	104 (5.3%)	8 (5.7%)	93 (4.5%)
Platelet, bleeding and clotting disorders				
Total	1 (1.3%)	24 (1.2%)	5 (3.5%)	14 (0.7%)
Haematoma	0 (0.0%)	8 (0.4%)	3 (2.1%)	8 (0.4%)
Post-operative haemorrhage	1 (1.3%)	11 (0.6%)	2 (1.4%)	2 (0.1%)
Haemorrhage NOS	0 (0.0%)	3 (0.2%)	0 (0.0%)	1 (0.0%)
GI haemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.1%)
Dissem. Intravascular. coagulation	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Haematuria	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Melaena	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Purpura	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Secondary terms				
Total	1 (1.3%)	12 (0.6%)	1 (0.7%)	14 (0.7%)
Surgical site reaction	1 (1.3%)	9 (0.5%)	1 (0.7%)	11 (0.5%)
Inflicted injury	0 (0.0%)	1 (0.1%)	0 (0.0%)	3 (0.1%)
Post-operative pain	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Spinal cord compression[a]	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Cardiovascular disorders, general				
Total	0 (0.0%)	8 (0.4%)	0 (0.0%)	14 (0.7%)
Cardiac failure	0 (0.0%)	4 (0.2%)	0 (0.0%)	12 (0.6%)
Cardiac failure left	0 (0.0%)	1 (0.1%)	0 (0.0%)	2 (0.1%)
Hypotension	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
Fluid overload	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Respiratory system disorders				
Total	0 (0.0%)	13 (0.7%)	0 (0.0%)	9 (0.4%)
Pneumonia	0 (0.0%)	7 (0.4%)	0 (0.0%)	3 (0.1%)
Respiratory insufficiency	0 (0.0%)	4 (0.2%)	0 (0.0%)	3 (0.1%)
Dyspnoea	0 (0.0%)	2 (0.1%)	0 (0.0%)	1 (0.0%)
Respiratory depression	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Bronchospasm	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Cyanosis	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Hypoxia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Myo-, endo-, pericardial and valve disorders				
Total	0 (0.0%)	7 (0.4%)	0 (0.0%)	12 (0.6%)
Myocardial infarction	0 (0.0%)	7 (0.4%)	0 (0.0%)	10 (0.5%)
Angina pectoris	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.1%)
Myocardial ischaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)

(continued)

Table (9.2.2.1) 1 - Number (%) of Patients Experiencing Serious Adverse Events During Treatment Period by WHO Organ Class and Preferred Term - All Treated Patients in Orthopedic Surgery Studies With Pre-Operative Randomization (continued)

WHO Organ Class Serious Adverse Events (WHO Preferred Term)	Org31540/SR90107A <2.5 mg (N = 77)	 2.5 mg (N = 1971)	 >2.5 mg (N = 141)	Enoxaparin 40 mg od (N = 2050)
Body as a whole - General disorders				
Total	0 (0.0%)	11 (0.6%)	1 (0.7%)	7 (0.3%)
Death	0 (0.0%)	3 (0.2%)	0 (0.0%)	1 (0.0%)
Oedema peripheral	0 (0.0%)	2 (0.1%)	0 (0.0%)	2 (0.1%)
Wound drainage increased	0 (0.0%)	1 (0.1%)	0 (0.0%)	2 (0.1%)
Chest pain	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.0%)
Fever	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Allergic reaction	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Fatigue	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Leg pain	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Pallor	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Rigors	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Vascular (extracardiac) disorders				
Total	0 (0.0%)	7 (0.4%)	0 (0.0%)	8 (0.4%)
Cerebrovascular disorder	0 (0.0%)	6 (0.3%)	0 (0.0%)	8 (0.4%)
Transient ischaemic attack	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Gastro-intestinal system disorders				
Total	0 (0.0%)	7 (0.4%)	0 (0.0%)	6 (0.3%)
Ileus paralytic	0 (0.0%)	1 (0.1%)	0 (0.0%)	3 (0.1%)
Ileus	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Intestinal perforation	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
Oesophagitis	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Colitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Duodenal ulcer	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Gastric ulcer	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Gastritis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Intestinal obstruction	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Pancreatitis	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Peptic ulcer haemorrhagic	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Central and peripheral nervous system disorders				
Total	0 (0.0%)	8 (0.4%)	0 (0.0%)	4 (0.2%)
Coma	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Confusion	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
Gait abnormal	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Paresis	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Brain stem disorder	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Convulsions	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Convulsions grand mal	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Paraesthesia	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Red blood cell disorders				
Total	0 (0.0%)	6 (0.3%)	2 (1.4%)	3 (0.1%)
Anaemia	0 (0.0%)	5 (0.3%)	2 (1.4%)	3 (0.1%)
Anaemia haemolytic	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)

(continued)

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Table (9.2.2.1.) 1 - Number (%) of Patients Experiencing Serious Adverse Events Durin; Treatment Period by WHO Organ Class and Preferred Term - All Treated Patients in Orthopedic Surgery Studies With Pre-Operative Randomization (continued)

WHO Organ Class Serious Adverse Events (WHO Preferred Term)	Org31540/SR90107A			Enoxaparin
	<2.5 mg (N = 77)	2.5 mg (N = 1971)	>2.5 mg (N = 141)	40 mg od (N = 2050)
Heart rate and rhythm disorders				
Total	0 (0.0%)	4 (0.2%)	0 (0.0%)	3 (0.1%)
Fibrillation atrial	0 (0.0%)	3 (0.2%)	0 (0.0%)	1 (0.0%)
Cardiac arrest	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Tachycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Resistance mechanism disorders				
Total	0 (0.0%)	4 (0.2%)	1 (0.7%)	2 (0.1%)
Post-operative wound infection	0 (0.0%)	1 (0.1%)	1 (0.7%)	2 (0.1%)
Sepsis	0 (0.0%)	3 (0.2%)	0 (0.0%)	0 (0.0%)
Liver and biliary system disorders				
Total	1 (1.3%)	3 (0.2%)	0 (0.0%)	1 (0.0%)
Cholelithiasis	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
Hepatic function abnormal	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Hepatic failure	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Musculo-skeletal system disorders				
Total	0 (0.0%)	2 (0.1%)	0 (0.0%)	3 (0.1%)
Bone disorder	0 (0.0%)	2 (0.1%)	0 (0.0%)	1 (0.0%)
Arthrosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Osteosclerosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Urinary system disorders				
Total	0 (0.0%)	3 (0.2%)	0 (0.0%)	2 (0.1%)
Renal failure acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)
Renal function abnormal	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Renal tubular disorder	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Urinary tract infection	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Neoplasm				
Total	0 (0.0%)	1 (0.1%)	0 (0.0%)	2 (0.1%)
Basal cell carcinoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Neoplasm malignant	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Pulmonary carcinoma	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Skin and appendages disorders				
Total	0 (0.0%)	2 (0.1%)	0 (0.0%)	1 (0.0%)
Melanoma malignant	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Sweating increased	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Application site disorders				
Total	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Cellulitis	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)

(continued)

Table (9.2.2.1.) 1 - Number (%) of Patients Experiencing Serious Adverse Events During Treatment Period by WHO Organ Class and Preferred Term - All Treated Patients in Orthopedic Surgery Studies With Pre-Operative Randomization (continued)

WHO Organ Class Serious Adverse Events (WHO Preferred Term)	Org31540/SR90107A <2.5 mg (N = 77)	 2.5 mg (N = 1971)	 >2.5 mg (N = 141)	Enoxaparin 40 mg od (N = 2050)
Autonomic nervous system disorders				
Total	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
Syncope	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
Metabolic and nutritional disorders				
Total	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Dehydration	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Diabetes mellitus aggravated	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Psychiatric disorders				
Total	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Delirium	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Psychosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Foetal disorders				
Total	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Hernia congenital	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Reproductive disorders, female				
Total	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Breast neoplasm malignant female	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)

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NOTE: includes studies ACT1840, ACT2545, 63118 and EFC2698; nadroparin column (study ACT1840) is not displayed because no serious adverse events were reported in this treatment group

Dissem. Intravascular = disseminated intravascular; GI = gastro-intestinal; NOS = not otherwise specified

[a] Compression due to metastases

Ref.: Appendix 2.5.3.41

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Table (9.2.2.1) 2 - Number (%) of Patients Experiencing Serious Adverse Events During Treatment Period by WHO Organ Class and Preferred Term - All Treated Patients in Orthopedic Surgery Studies With Post-Operative Randomization

WHO Organ Class Serious Adverse Events (WHO Preferred Term)	Org31540/SR90107A <2.5 mg (N = 517)	 2.5 mg (N = 1645)	 >2.5 mg (N = 472)	Enoxaparin 30 mg bid (N = 1906)
Any event	20 (3.9%)	92 (5.6%)	41 (8.7%)	86 (4.5%)
Platelet, bleeding and clotting disorders				
Total	2 (0.4%)	15 (0.9%)	22 (4.7%)	12 (0.6%)
Post-operative haemorrhage	0 (0.0%)	1 (0.1%)	14 (3.0%)	5 (0.3%)
Haematoma	0 (0.0%)	6 (0.4%)	6 (1.3%)	3 (0.2%)
Haematuria	0 (0.0%)	2 (0.1%)	0 (0.0%)	1 (0.1%)
Coagulation disorder	1 (0.2%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
GI haemorrhage	0 (0.0%)	1 (0.1%)	1 (0.2%)	0 (0.0%)
Haemorrhage NOS	0 (0.0%)	1 (0.1%)	1 (0.2%)	0 (0.0%)
Melaena	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Haemarthrosis	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Haematemesis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Haemorrhage rectum	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Haemorrhage retroperitoneal	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Thrombocytopenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Secondary terms				
Total	3 (0.6%)	8 (0.5%)	6 (1.3%)	17 (0.9%)
Surgical site reaction	3 (0.6%)	3 (0.2%)	6 (1.3%)	15 (0.8%)
Inflicted injury	0 (0.0%)	4 (0.2%)	0 (0.0%)	1 (0.1%)
Post-operative pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Spinal cord compression	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Gastro-intestinal system disorders				
Total	3 (0.6%)	14 (0.9%)	1 (0.2%)	9 (0.5%)
Ileus	0 (0.0%)	6 (0.4%)	1 (0.2%)	4 (0.2%)
Intestinal obstruction	1 (0.2%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
Nausea	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Vomiting	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
Diarrhoea	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Diarrhoea, clostridium difficile	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Dysphagia	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Enterocolitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Gastritis	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Haemorrhoids	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Ileus paralytic	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Intestinal necrosis	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intestinal perforation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Megacolon congenital	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Oesophagitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)

(continued)

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Table (9.2.2.1) 2 - Number (%) of Patients Experiencing Serious Adverse Events During Treatment Period by WHO Organ Class and Preferred Term - All Treated Patients in Orthopedic Surgery Studies With Post-Operative Randomization (continued)

WHO Organ Class	Org31540/SR90107A			Enoxaparin
Serious Adverse Events (WHO Preferred Term)	<2.5 mg (N = 517)	2.5 mg (N = 1645)	>2.5 mg (N = 472)	30 mg bid (N = 1906)
Body as a whole - General disorders				
Total	0 (0.0%)	10 (0.6%)	4 (0.8%)	7 (0.4%)
Fever	0 (0.0%)	5 (0.3%)	2 (0.4%)	1 (0.1%)
Chest pain	0 (0.0%)	2 (0.1%)	0 (0.0%)	1 (0.1%)
Pain	0 (0.0%)	1 (0.1%)	0 (0.0%)	2 (0.1%)
Wound drainage increased	0 (0.0%)	0 (0.0%)	2 (0.4%)	0 (0.0%)
Abdomen enlarged	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Asthenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Death	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Hypovolaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Leg pain	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Oedema peripheral	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Respiratory system disorders				
Total	3 (0.6%)	9 (0.5%)	1 (0.2%)	7 (0.4%)
Pneumonia	1 (0.2%)	5 (0.3%)	1 (0.2%)	2 (0.1%)
Hypoxia	1 (0.2%)	0 (0.0%)	0 (0.0%)	3 (0.2%)
Atelectasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Bronchitis	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Cheyne-stokes respiration	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dyspnoea	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Pneumonitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Pulmonary oedema	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Respiratory depression	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Heart rate and rhythm disorders				
Total	0 (0.0%)	9 (0.5%)	1 (0.2%)	9 (0.5%)
Fibrillation atrial	0 (0.0%)	1 (0.1%)	0 (0.0%)	3 (0.2%)
Tachycardia	0 (0.0%)	2 (0.1%)	0 (0.0%)	2 (0.1%)
Tachycardia supraventricular	0 (0.0%)	2 (0.1%)	0 (0.0%)	2 (0.1%)
Arrhythmia	0 (0.0%)	1 (0.1%)	1 (0.2%)	1 (0.1%)
Cardiac arrest	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
Sick sinus syndrome	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Tachycardia ventricular	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Myo-, endo-, pericardial and valve disorders				
Total	3 (0.6%)	4 (0.2%)	1 (0.2%)	5 (0.3%)
Myocardial infarction	3 (0.6%)	3 (0.2%)	0 (0.0%)	2 (0.1%)
Angina pectoris	0 (0.0%)	1 (0.1%)	1 (0.2%)	2 (0.1%)
Myocardial ischaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Red blood cell disorders				
Total	1 (0.2%)	6 (0.4%)	4 (0.8%)	2 (0.1%)
Anaemia	1 (0.2%)	6 (0.4%)	4 (0.8%)	2 (0.1%)

(continued)

Table (9.2.2.1) 2 - Number (%) of Patients Experiencing Serious Adverse Events During Treatment Period by WHO Organ Class and Preferred Term - All Treated Patients in Orthopedic Surgery Studies With Post-Operative Randomization (continued)

WHO Organ Class Serious Adverse Events (WHO Preferred Term)	Org31540/SR90107A <2.5 mg (N = 517)	 2.5 mg (N = 1645)	 >2.5 mg (N = 472)	Enoxaparin 30 mg bid (N = 1906)
Central and peripheral nervous system disorders				
Total	1 (0.2%)	4 (0.2%)	0 (0.0%)	7 (0.4%)
Confusion	0 (0.0%)	1 (0.1%)	0 (0.0%)	2 (0.1%)
Hypoaesthesia	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)
Neuropathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)
Coma	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Convulsions	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Dizziness	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Encephalopathy	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Gait abnormal	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Paralysis	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Resistance mechanism disorders				
Total	0 (0.0%)	6 (0.4%)	0 (0.0%)	2 (0.1%)
Post-operative wound infection	0 (0.0%)	5 (0.3%)	0 (0.0%)	1 (0.1%)
Infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Moniliasis	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Urinary system disorders				
Total	1 (0.2%)	4 (0.2%)	1 (0.2%)	2 (0.1%)
Renal failure acute	1 (0.2%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Micturition disorder	0 (0.0%)	1 (0.1%)	1 (0.2%)	0 (0.0%)
Renal tubular necrosis	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)
Urinary tract infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Cardiovascular disorders, general				
Total	3 (0.6%)	2 (0.1%)	1 (0.2%)	1 (0.1%)
Cardiac failure	1 (0.2%)	0 (0.0%)	1 (0.2%)	1 (0.1%)
Cardiac failure left	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypertension	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Hypotension	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypotension postural	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Application site disorders				
Total	0 (0.0%)	3 (0.2%)	0 (0.0%)	3 (0.2%)
Cellulitis	0 (0.0%)	3 (0.2%)	0 (0.0%)	3 (0.2%)
Vascular (extracardiac) disorders				
Total	1 (0.2%)	0 (0.0%)	1 (0.2%)	4 (0.2%)
Transient ischaemic attack	1 (0.2%)	0 (0.0%)	0 (0.0%)	2 (0.1%)
Vascular disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)
Cerebrovascular disorder	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
Metabolic and nutritional disorders				
Total	1 (0.2%)	1 (0.1%)	1 (0.2%)	1 (0.1%)
Dehydration	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Gout	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hyperglycaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
NPN increased	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)

(continued)

Table (9.2.2.1) 2 - Number (%) of Patients Experiencing Serious Adverse Events During Treatment Period by WHO Organ Class and Preferred Term - All Treated Patients in Orthopedic Surgery Studies With Post-Operative Randomization (continued)

WHO Organ Class Serious Adverse Events (WHO Preferred Term)	Org31540/SR90107A <2.5 mg (N = 517)	 2.5 mg (N = 1645)	 >2.5 mg (N = 472)	Enoxaparin 30 mg bid (N = 1906)
Musculo-skeletal system disorders				
Total	0 (0.0%)	2 (0.1%)	0 (0.0%)	2 (0.1%)
Arthralgia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Arthritis	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Arthropathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Bone disorder	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Psychiatric disorders				
Total	1 (0.2%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Delirium	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Withdrawal syndrome	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Skin and appendages disorders				
Total	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Angioedema	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Skin ulceration	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
White cell and reticulo endothelial system disorders				
Total	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
Myelomatosis multiple	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)

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NOTE: includes studies DRI2643, EFC2442, 095-001 and 095-002
GI = gastro-intestinal; NOS = not otherwise specified; NPN = non protein nitrogen
Ref.: Appendix 2.5.3.42

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Premature Discontinuations Due to an Adverse Event
The premature discontinuation rates for fondaparinux 2.5 mg and enoxaparin were 2.7% and 2.8% respectively. The most frequent reason for premature discontinuations due to an adverse event for all orthopedic studies was platelet, bleeding, and clotting disorders. This category accounted for 1% of all fondaparinux and 0.7% of all enoxaparin discontinuations.

Laboratory Results
There were no statistically significant differences between treatment groups in the orthopedic studies for hemoglobin and hematocrit. Both the fondaparinux and enoxaparin treatment groups experienced a decrease in hemoglobin and hematocrit from baseline. The sponsor's table below shows the number of patients experiencing a decrease in hemoglobin $\geq$ 2 g/dL.

Reviewer's Comment: The fondaparinux 2.5 mg treatment group had a greater percentage of patients experiencing a decrease in hemoglobin $\geq$ 2 g/dL.

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Table (10.2.1.1) 2 - Number (%) of Treated Patients With a Decrease in Hemoglobin ≥2 g/dL During Treatment Period Compared to First Post-Operative Value (Baseline) According to Study Type - All Treated Patients in Orthopedic Surgery Studies

Hemoglobin	Org31540/SR90107A			Enoxaparin	Nadroparin[a]
Studies with pre-operative randomization[b]					
	<2.5 mg	2.5 mg	>2.5 mg	40 mg od	
Decrease ≥ 2g/dL[c]	9/76 (11.8%)	424/1930 (22.0%)	42/138 (30.4%)	321/2001 (16.0%)	5/45 (11.1%)
Studies with post-operative randomization[d]					
	<2.5 mg	2.5 mg	>2.5 mg	30 mg bid	NA
Decrease ≥2 g/dL[c]	207/496 (41.7%)	911/1641 (55.5%)	234/454 (51.5%)	941/1896 (49.6%)	NA

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NA = not applicable

[a] 100 CIU/kg od pre-operatively and until Day 3 then 150 CIU/kg od for the last 3 days (study ACT1840)

[b] Includes studies ACT1840, ACT2545, 63118 and EFC2698

[c] Only patients with evaluation at baseline and at least one evaluation post baseline were taken into account

[d] Includes studies DRI2643, EFC2442, 095-001 and 095-002

Ref.: Appendix 2.2.42

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Platelets

The sponsor's table below shows that approximately 3% of orthopedic surgery patients treated with 2.5 mg of fondaparinux or enoxaparin experienced thrombocytopenia. Eight fondaparinux patients had platelet counts below 50,000/cc[3] compared with one enoxaparin patient.

Reviewer's Comment: The thrombocytopenia event rates are not statistically significantly different.

Table (10.1.2.1) 2 - Number (%) of Patients With a Decrease in Platelet Count to Values Included in the [50 x 10^9/L - 100 x 10^9/L[Range or <50 x 10^9/L According to Study Type - All Treated Patients in Orthopedic Surgery Studies

Platelet counts	Org31540/SR90107A			Enoxaparin	Nadroparin[a]
Studies with pre-operative randomization[b]					
	<2.5 mg	2.5 mg	>2.5 mg	40 mg od	
[50 x 10^9/L - 100 x 10^9/L[[c,d]	0/75 (0.0%)	66/1943 (3.4%)	0/139 (0.0%)	75/2016 (3.7%)	0/45 (0.0%)
<50 x 10^9/L[c,e]	0/75 (0.0%)	6/1943 (0.3%)	0/139 (0.0%)	0/2016 (0.0%)	0/45 (0.0%)
<100 x 10^9/L[c,d]	0/75 (0.0%)	70/1943 (3.6%)	0/139 (0.0%)	75/2016 (3.7%)	0/45 (0.0%)
Studies with post-operative randomization[f]					
	<2.5 mg	2.5 mg	>2.5 mg	30 mg bid	NA
[50 x 10^9/L - 100 x 10^9/L[[c,d]	19/500 (3.8%)	37/1639 (2.3%)	14/460 (3.0%)	49/1895 (2.6%)	NA
<50 x 10^9/L[c,e]	2/500 (0.4%)	0/1639 (0.0%)	0/460 (0.0%)	1/1895 (0.1%)	NA
<100 x 10^9/L[c,d]	20/500 (4.0%)	37/1639 (2.3%)	14/460 (3.0%)	49/1895 (2.6%)	NA

PGM: [redacted] OUT: output/OS101312b (15JAN01 - 15:35)

NA = not applicable

[a] 100 CIU/kg od pre-operatively and until Day 3 then 150 CIU/kg od for the last 3 days (study ACT1840)

[b] Includes studies ACT1840, ACT2545, 63118 and EFC2698

[c] After the first study drug injection

[d] With baseline value ≥100 x 10^9/L or missing

[e] With baseline value ≥50 x 10^9/L or missing

[f] Includes studies DRI2643, EFC2442, 095-001 and 095-002

Ref.: Appendix 2.6.11

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The sponsor's table below shows the number of patients in phase III orthopedic studies that develop positive ELISA and serotonin tests after receiving study treatment (fondaparinux or enoxaparin).

Reviewer's Comment: The reason for the differences in percentage positive for ELISA and serotonin release between preoperative and post-operative randomization is not known. Clearly both treatments were associated with ELISA positivity and a positive serotonin release test..

Table (10.1.3.1) 1 - Number (%) of Patients With ELISA and Serotonin Tests (Among Positive ELISA Tests) Which Became Positive After Beginning of Active Study Drug According to Study Type - Phase III Orthopedic Surgery Studies

Test	Org31540/SR90107A	Enoxaparin
Studies with pre-operative randomization[a]		
	2.5 mg	**40 mg od**
Positive ELISA test	99/1810 (5.5%)	65/1817 (3.6%)
Positive Serotonin release test	20/99 (20.2%)	11/65 (16.9%)
Studies with post-operative randomization[b]		
	2.5 mg	**30 mg bid**
Positive ELISA test	40/1379 (2.9%)	40/1350 (3.0%)
Positive Serotonin release test	3/40 (7.5%)	1/40 (2.5%)

PGM: [redacted] OUT: output/OS10141 (15JAN01 - 14:11)

[a] Studies 63118 and EFC2698

[b] Studies EFC2442 and 095-002

Ref.: Appendix 2.6.24

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The following table shows the number of patients in phase III orthopedic studies with VTE according to their ELISA test result.

Reviewer's Comment: In these studies, both fondaparinux and enoxaparin patients developed VTE and became positive for ELISA.

Table (10.1.3.1) 2 - Number (%) of Patients With a VTE According ELISA Test Result and Study Type - Phase III Orthopedic Surgery Studies

	Org31540/SR90107A	Enoxaparin	Total
Studies with pre-operative randomization[a]			
Patients with VTE among patients with:	**2.5 mg**	**40 mg od**	
Positive ELISA test	8/98 (8.2%)	9/63 (14.3%)	17/161 (10.6%)
Negative ELISA test	72/1696 (4.2%)	182/1739 (10.5%)	254/3435 (7.4%)
Studies with post-operative randomization[b]			
Patients with VTE among patients with:	**2.5 mg**	**30 mg bid**	
Positive ELISA test	1/37 (2.7%)	1/39 (2.6%)	2/76 (2.6%)
Negative ELISA test	77/1195 (6.4%)	132/1172 (11.3%)	209/2367 (8.8%)

PGM: [redacted] OUT: output/OS10142b (15JAN01 - 16:48)

[a] Includes studies 63118 and EFC2698

[b] Includes studies EFC2442 and 095-002

Ref.: Appendix 2.6.26

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The sponsor's table below shows the number of patients with a platelet count less than 100,00/cc^3 by ELISA result.

Reviewer's Comment: In both treatment groups, thrombocytopenic patients may also be ELISA positive.

Table (10.1.3.1) 3 - Number (%) of Patients With a Platelet Count <100 x 10^9/L According to ELISA Test Result and Study Type - Phase III Orthopedic Surgery Studies

	Org31540/SR90107A	Enoxaparin	Total
Studies with pre-operative randomization[a]			
Patient with platelet count <100 x 10^9/L among patients with:	**2.5 mg**	**40 mg od**	
Positive ELISA test	2/99 (2.0%)	2/65 (3.1%)	4/164 (2.4%)
Negative ELISA test	63/1708 (3.7%)	66/1750 (3.8%)	129/3458 (3.7%)
Studies with post-operative randomization[b]			
Patient with platelet count <100 x 10^9/L among patients with:	**2.5 mg**	**30 mg bid**	
Positive ELISA test	2/40 (5.0%)	1/40 (2.5%)	3/80 (3.8%)
Negative ELISA test	30/1338 (2.2%)	29/1310 (2.2%)	59/2648 (2.2%)

PGM: [redacted] OUT: output/OS10142c (15JAN01 - 16:48)

[a] Includes studies 63118 and EFC2698

[b] Includes studies EFC2442 and 095-002

Ref.: Appendix 2.6.28

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Reviewer's Comment: These results suggest that fondaparinux may be associated with heparin induced thrombocytopenia (HIT) and thrombosis (HITTS), similar to unfractionated heparin and low molecular weight heparins, such as enoxaparin.

Transaminases
The sponsor's table below shows the laboratory results for transaminases.

Reviewer's Comment: Elevated transaminases were seen in all treatment groups.

APPEARS THIS WAY
ON ORIGINAL

Table (10.2.2.1) 2 - Number (%) of Patients With No Increase or With an Increase in AST and/or ALT to Values Above One or Three Times the Upper Limit During Treatment Period Compared to First Post-Operative Values (Baseline) According to Study Type - All Treated Patients in Orthopedic Surgery Studies

Transaminase	Org31540/SR90107A			Enoxaparin	Nadroparin[a]
Studies with pre-operative randomization[b]					
	<2.5 mg	2.5 mg	>2.5 mg	40 mg od	
AST					
No increase[c]	30/71 (42.3%)	1306/1762 (74.1%)	83/140 (59.3%)	1148/1826 (62.9%)	27/45 (60.0%)
Increase]ULN - 3 ULN][d]	38/71 (53.5%)	424/1762 (24.1%)	51/140 (36.4%)	610/1826 (33.4%)	18/45 (40.0%)
Increase >3 ULN[e]	3/71 (4.2%)	32/1762 (1.8%)	6/140 (4.3%)	68/1826 (3.7%)	0/45 (0.0%)
ALT					
No increase[c]	40/71 (56.3%)	1288/1803 (71.4%)	87/140 (62.1%)	1151/1859 (61.9%)	29/45 (64.4%)
Increase]ULN - 3 ULN][d]	24/71 (33.8%)	449/1803 (24.9%)	45/140 (32.1%)	604/1859 (32.5%)	14/45 (31.1%)
Increase >3 ULN[e]	7/71 (9.9%)	66/1803 (3.7%)	8/140 (5.7%)	104/1859 (5.6%)	2/45 (4.4%)
AST or ALT					
No increase[c]	29/71 (40.8%)	1166/1814 (64.3%)	74/140 (52.9%)	998/1878 (53.1%)	24/45 (53.3%)
Increase]ULN - 3 ULN][d]	34/71 (47.9%)	575/1814 (31.7%)	57/140 (40.7%)	756/1878 (40.3%)	19/45 (42.2%)
Increase >3 ULN[e]	8/71 (11.3%)	73/1814 (4.0%)	9/140 (6.4%)	124/1878 (6.6%)	2/45 (4.4%)
Studies with post-operative randomization[f]					
	<2.5 mg	2.5 mg	>2.5 mg	30 mg bid	NA
AST					
No increase[c]	420/497 (84.5%)	1183/1495 (79.1%)	363/450 (80.7%)	1201/1719 (69.9%)	NA
Increase]ULN - 3 ULN][d]	72/497 (14.5%)	289/1495 (19.3%)	78/450 (17.3%)	471/1719 (27.4%)	NA
Increase >3 ULN[e]	5/497 (1.0%)	23/1495 (1.5%)	9/450 (2.0%)	47/1719 (2.7%)	NA
ALT					
No increase[c]	436/497 (87.7%)	1238/1474 (84.0%)	377/450 (83.8%)	1296/1698 (76.3%)	NA
Increase]ULN - 3 ULN][d]	52/497 (10.5%)	217/1474 (14.7%)	59/450 (13.1%)	368/1698 (21.7%)	NA
Increase >3 ULN[e]	9/497 (1.8%)	19/1474 (1.3%)	14/450 (3.1%)	34/1698 (2.0%)	NA
AST or ALT					
No increase[c]	401/497 (80.7%)	1123/1504 (74.7%)	350/450 (77.8%)	1133/1730 (65.5%)	NA
Increase]ULN - 3 ULN][d]	87/497 (17.5%)	349/1504 (23.2%)	84/450 (18.7%)	535/1730 (30.9%)	NA
Increase >3 ULN[e]	9/497 (1.8%)	32/1504 (2.1%)	16/450 (3.6%)	62/1730 (3.6%)	NA

PGM: OUT: output/OS102212 (15JAN01 - 17:30)

NA = not applicable

[a] 100 CIU/kg od pre-operatively and until Day 3 then 150 CIU/kg od for the last 3 days (study ACT1840)

[b] Includes studies ACT1840, ACT2545, 63118 and EFC2698

[c] No increase: values remained in the same range (i.e., ≤ULN,]ULN - 3 ULN] or >3 ULN) after the beginning of treatment compared to baseline values, or values decreased

[d] Increase]ULN - 3 ULN]: values increased from baseline at least once to a value >ULN but remained ≤3 ULN

[e] Increase >3 ULN: values increased from baseline at least once to a value >3 ULN

[f] Includes studies DRI2643, EFC2442, 095-001 and 095-002

Ref.: Appendix 2.6.62

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Total Bilirubin

The sponsor's table below shows the number of patients with total bilirubin values ≥ 2 mg/dL during the treatment period.

Reviewer's Comment: With increasing dose of fondaparinux there was an increased incidence of an elevated bilirubin ≥ 2 mg/dL.

Table (10.2.3.1) 2 - Number (%) of Patients With Total Bilirubin Values >2 mg/dL During Treatment Period After First Study Drug Administration According to Study Type - All Treated Patients Orthopedic Surgery Studies

Total Bilirubin	Org31540/SR90107A			Enoxaparin	Nadroparin[a]
Studies with pre-operative randomization[b]					
	<2.5 mg	2.5 mg	>2.5 mg	40 mg od	
Value >2 mg/dL[c]	1/71 (1.4%)	55/1795 (3.1%)	5/140 (3.6%)	41/1854 (2.2%)	2/45 (4.4%)
Studies with post-operative randomization[d]					
	<2.5 mg	2.5 mg	>2.5 mg	30 mg bid	NA
Value >2 mg/dL[c]	9/497 (1.8%)	15/1465 (1.0%)	11/450 (2.4%)	12/1682 (0.7%)	NA

PGM: [redacted] OUT: output/OS102312 (22DEC00 - 12:40)

[a] 100 CIU/kg od pre-operatively and until Day 3 then 150 CIU/kg od for the last 3 days (study ACT1840)

[b] Includes studies ACT1840, ACT2545, 63118 and EFC2698

[c] With baseline value ≤2 mg/dL (or missing)

[d] Includes studies DRI2643, EFC2442, 095-001 and 095-002

Ref.: Appendix 2.6.83

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White Blood Cells
There were no significant changes in white blood cells and white blood cell count differentials between treatment groups in Phase II orthopedic studies.

Biochemistry Parameters
There was a mean increase in alkaline phosphatase; however, few patients experienced an increase greater than 3 times the upper limit of normal (ULN). There was a mean increase in gamma glutamyl transferase (GGT); however, no patient experienced an increase to greater than 3 times the ULN.

Phase I studies

Bleeding
No bleeding events were adjudicated. Bleeding events were reported as AEs.

Platelet, bleeding, and clotting disorders were the most frequent adverse event compared with placebo.

There were no deaths reported in phase I studies.

There was only one SAE reported during the single dose phase I studies. Subject #63105-0032-0046 experienced angina on Day 20, which lasted until Day 42. The investigator determined the adverse event was unrelated to study drug. There were no SAEs reported in the multiple dose and renal impairment study. There was one SAE in the digoxin-fondaparinux interaction study, where a subject (# INT3933-1301-0005) experienced second degree heart block after five days of digoxin and fondaparinux co-administration. The drug was stopped and the second degree heart block resolved within 8 hours. The subject was discontinued from the study after stopping the medication.

Only two other patients discontinued from single and multiple dose studies; both discontinued for bleeding events.

Studies in Other Indications

The table below shows the ongoing and completed studies for other indications.

Ongoing and Completed Fondaparinux Studies and Trials

Study	Objective	Status
TDU4089	Phase I- Pharmacokinetic (PK) study for subcutaneous (SC) and intravenous (IV) administration	Completed
TDU4289	Phase I-Safety and PK study for SC administration	Completed
DRI2440-	Dose ranging study for the treatment of	Completed
EFC2441-	Phase III Efficacy and Safety of daily fondaparinux compared with enoxaparin for treatment of	Ongoing
63123-	Phase III Efficacy and Safety of daily fondaparinux compared with unfractionated heparin for treatment of	Ongoing
63119-	Phase IIb- dose ranging study in patients with	Ongoing
ACT2445	Pilot Efficacy and Safety study in patients undergoing	Completed
DRI-3196-	Dose Ranging study for concomitant administration of fondaparinux with	Completed
CSCRO-63113-EN-E01	Pilot safety and efficacy study to	Completed

Reviewer's Table

Bleeding
Study DRI2440 (treatment of used the Hamilton Criteria and an adjudication committee. In study DRI3196 intracranial bleeding and blood transfusion were considered the primary safety endpoint. Transfusion rates were reported as bleeding in both studies.

Study DRI2440

The sponsor's table below shows the bleeding rate for patients during study drug treatment.

Reviewer's Comment: Major bleeding is increased with fondaparinux compared with dalteparin.

APPEARS THIS WAY
ON ORIGINAL

Table (8.2.1.1) 1 - Number (%) of Patients Experiencing an Adjudicated Bleeding Event During the Treatment Period - Study in Treatment of [redacted] (Study DRI2440)

Patients With:	Org31540/SR90107A >2.5 mg (N = 334)	Dalteparin 100 IU/kg bid SC (N = 119)
Major bleeding 95% CI	6 (1.8%) [0.7;3.9]	0 (0.0%) [0.0 ;0.0]
Minor bleeding only 95% CI	17 (5.1%) [3.0;8.0]	13 (10.9%) [5.9;18.0]
Any bleeding 95% CI	23 (6.9%) [4.4;10.2]	13 (10.9%) [5.9;18.0]

PGM: [redacted] OUT: output/OT8211 (05JAN01 - 13:29)
Ref: Appendix 4.4.1

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Study DRI3196 ([redacted])

The sponsor's table below shows the bleeding rate for patients during study drug treatment.

Table (8.2.1.2) 1 - Number (%) of Patients who Reached a Primary Endpoint for Safety During the Treatment Period - [redacted] Study DRI3196)

Patients With:	Org31540/SR90107A >2.5 mg - SC (N = 241)	UFH* (N = 85)
Intracranial bleeding	1 (0.4%)	0 (0.0%)
Blood transfusion 95% CI	9 (3.7%) [1.7;7.0]	6 (7.1%) [2.6;14.7]
Total of patients who reached the primary endpoint for safety 95% CI	10 (4.1%) [2.0;7.5]	6 (7.1%) [2.6;14.7]

PGM: [redacted] OUT: output/OT8213 (05JAN01 - 10:37)
* 5000 IU IV bolus then 1000 IU/kg infusion
Ref: Appendix 4.4.7

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The most frequently reported adverse event category for fondaparinux compared with unfractionated heparin was platelet, bleeding, and clotting disorders (primarily hematoma 26.6% and 11.8% respectively).

Deaths
Only one death occurred on treatment in studies for other indications. This patient was enrolled in the study of fondaparinux as [redacted] and died of cardiac failure.

Serious Adverse Events in [redacted] study
The sponsor's table below lists the serious adverse events, which occurred during treatment for [redacted]

Reviewer's Comment: The adverse event category with the greatest number of patients with events attributable to the drug is platelet, bleeding, and clotting disorders.

Table (9.2.2.3) 1 - Number (%) of Patients Experiencing Serious Adverse Events During the Treatment Period by WHO Organ Class and Preferred Term - Treatment of —— (Study DRI2440)

WHO Organ Class Serious Adverse Events (WHO Preferred term)	Org31540/SR90107A >2.5 mg - SC (N = 334)	Dalteparin 100 IU/kg bid - SC (N = 119)
Any event	13 (3.9%)	1 (0.8%)
Gastro-intestinal system disorders		
Total	5 (1.5%)	0 (0.0%)
Colon carcinoma	1 (0.3%)	0 (0.0%)
Gastric carcinoma	1 (0.3%)	0 (0.0%)
Gastrointestinal neoplasm malignant	1 (0.3%)	0 (0.0%)
Pancreas neoplasm malignant	1 (0.3%)	0 (0.0%)
Rectal carcinoma	1 (0.3%)	0 (0.0%)
Platelet, bleeding and clotting disorders		
Total	5 (1.5%)	0 (0.0%)
Haematoma	3 (0.9%)	0 (0.0%)
Haematuria	1 (0.3%)	0 (0.0%)
Purpura	1 (0.3%)	0 (0.0%)
Body as a whole - General disorders		
Total	2 (0.6%)	0 (0.0%)
Influenza-like symptoms	2 (0.6%)	0 (0.0%)
Cardiovascular disorders, general		
Total	1 (0.3%)	0 (0.0%)
Cardiac failure	1 (0.3%)	0 (0.0%)
Reproductive disorders, female		
Total	1 (0.3%)	0 (0.0%)
Ovarian carcinoma	1 (0.3%)	0 (0.0%)
Skin and appendages disorders		
Total	0 (0.0%)	1 (0.8%)
Bullous eruption	0 (0.0%)	1 (0.8%)

PGM: —— OUT: output/OT93231 (03JAN01 - 14:44)
Ref: Appendix 4.5.37

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Serious Adverse Events in Adjunctive Study to —— study
The sponsor's table below lists the serious adverse events occurring during treatment.
Reviewer's Comment: The adverse event category with the greatest number of patients with events attributable to the drug is platelet, bleeding, and clotting disorders.

APPEARS THIS WAY
ON ORIGINAL

Table (9.2.2.3) 2 - Number (%) of Patients Experiencing Serious Adverse Events During th Treatment Period by WHO Organ Class and Preferred Term - [redacted] (Study DRI3196)

WHO Organ Class Serious Adverse Events (WHO Preferred term)	Org31540/SR90107A >2.5 mg - SC (N = 241)	UFH[a] (N = 85)
Any event	18 (7.5%)	5 (5.9%)
Platelet, bleeding and clotting disorders		
Total	10 (4.1%)	3 (3.5%)
Haemorrhage NOS	4 (1.7%)	1 (1.2%)
Haematoma	1 (0.4%)	1 (1.2%)
Cerebral haemorrhage	1 (0.4%)	0 (0.0%)
Epistaxis	1 (0.4%)	0 (0.0%)
Haematemesis	1 (0.4%)	0 (0.0%)
Haemorrhage retroperitoneal	1 (0.4%)	0 (0.0%)
Ocular haemorrhage	0 (0.0%)	1 (1.2%)
Thrombophlebitis arm superficial	1 (0.4%)	0 (0.0%)
Cardiovascular disorders, general		
Total	6 (2.5%)	1 (1.2%)
Cardiac failure	2 (0.8%)	1 (1.2%)
Cardiac failure left	1 (0.4%)	0 (0.0%)
Circulatory failure	1 (0.4%)	0 (0.0%)
Hypotension	1 (0.4%)	0 (0.0%)
Ventricular septal defect	1 (0.4%)	0 (0.0%)
Respiratory system disorders		
Total	2 (0.8%)	0 (0.0%)
Pulmonary oedema	2 (0.8%)	0 (0.0%)
Body as a whole - General disorders		
Total	1 (0.4%)	0 (0.0%)
Chest pain	1 (0.4%)	0 (0.0%)
Myo-, endo-, pericardial and valve disorders		
Total	1 (0.4%)	0 (0.0%)
Pericardial effusion	1 (0.4%)	0 (0.0%)
Urinary system disorders		
Total	0 (0.0%)	1 (1.2%)
Hydronephrosis	0 (0.0%)	1 (1.2%)
Vascular (extracardiac) disorders		
Total	1 (0.4%)	0 (0.0%)
Cerebrovascular disorder	1 (0.4%)	0 (0.0%)

PGM: [redacted] OUT: output/OT93233 (03JAN01 - 14:45)
NOS = not otherwise specified
[a] 5000 IU IV bolus then 1000 IU/kg infusion
Ref.: Appendix 4.5.41

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Ongoing Studies

Safety information for these studies was limited to information prior to May 2000.

Results of bleeding adjudication were not given for these studies.

Deaths
Deaths were reported in the dose ranging study for ——— These results are blinded and the treatment group is not known. The sponsor's table below shows the etiology.

Table (9.2.1.4) 1 - Number of Patients With Serious Adverse Events Leading to Death During Treatment Period by WHO Organ Class and Preferred Term - Ongoing Study in ——— (Study 63119)

WHO Organ Class Serious Adverse Events (WHO preferred Term)	Double-blind (N = 343)
Any event	5 (1.5%)
Heart rate and rhythm disorders	
Total	3 (0.9%)
Bradycardia	1 (0.3%)
Cardiac arrest	1 (0.3%)
Fibrillation ventricular	1 (0.3%)
Cardiovascular disorders, general	
Total	2 (0.6%)
Cardiac failure	2 (0.6%)
Myo-, endo-, pericardial and valve disorders	
Total	2 (0.6%)
Cardiac tamponade	1 (0.3%)
Myocardial rupture (post infarct)	1 (0.3%)

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No other ongoing studies reported deaths.

Serious Adverse Events
The only SAEs reported before the cutoff date were observed in the ——— study. The sponsor's table below lists these events.

Reviewer's Comment: The patient who experienced an intracranial hemorrhage was also on ticlopidine and heparin.

APPEARS THIS WAY
ON ORIGINAL

Table (9.2.2.4) 1 - Number (%) of Patients Experiencing Serious Adverse Events During the Treatment Period by WHO Organ Class and Preferred Term - Ongoing Study in ——— (Study 63119)

WHO Organ Class Serious Adverse Events (WHO preferred Term)	Double-blind (N = 343)
Any event	8 (2.3%)
Heart rate and rhythm disorders	
Total	4 (1.2%)
Fibrillation ventricular	2 (0.6%)
Bradycardia	1 (0.3%)
Cardiac arrest	1 (0.3%)
Myo-, endo-, pericardial and valve disorders	
Total	3 (0.9%)
Cardiac tamponade	1 (0.3%)
Myocardial infarction	1 (0.3%)
Myocardial rupture (post infarct)	1 (0.3%)
Cardiovascular disorders, general	
Total	2 (0.6%)
Cardiac failure	2 (0.6%)
Platelet, bleeding and clotting disorders	
Total	2 (0.6%)
Haemorrhage intracranial	1 (0.3%)
Haemorrhage rectum	1 (0.3%)
Gastro-intestinal system disorders	
Total	1 (0.3%)
Rectal carcinoma	1 (0.3%)

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Premature Discontinuations
Two patients discontinued from the ——— study. One patient developed flu-like symptoms and the other developed purpura. In the trial of ———, patients discontinued primarily for platelet, bleeding, and clotting disorders (7.5%) and cardiovascular causes (2.1%).

VIII. Assessment of Dosing/Regimen/Administration Issues

The sponsor proposes the following regimen and indication: fondaparinux 2.5 mg subcutaneously daily for **the prevention of venous thromboembolic events in patients undergoing major orthopedic surgery of the lower limbs such as hip fracture, major knee or hip replacement surgeries.**

Reviewer's Comment: The sponsor's proposed all-inclusive category of orthopedic surgery of the lower limbs includes foot and ankle surgeries. The sponsor did not study these indications. Thus the indication would need to be reworded to reflect the indications studied.

The sponsor proposes under the Dosage and Administration section: **The average duration of treatment with ——— in controlled clinical trials was 7 ± 2 days and administration up to 11 days was well tolerated.** ———

Reviewer's Comment: The phase II and III orthopedic studies treated patients to a maximum of 11 days. The risk of VTE is increased following orthopedic surgery for several weeks. The data

do not support the statement that [redacted]

The sponsor performed four phase II studies:

1) one study for knee replacement 095001
2) three studies for hip replacement
   a) ACT 1840
   b) ACT 2545
   c) DRI-2643- [redacted]

The sponsor performed four phase III trials:

1) ECF2698- [redacted] (hip fracture)
2) ECF2442- [redacted] (hip replacement)
3) 63118 EPHESUS (hip replacement)
4) 095002 [redacted] (knee replacement)

Human Pharmacokinetics and Pharmacodynamics
Fondaparinux is an indirect thrombin generation inhibitor with nearly complete bioavailability (107%) after SC injection compared with IV administration. The half-life is approximately 17 hours with t_{max} occurring 1.7 $\pm$ 0.4 hours. Renal excretion is the major elimination mechanism. Drug-drug interaction studies did not reveal any significant interactions.

Dose regimen selection
The sponsor proposes fondaparinux 2.5 mg administered subcutaneously once daily. The sponsor did not use the 2.5 mg fondaparinux dose until the phase III trials. The sponsor studied a range of single daily doses: 0.75 mg, 1.5 mg, 3.0 mg, 6.0 mg, and 8.0 mg. The sponsor also studied fondaparinux 2 mg and 4 mg BID. The 6.0mg and 8.0mg doses were terminated because of excessive major bleeding. The BID dosing regimens were associated with excessive major bleeding with no or minimal improvement in efficacy compared with the once daily regimen. In study 095001, the 0.75mg dose was terminated due to lack of efficacy. For details, the reader is referred to the individual efficacy and safety reviews. The final dose ranging trial (DRI2643) suggested that the optimal dose was between 0.75 mg and 3.0 mg. The table below shows the efficacy and safety results for doses 0.75mg to 3.0 mg.

Selected Efficacy and Safety results from Study DRI2643

Dose/Endpoint	Fondaparinux 0.75 mg (N=102)	Fondaparinux 1.50 mg (N=101)	Fondaparinux 3.0 mg (N=101)	Enoxaparin (N=150)
Primary Outcome (VTE)				
Per-Protocol population	13 (12.7%)	6 (5.9%)	2 (2.0%)	14 (9.3%)
ITT population	14 (11.8%)	8 (6.7%)	2 (1.7%)	16 (9.4%)
Major Bleeding	0	1 (0.5%)	8 (4.5%)	9 (3.5%)

Reviewer's table

The sponsor performed modeling analyses and decided that a fondaparinux dose $\leq$ 3.0 mg given once subcutaneously daily would provide the optimal benefit/risk (VTE prophylaxis/hemorrhage)

ratio for comparison trials with enoxaparin. The sponsor then chose 2.5 mg to reduce the major bleeding rate observed with fondaparinux.
Reviewer's Comment: The efficacy and safety results from the phase III trials combined with the data obtained in the dose ranging trials support fondaparinux 2.5 mg SC once daily.

Renal Impairment Issue
Data obtained from a single dose phase II pharmacokinetic study suggest that decreasing kidney function is associated with decreased plasma clearance and higher fondaparinux plasma levels. Clinical orthopedic phase III trials excluded patients with serum creatinine > 2.0 mg/dL. In phase II/III orthopedic studies, the major bleeding and AE rates increased with decreased creatinine clearance. Major bleeding rates were: < 30 mL/min: 4.8%, 30-50 mL/min: 3.8%, 50-80 mL/min: 2.4%, > 80 mL/min: 1.6%.

Reviewer's Comment: This reviewer does not recommend additional studies in renally impaired patients. This reviewer recommends the information about increased bleeding risk with decreased kidney function be placed in the labeling.

Hepatic Impairment Issue
No trial was conducted in hepatic impairment subjects/patients.

Reviewer's Comment: This drug is an anticoagulant and its most common side effect is major bleeding. Satisfactory hemostasis requires the adequate production of coagulation factors in the liver. Thus, it would be important to evaluate the safety of this drug in hepatic impairment patients whose coagulation production may be impaired.

IX. Use in Special Populations

The sponsor performed clinical studies with elderly subjects and renal impairment subjects. The sponsor did not study hepatic impairment subjects/patients. The sponsor requested and was granted a waiver for pediatric studies. From the clinical trials, efficacy and safety data were analyzed for gender, age, renal function, and ethnicity effects.

A. Gender Analyses

In Phase II/III orthopedic studies, efficacy and safety analyses (bleeding and AE) did not demonstrate a statistically significant difference between male and female patients.

B. Pediatric Program

The Agency granted a pediatric waiver on February 2, 2001 for the following indications: reducing the risk of venous thromboembolism in patients undergoing the hip fracture surgery, hip replacement surgery, and major knee surgery.

C. Race

The sponsor's data concerning effect of ethnicity are:

1) The sponsor performed covariate analyses in each study, which suggested there was no race drug interaction.
2) The sponsor stated that there were too few non-Caucasians in the studies to allow any conclusion of race effect on bleeding and AEs.
3) The sponsor evaluated information on plasma clearance in Black patients in a phase II trial, which suggested no significant differences compared with Caucasian patients.
4) The sponsor performed several PK/PD bridging studies in Japanese healthy volunteers, which suggested there is no race-drug interaction.

Reviewer's Comment: The sponsor's data on race effect is deficient. The population studied should reflect the population that will receive the drug. The sponsor's demographic tables did not list Hispanic patients and the sponsor did not comment on race drug interaction for Hispanic

patients. [ ]

D. Other special populations

Elderly

In Phase II/III orthopedic studies, there was no difference for major bleeding and AEs rates between fondaparinux and enoxaparin treatment groups. However, the fondaparinux major bleeding rates increased with increasing age (< 65 years: 1.8%, 65-75 years:2.2%, ≥ 75 years: 2.7%). When major bleeding was adjusted for other baseline covariates, including renal function and weight, the age effect was no longer evident.

Renal impairment

Fondaparinux is renally excreted and pharmacokinetic data obtained from phase II studies suggest that decreasing kidney function is associated with decreased plasma clearance and higher fondaparinux plasma levels. In phase II/III orthopedic studies, the major bleeding and AEs rates increased with decreased creatinine clearance. Major bleeding rates were: < 30 mL/min: 4.8%, 30-50 mL/min: 3.8%, 50-80 mL/min: 2.4%, > 80 mL/min: 1.6%.

Reviewer's Comment: See additional comments in the Dosing/Regimen/Administration section of the labeling.

Hepatic impairment

There were no studies performed in hepatic impairment subjects/patients.

Reviewer's Comment: This reviewer is concerned about administration of this drug in hepatic impairment patients, who may have acquired coagulation factor deficiencies and therefore impaired hemostasis. This reviewer recommends the sponsor collect information on the safe use of fondaparinux in hepatic impairment patients.

Pregnancy

There were no studies performed in pregnant subjects or patients.

Reviewer's Comment: The proposed fondaparinux indications are infrequently seen among women of child-bearing potential. This reviewer does not recommend additional study in pregnant women for the proposed indications.

Weight

In Phase II/III orthopedic studies, there was an increase in fondaparinux associated major bleeding incidence in patients with decreasing body weight (< 50 kg: 5.4%, 50-100 kg: 2.1%, ≥ 100 kg: 2.3%). However, when major bleeding was adjusted for other baseline covariates, the weight effect was no longer evident. Overall, there was an increased AE rate with decreasing weight. For non-hemorrhagic AEs, there was an increased incidence of atrial fibrillation in patients weighing less than 50 kg.

Reviewer's Comment: This reviewer recommends the labeling reflect the increased risk of hemorrhage with decreased weight.

X. Conclusions

The sponsor submitted this NDA for Arixtra, fondaparinux sodium, a synthetic pentasaccharide, an indirect thrombin inhibitor/anticoagulant to support the following regimen and indication: fondaparinux 2.5 mg once daily administered post-operatively by subcutaneous injection for the prevention of venous thromboembolic events in patients undergoing major orthopedic surgery of the lower limbs such as hip fracture, major knee or hip replacement surgeries with a treatment

duration up to 11 days. The sponsor submitted pre-clinical and clinical phase I, II, and III data for review. In the phase III trials for approval, the sponsor compared the efficacy and safety of fondaparinux to an approved enoxaparin regimen.

The NDA review is split into separate efficacy and safety reviews. Dr. Min Lu reviewed the efficacy portion of the NDA. For details regarding fondaparinux's efficacy, please see Dr. Min Lu's Medical Officer Efficacy review. This safety review discusses the fondaparinux NDA pre-clinical and clinical safety database and reviews the sponsor's proposed labeling. The application is approvable from a clinical safety perspective in the requested population. The reader is referred to Dr. Min Lu's Medical Officer Efficacy review of this NDA for approvability from an efficacy perspective.

Potential benefits of this product include:
1) first anticoagulant approved for hip fracture
2) proven efficacy for the following indications
   a) hip replacement
   b) knee replacement
3) once daily dosing

Potential risks of this product include:
1) long half-life (approximately 17 hours in patients with normal renal function)
2) bleeding (increased risk in patients < 50 kg, elderly, and those with reduced renal function)
3) thrombocytopenia
4) heparin antibody formation
5) adverse skin reactions
6) transaminase elevation

Fondaparinux risk management steps include collecting the necessary data listed below prior to approval and revision of the sponsor's proposed labeling. No additional risk management steps need to be taken at this time.

The current application for fondaparinux has deficiencies and thus cannot be approved at this time. The following issues would need to be resolved prior to fondaparinux being approved for marketing:

Risk Management

1. The sponsor should revise the label as recommended (See Appendix F).

Phase 4 Commitments

2. The sponsor should collect safety information on the use of the drug in hepatic impairment patients.

[

]

Other Recommendation

[ ]

XI. Appendices

A. Individual Study Safety reviews for Phase II studies for Thromboprophylaxis in Orthopedic Surgery

Trial - 095001 ——— (knee replacement) – A Multicenter, Concurrent Control, Randomized, Open-label, Assessor-Blind, Dose ranging trial for thromboprophylaxis (knee replacement)

Three hundred and eighteen patients were enrolled and randomized to one of the following post-operative fondaparinux dose regimens for 5-10 days:

1) fondaparinux 0.75 mg SC once daily
2) fondaparinux 1.5 mg SC once daily
3) fondaparinux 3.0 mg SC once daily
4) fondaparinux 6.0 mg SC once daily
5) fondaparinux 8.0 mg SC once daily

The protocol stipulated that the administration of the first post-operative dose was approximately 6 hours after surgery.

Two separate adjudication criteria were used to report the safety results from this trial. The original protocol/study report used Dr. Miller's adjudication committee. The Hamilton criteria were later used in the phase III trials and provided a comparison between safety data collected in phase II and phase III trials.

The table below shows the incidence of major and minor bleeding as adjudicated by Dr. Miller's Group (Central Independent Adjudication Committee (CIAC)) and Dr. Prin's group (Central Independent Adjudication Committee) using the Hamilton criteria. Dr. Miller's group defined bleeding using the following criteria:

Major Bleeding

- Death due to bleeding
- Intra-cranial bleeding or bleeding within a critical organ (e.g., eye, or adrenal gland)
- Re-operation due to bleeding (hematoma) in the surgical area
- Clinically overt bleeding and/or quantitative blood loss which the CIAC deemed to be a major bleed.

Overt unusual bleeding not meeting the criteria for major bleeding was classified as a minor bleed.

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Amendments 4 and 5 further clarified quantitative blood loss as follows:

The mean blood loss +1 standard deviation (SD) and +2 SD in subjects undergoing unilateral or bilateral total knee replacement will be calculated from the start of treatment (D1) to the end of treatment.

Bleeding grades based on laboratory data of quantified blood loss will be as follows:

- Insignificant (no bleed): Blood loss (ml) up to +1 SD of mean blood oss
- Minor Bleed: Blood loss between +1 and + 2SD of mean blood loss
- Major Bleed: Blood loss > + 2SD of mean blood loss

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Dr. Prin's group used the Hamilton criteria:

- Major bleeding was defined as:
  - fatal bleeding
  - clinically overt bleeding including retroperitoneal or intracranial bleeding, or bleeding into a critical organ (eye, adrenal gland, pericardium, spine)
  - bleeding necessitating medical or surgical intervention at the operative site
  - clinically overt bleeding leading to a fall in Hgb of ≥2 g/dL (1.6 mmol/L) and/or a transfusion of ≥2 units of packed red blood cells (PRBCs) or whole blood and for which the combined calculated index was ≥2 (the combined bleeding index was calculated within 48 hours of the bleed as follows: number of units of RBCs transfused + prebleed hemoglobin value [g/dL] - postbleed hemoglobin value [g/dL]).

- Minor bleeding was defined as clinically overt bleeding not meeting the criteria for major bleeding and considered more than expected in the clinical context.

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Reviewer's Comment: Phase III orthopedic trials used the Hamilton criteria.

Results
The table below lists the frequency of bleeding events by fondaparinux dose. Doses 6.0 mg and 8.0 mg were terminated for safety reasons (bleeding). There were no fatal bleeds.

Reviewer's Comment: In general with increasing fondaparinux dose there was increased bleeding.

Number of patients with a bleeding events for trial 095001[a] during the entire trial

Dose	0.75 mg (N=54)	1.5 mg[b] (N=91)	3.0 mg (N=88)	6.0 mg (N=49)	8.0 mg (N=34)
Dr. Miller's group					
Major bleeding	2 (3.7%)	3 (3.3%)	4 (4.5%)	6 (12.2%)	4 (11.8%)
Minor bleeding	2 (3.7%)	9 (9.9%)	5 (5.7%)	9 (18.4%)	4 (11.8%)
Dr. Prin's group (Hamilton)					
Major bleeding	1 (1.9%)	1 (1.1%)	3 (3.4%)	7 (14.3%)	3 (8.8%)
Minor bleeding	3 (5.6%)	2 (2.2%)	6 (6.8%)	5 (10.2%)	1 (2.9%)

[a]Patients were counted only once. Patients with major and minor bleeds were counted as having a major bleed.
[b]One patient (1.5 mg) not classified secondary to lack of adequate information on adjudication form.
Patients were counted only once. Patients with major and minor bleeds were counted as having a major bleed.
Reviewer's table

Major bleeding event
In general, major bleeds were seen with the higher doses of drug (i.e., 6.0 and 8.0 mg).
Three of the fifteen patients with a major bleed had a reoperation at the original surgical site.

Reviewer's Comment: The category of major bleed was not easily reviewed. For instance, not all patients listed by the sponsor as having a major bleed could be located. Information on five patients (subject numbers 01016, 01023, 01082, 01130, and 02012) could not be found in the Case Report Forms section, Crosstabulations section, or in the Subject Narratives. Additionally, patients had to have a clinically overt bleed to be categorized as a major or minor bleed. For instance, patient 03002 underwent bilateral TKR and had an SAE because of prolonged hospitalization secondary to bleeding requiring 5 units of blood. The patient did not meet the requirement for either a major or minor bleed because the patient had no overt signs of bleeding. Both CIAC (Dr. Miller's and Dr. Prin's) coded this event as no bleed. Despite the limitations of the data, the results suggest that increased risk of major bleeding is observed with increasing fondaparinux dose.

Transfusion Requirements
In general, transfusions were given post-operatively and the number of patients transfused was the highest in the 6.0 and 8.0-mg dose categories.

Adverse Events
The sponsor's table below shows the adverse event information during the treatment period.

Reviewer's Comment: SAEs and investigator determined drug-related SAEs rates increased with increasing fondaparinux dose.

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Table 24 Overview of Subjects with At Least One Adverse Event by Dose Group During the Treatment Period- All-Subjects-Treated Group

	Dose group (mg o.d.)				
	0.75 (N = 54)	1.5 (N = 91)	3.0 (N = 88)	6.0 (N = 49)	8.0 (N = 34)
	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with AEs[a]	48(88.9)	86(94.5)	80(90.9)	49(100.0)	34(100.0)
Subjects with drug-related AEs[b]	6(11.1)	9(9.9)	10(11.4)	12(24.5)	9(26.5)
Subjects with any AEs of severe intensity	8(14.8)	13(14.3)	11(12.5)	12(24.5)	6(17.6)
Subjects with SAEs	1(1.9)	1(1.1)	1(1.1)	5(10.2)	4(11.8)
Subjects with drug-related SAEs[b]	0(0)	0(0)	0(0)	4(8.2)	3(8.8)
Subjects permanently discontinued study drug for any AE	2(3.7)	1(1.1)	4(4.5)	4(8.2)	4(11.8)

[a] AEs and SAEs
[b] Relationship to study drug judged as possible, probable, or definite by the Investigator or missing
Note: Treatment period is defined as from the first dose to 48 hours after the last dose.
Data were taken from Appendix 13.7.1.17.1.

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Discontinuation Due to Adverse Events
The sponsor's table below shows the reasons for study drug discontinuation.

Reviewer's Comment: The major reason for study drug discontinuation was excessive bleeding.

Table 28 Number (%) of Subjects Who Discontinued Study Drug Due to Adverse Events by WHOART System-Organ Class and Preferred Term and Dose Group - All-Subjects-Treated Group

System-organ class	Preferred term	Dose group (mg o.d.)				
		0.75 (N = 54)	1.5 (N = 91)	3.0 (N = 88)	6.0 (N = 49)	8.0 (N = 34)
		n (%)	n (%)	n (%)	n (%)	n (%)
Cardiovascular disorders, general	Oedema	0(0.0)	0(0.0)	1(1.1)	0(0.0)	1(2.9)
Platelet, bleeding & clotting disorders	Haematemesis	0(0.0)	0(0.0)	1(1.1)	0(0.0)	0(0.0)
	Haematoma	0(0.0)	0(0.0)	0(0.0)	1(2.0)	1(2.9)
	Post-operative haemorrhage	0(0.0)	1(1.1)	1(1.1)	2(4.1)	0(0.0)
	Thrombocytopenia	2(3.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Red blood cell disorders	Anaemia	0(0.0)	0(0.0)	1(1.1)	1(2.0)	2(5.9)

Note: Each subject was counted only once in this table.
Data were taken from Appendix 13.7.1.17.5.

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Serious Adverse Events
Twelve patients had SAEs during the treatment period and eight patients had SAEs in the follow up period. All discontinuations due to SAE during the treatment period were for bleeding/anemia except for the following cases:

1) patient (30008) discontinued due to fever
2) patient (10130) discontinued due to pneumonia
3) patient (10024) discontinued due to cerebrovascular cause

Reviewer's Comment: Subject Narratives, Crosstabulations, and Case Report Forms could not be located for patient (10024). Subject Narratives and Case report Forms could not be located for patient (30008).

Two patients had investigator-determined SAEs in the follow up period. One patient had a DVT and the other (patient 04005) had a hematoma after a fall requiring reoperation.

Deaths
No deaths occurred during this trial.

Laboratory Abnormalities

Thrombocytopenia
Six patients had thrombocytopenia during the trial. All but one in the 8.0 mg dose group were considered drug-related by the investigator. Two subjects discontinued due to thrombocytopenia. One patient (18002) with a history of lupus, splenectomy, and bone marrow examination entered the study with a platelet count of 112,00/cc^3 and on post-operative day 1 was listed as having a platelet count of 52,000/cc^3. The patient was discontinued on day 2. Reportedly her platelet count recovered to 202,000/cc^3. The other patient (02006) entered the study with a platelet count of 118,000/cc^3 and on post-operative day 1 had a platelet count of 106,000/cc^3. The patient was removed on post-operative day 2 due to a low platelet count. No further follow up was provided. *Reviewer's Comment: This reviewer examined all platelet count trends observed during this study. Unfortunately the assessment is hampered by the paucity of complete platelet count data since not all patients received post-treatment platelet counts.*

Liver function testing
The sponsor's table below shows liver function abnormalities that occurred during the trial.

Reviewer's Comment: Overall, the table suggests that with increasing fondaparinux dose from 0.75 mg to 3.0 mg, there was an increased AST elevation rate. Elevations of alkaline phosphatase and gamma-glutamyl transferase were seen during the trial, particularly for the higher dose groups.

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Table 30 Number (%) of Subjects (Postbaseline) with No Increase in ALT and AST, with an Increase to One to Three Times the Upper Normal Limit, or with an Increase to More than Three Times the Upper Normal Limit by Dose Group - All-Subjects Treated Group

Parameter	Subjects with	Dose group (mg o.d.)									
		0.75 (N = 54)		1.5 (N = 91)		3.0 (N = 88)		6.0 (N = 49)		8.0 (N = 34)	
		n	%	n	%	n	%	n	%	n	%
ALT[a]	No increase	39	72.2	72	79.1	65	73.9	40	81.6	24	70.6
	Increase]1U-3U]	10	18.5	9	9.9	11	12.5	4	8.2	6	17.6
	Increase >3U	1	1.9	3	3.3	4	4.5	2	4.1	2	5.9
	No assessment	4	7.4	7	7.7	8	9.1	3	6.1	2	5.9
AST[b]	No increase	43	79.6	71	78.0	63	71.6	38	77.6	25	73.5
	Increase]1U-3U]	7	13.0	12	13.2	15	17.0	6	12.2	6	17.6
	Increase >3U	0	0	1	1.1	2	2.3	2	4.1	1	2.9
	No assessment	4	7.4	7	7.7	8	9.1	3	6.1	2	5.9

[a] Normal range = 0-48 IU/L
[b] Normal range = 0-42 IU/L (<65 years) or 0-55 IU/L (≥65 years).
U = upper normal limit
Data were taken from Appendices 13.7.1.19.48 and 13.7.1.19.49.

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Hemostasis Parameters
Information on these parameters was not collected during the trial.

Biochemistry Parameters
There were no trends or abnormalities noted for sodium, potassium, glucose, BUN, creatinine, phosphorus, and calcium.

Vital signs
No significant differences were noted between baseline and post-treatment in blood pressure and heart rate.

Post-treatment
There were 8 investigator-determined SAEs and 4 AEs during the follow up period. All SAEs were related to bleeding except for one patient who had a patella fracture and one patient who experienced back pain and was treated with a brace.

Trial- ACT 1840 (hip replacement)-multicenter, dose-ranging, open-label, randomized phase II trial with preoperative and postoperative dosing for thromboprophylaxis in hip replacement

One hundred and fifteen patients were enrolled and randomized to one of the following dose regimens for 8 days:

1) fondaparinux 3.0 mg SC twice daily preoperatively and 2 mg SC twice daily postoperatively for a total of 7 days
2) nadroparin 100 anti-Xa ICU/kg SC once daily for days 1-3 and 150 ICU/kg SC once daily for days 4-6

The preoperative doses were given 10-12 hours prior to surgery and the postoperative doses were started at least 6 hours after surgery in the fondaparinux treatment group and at least 24 hours after the last nadroparin dose in the nadroparin treatment group.

The sponsor's safety analysis included all patients who received at least one dose of the drug and underwent hip replacement. Patients were treated with either fondaparinux or [redacted] (nadroparin). The safety analysis included 64 fondaparinux patients and 45 nadroparin patients.

The sponsor's table below shows the number of patients with adverse events during the trial. Only those adverse event categories were listed where the adverse event rate was at least 5%.

Reviewer's Comment: Serious adverse events and haemic/lymphatic adverse events were more frequent in the fondaparinux group.

Table (5.5.1) 1 - Number (%) of Patients Adverse Events

Characteristic	SR 90107/ORG 3 1540 [3 mg BID] (N = 64)	[redacted] (N = 45)	p-Value
Any Adverse Event	37 (57.8%)	26 (57.8%)	>0.999
Any Serious Adverse Event	4 (6.3%)	0 (0.0%)*	
By Body System			
Digestive System	18 (28.1%)	12 (26.7%)	>0.999
Haemic & Lymphatic System	14 (21.9%)	3 (6.7%)	0.059
Body as a Whole	8 (12.5%)	8 (17.8%)	0.623
Cardiovascular System	10 (15.6%)	4 (8.9%)	0.457
Metabolic and Nutritional System	5(7.8%)	3 (6.7%)	>0.999
Skin & Appendages	5 (7.8%)	2 (4.4%)	0.697
Nervous System	4 (6.3%)	2 (4.4%)	>0.999
Respiratory System	1 (1.6%)	3 (6.7%)	0.304

* Two cases of thrombosis in the [redacted] group were classified as serious adverse events in error and were not, therefore, reported to Regulatory Authorities as serious adverse events.

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The sponsor's table below shows the adverse event rates which occurred at greater than 5%.

Reviewer's Comment: There was a statistically significant difference between the two treatment groups for anemia (higher in the fondaparinux group). No other difference was significant. In the fondaparinux treatment group, only one patient had a serious anemia; all others were non-serious. In the nadroparin treatment group, no anemia was serious.

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Table (5.5.1) 4 - Incidence of Adverse Events which Occurred with a Rate of 5% or More in One Treatment Group

COSTART Term	SR 90107A/ORG 31540 [3 mg BID] (N = 64)	[redacted] (N = 45)	p-Value
Anaemia	11 (17.2%)	1 (2.2%)	0.014
Liver Function Tests Abnormal	7 (10.9%)	3 (6.7%)	0.519
Diarrhoea	4 (6.3%)	2 (4.4%)	>0.999
Pain	5 (7.8%)	1 (2.2%)	0.397
Vesiculobullous Rash	5 (7.8%)	1 (2.2%)	0.397
Gamma GT Increased	4 (6.3%)	1 (2.2%)	0.402

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The serious adverse events for fondaparinux included:

1) Hemoglobin drop from 13.3 (Day 0) to 5.8 (Day 3)
2) Accidental overdose of study drug without sequelae
3) Re-operation for subcutaneous hematoma (Day 0 hemoglobin - 11.7g/dl; Day 7 hemoglobin - 9.20g/dl)

The sponsor's table below shows the bleeding events and thrombocytopenia rates for both groups.

Reviewer's Comment: The fondaparinux treatment group had a higher percentage of events, for all categories listed below.

Table (5.5.1) 7 - Incidence of Bleeding* and Thrombopenia

	SR 90107A/ORG 31540 [3 mg BID] (N = 64)	[redacted] (N = 45)
Number of Patients with Major Bleeding	3 (4.7%)	0 (0.0%)
Number of Patients with Minor Bleeding	12 (18.8%)	4 (8.9%)
Number of Patients with Any Bleeding	15 (23.4%)	4 (8.9%)
Number of Patients with Thrombopenia	7 (10.9%)	2 (4.4%)

* according to independent rewiever's assessment

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The sponsor's tables below show the platelet values for the 7 fondaparinux and the 2 dalteparin patients who developed thrombocytopenia, defined as platelet counts less than 100,000/cc during the trial.

Reviewer's Comment: The only patient removed from the study due to thrombocytopenia was 6/610 (fondaparinux treatment group).

Table (5.5.1) 9 - SR90107A/ORG31540 Patients Defined as having Severe Thrombopenia [Platelet count (G/1)]

Patient Number	Day -1	Day 0	Day 1	Day 3	Day 5	Day 7
3/302	[redacted]					
4/406						
5/506						
6/610						
8/806						
9/906						
11/1106						

NA: not applicable
T: thrombopenia
* judged by the investigator as clinically significant

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Table (5.5.1) 10 - [redacted] Patients Defined as having Severe Thrombopenia [Platelet count (G/1)]

Patient Number	Day -1	Day 0	Day 1	Day 3	Day 5	Day 7
2/228	[redacted]					
7/708						

NA: not applicable
T: thrombopenia

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Blood Loss
Mean and median intra-operative and post-operative blood losses were not significantly different between treatment groups, although there was a higher overall blood loss for the fondaparinux treatment group.

Statistically significant hemoglobin and hematocrit differences between the two treatment groups were observed in favor of nadroparin.

There was no statistically significant difference between treatment groups for EKG changes, vital signs, white blood cells, white blood cell differentials, ATIII levels, and serum chemistries.

Trial- ACT 2545 (hip replacement) - Multicenter, open-label, randomized, dose-ranging phase II trial for thromboprophylaxis in hip replacement surgery

Two hundred and forty-three patients were enrolled and randomized to one of the following dose regimens for 7-8 days:

1) fondaparinux 2 mg SC once daily (post-operatively only)
2) fondaparinux 4 mg SC once daily (post-operatively only)
3) enoxaparin 40 mg SC once daily (pre- and post-operatively)

The pre-operative enoxaparin dose was given 10-12 hours prior to surgery. The first post-operative fondaparinux and enoxaparin doses were given 6 hours after surgery.

The sponsor's safety analysis included all patients who received at least one dose of the drug. The sponsor's table below shows the most frequent adverse events seen during the trial.

Reviewer's Comment: Hemorrhage of the operative wound is higher for both fondaparinux treatment groups compared with enoxaparin. For unclear reasons, most AEs listed below have a higher rate for the 2 mg fondaparinux patients compared with the 4 mg patients.

Table (8.5.2.1) 2 - Most frequent adverse events by preferred term and treatment

WHO PREFERRED TERM	SR_4 mg (N=77) n(AE) %	SR_2 mg (N=77) n(AE) %	Enox (N=75) n(AE) %
HEMORRHAGE OF OPERATIVE WOUND	14(15)18.18	13(13)16.88	11(12)14.67
ANAEMIA	5(5) 6.49	13(14)16.88	10(10)13.33
NAUSEA	6(6) 7.79	10(10)12.99	8(10)10.67
VOMITING	5(5) 6.49	10(10)12.99	6(6) 8.00
HYPOTENSION	5(5) 6.49	7(7) 9.09	10(10)13.33
INJECTION SITE REACTION	5(5) 6.49	6(6) 7.79	2(3) 2.67
PAIN	4(4) 5.19	2(2) 2.60	2(2) 2.67

n = number of patients, (AE) = number of adverse events, % = percentage of patients
Each patient may have had more than one adverse event
SR90107 ACT2545 Date of produce : 25OCT96 at 12:33
AE.sas AE92

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The sponsor's table below shows the bleeding pattern seen in the trial.

Reviewer's Comment: Hemorrhage of operative wound was the most common bleeding event for all treatment groups. Most of these events were minor. Major bleeds were reported only for hemorrhage of operative wound and GI hemorrhage. Total major bleeds accounted for less than 2% for each treatment group.

APPEARS THIS WAY
ON ORIGINAL

Table (8.5.2.1) 3 - Incidence of bleeding events (number of patients and events)

PREFERRED TERM	SR_4mg (N=77) n(AE)%	SR_2mg (N=77) n(AE)%	Enox (N=75) n(AE)%
HEMORRHAGE OF OPERATIVE WOUND	14(15) 18.18	13(13) 16.88	11(12) 14.67
INJECTION SITE REACTION	5(5) 6.49	6(6) 7.79	2(3) 2.67
HAEMATOMA	2(2) 2.60	3(3) 3.90	
GI HAEMORRHAGE			1(1) 1.33
All for organ class	**19(22) 24.68**	**19(22) 24.68**	**13(16) 17.33**

n = number of patients, (AE) = number of adverse events, % = percentage of patients
Each patient may have had more than one adverse event
SR90107 ACT2545 Date of produce : 02JUL97 at 19:50
AEhaem.sas AEhaem91

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Serious Adverse Events

No deaths occurred during the trial.

The sponsor's table below shows the serious adverse event rates.

Reviewer's Comment: Most serious adverse events were related to bleeding.

Table (8.5.2.4) 1 - Incidence of serious adverse events

ORGAN CLASS	SR_4mg (N=77) n(AE)%	SR_2mg (N=77) n(AE)%	Enox (N=75) n(AE)%
LIVER AND BILIARY SYSTEM DISORDERS		1(1) 1.30	
RED BLOOD CELL DISORDERS	1(1) 1.30		1(1) 1.33
PLATELET, BLEEDING & CLOTTING DISORDERS	4(4) 5.19	1(1) 1.30	4(4) 5.33
BODY AS A WHOLE - GENERAL DISORDERS	1(1) 1.30	1(1) 1.30	
RESISTANCE MECHANISM DISORDERS	1(1) 1.30		
NUMBER OF SUBJECTS WITH SAE	5(7) 6.49	3(3) 3.90	4(5) 5.33

n = number of patients, (AE) = number of adverse events, % = percentage of patients
Each patient may have had more than one adverse event
SR90107 ACT2545 Date of produce : 28AUG96 at 15:44
SAEs.sas SAEs91

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Serious Adverse Events for the fondaparinux treatment group other than bleeding
One patient had elevated liver enzymes up to 6 times the normal GGT level. This same patient had elevated liver enzymes with a prior hip revision. The investigator deemed the liver enzyme elevation more likely related to cement used during the revision.

One patient experienced a subluxation of his prosthesis, which required re-operation and prolonged hospitalization.

One patient experienced a wound infection requiring 7 days of antibiotics.

Premature discontinuations due to an adverse event
One patient in each treatment group discontinued due to hemorrhage of the operative site or a decrease in hemoglobin.

Laboratory parameters
There were no statistically significant differences between treatment groups for hemoglobin, hematocrit, platelet count, biochemistry parameters, and coagulation parameters except for the following two differences.

There were statistically significant differences noted in this trial for total white blood cell counts at the end of the trial (Day 9). White blood cell count differences were higher for the fondaparinux treatment groups. These differences were not clinically significant.
There was a statistically significant difference in potassium levels on day 8 and 9 compared with baseline between treatment groups. More fondaparinux patients experienced a decrease in potassium levels. These differences were not clinically significant.

Although statistically significant differences were not seen between treatment groups for liver enzyme elevation the sponsor's table below shows the frequency of enzyme elevations 2x-4x normal.

Reviewer's Comment: The GGT enzyme appeared most sensitive to an increased fondaparinux dose.

Table (8.5.3.2) 1 - Number of patients with hepatic enzymes values two or four times the normal upper limit

Parameters (normal range)	Groups	Number of patients	]2N;4N]	≥4N
ALAT	SR_4 mg	76	7 (9 %)	4 (5 %)
(5-25 IU/l)	SR_2 mg	71	10 (14 %)	3 (4 %)
	Enox	74	8 (11 %)	1 (1 %)
ASAT	SR_4 mg	76	6 (8 %)	2 (3 %)
(8-25 IU/l)	SR_2 mg	71	11 (15 %)	2 (3 %)
	Enox	74	4 (5 %)	2 (3 %)
GGT	SR_4 mg	76	18 (24 %)	9 (12 %)
(5-29 IU/l)	SR_2 mg	71	12 (17 %)	7 (10 %)
	Enox	74	11 (15 %)	6 (8 %)
Alkaline	SR_4 mg	76	1 (1 %)	1 (1 %)
phosphatase	SR_2 mg	71	4 (6 %)	1 (1 %)
(32-72 IU/l)	Enox	74	1 (1 %)	0 (0 %)
2N: twice the normal range 4N: four times the normal range Ref: Appendices 5.2.40 and 5.2.42				

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There were no statistically significant differences between treatment groups for vital signs, volume of blood loss, transfusion volumes, and EKG changes during the trial.

Trial - DRI 2643 - ——— (hip replacement) Multicenter, randomized, double-blind,dose-ranging phase II thromboprophylaxis trial in hip replacement patients

Nine hundred and fifty patients were enrolled and randomized to one of the following post-operative dose regimens for 5 days:

1) fondaparinux 0.75 mg SC once daily
2) fondaparinux 1.5 mg SC once daily
3) fondaparinux 3.0 mg SC once daily
4) fondaparinux 6.0 mg SC once daily
5) fondaparinux 8.0 mg SC once daily
6) enoxaparin 30 mg SC twice daily

The fondaparinux regimens were started 6-8 hours after surgery and the enoxaparin regimen was started 12-24 hours after surgery.

The sponsor's safety analysis included all patients who received at least one dose of the drug. The start of treatment was defined from the first injection. The sponsor defined two safety evaluation periods. The treatment period was defined as Day 1 to 2 days after the last injection. The follow up period was defined as starting three days after the last injection to Day 42. The sponsor's table below shows the incidence of adjudicated major and minor bleeding during the treatment period.

Reviewer's Comment: All bleeding events occurred during the treatment period except for one patient who had a minor bleeding event three days after the last injection. The sponsor's table below suggests that increasing fondaparinux dose was associated with increasing major and minor hemorrhage rates. Pharmacokinetic data suggested that patients with a major bleeding event tended to have higher AUC and C_{maxSS} and C_{minSS}. As a result of bleeding events, the 6.0-mg and 8.0-mg doses were terminated during the conduct of the trial.

Table (8.1.1) 1 - Number (%) of patients [95% CI] per dose group experiencing a major or minor bleeding event during the whole study - All treated patients

		Org31540/SR90107A					
Patients with		0.75 mg (N=184)	1.5 mg (N=188)	3.0 mg (N=177)	6.0 mg (N=72)	8.0 mg (N=52)	Enoxaparin (N=260)
Major bleeding	n (%)	0 (0.0)	1 (0.5)	8 (4.5)	12 (16.7)	9 (17.3)	9 (3.5)
	95% CI	[0 ;1.98]	[0.01 ;2.93]	[1.97 ;8.71]	[8.92 ;27.3]	[8.23 ;30.33]	[1.59 ;6.47]
Minor bleeding only	n (%)	1 (0.5)	5(2.7)	6 (3.4)	2 (2.8)	2 (3.8)	8 (3.1)
	95% CI	[0.01 ;2.99]	[0.87 ;6.1]	[1.25 ;7.23]	[0.34 ;9.68]	[0.47 ;13.21]	[1.34 ;5.97]
Major or minor bleeding	n (%)	1(0.5)	6 (3.2)	14 (7.9)	14 (19.4)	11 (21.2)	17 (6.5)
	95% CI	[0.01 ;2.99]	[1.18 ;6.82]	[4.39 ;12.91]	[11.06;30.47]	[11.06;34.7]	[3.85 ;10.26]

a: Adjudication performed by the CIAC on a patient basis. When several events could be adjudicated as bleeding event, the most clinically relevant event was considered.
Ref: Appendices 13.2.3.1.1.3, 13.2.3.1.2.2 and 13.2.3.1.3.1
PGM: [redacted] OUT: output/BLREP01 (26OCT99 - 10:18)

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Serious bleeding adverse events were defined as:

- Death because of bleeding complication
- Intracranial bleeding or bleeding within a critical organ (e.g., eye, adrenal gland, etc.)
- Reoperation due to bleeding (hematoma) at the operative site

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The sponsor defined the following bleeding categories:

- Major bleeding event if the reported event was clinically overt and if it satisfied one of the following criteria:
  - bleeding at critical site, i.e., intracranial, retroperitoneal, intraocular, spinal or pericardial
  - bleeding index ≥ 2. The bleeding index was calculated within 48 hours of bleed as follows: units of RBC transfused + prebleed hemoglobin value (g/dL) - postbleed hemoglobin value(g/dL)
  - required medical intervention or surgical intervention at the operative site
- Minor bleeding event if the reported event was clinically overt but did not meet the criteria for major bleeding event
- No bleeding event if the reported event was not clinically overt or occurred before the start of study drug

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Adjudicated Major Bleeding
The sponsor's table below shows the major bleeding results.

Reviewer's Comment: Bleeding Index (BI) > 2 was the predominant contributor to the category of major bleeding.

Table (8.1.2) 1 - Number (%) of patients adjudicated to have experiencing a major bleeding event by adjudication criteria and treatment group - All treated patients

Patients with	Org31540/SR90107A					Enoxaparin
	0.75 mg (N=184)	1.5 mg (N=188)	3.0 mg (N=177)	6.0 mg (N=72)	8.0 mg (N=52)	(N=260)
Fatal bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non fatal bleeding into a critical organ:						
- Spinal	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Non fatal overt bleeding not into a critical organ:						
- BI ≥ 2 and intervention[a] at operative site	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.8%)	4 (7.7%)	1 (0.4%)
- BI ≥ 2 only	0 (0.0%)	1 (0.5%)	5 (2.8%)	7 (9.7%)	5 (9.6%)	8 (3.1%)
- Intervention[a] at operative site only	0 (0.0%)	0 (0.0%)	1 (0.6%)	2 (2.8%)	0 (0.0%)	0 (0.0%)
- Missing information	0 (0.0%)	0 (0.0%)	2 (1.1%)[b]	0 (0.0%)	0 (0.0%)	0 (0.0%)

a: Medical or surgical intervention
b: For Patients 120072 and 170007, the CIAC failed to cross the appropriate box on the adjudication form but specified in the comment field that 2 units of PRBC were transfused
Ref: Appendix 13.2.3.1.2.9
PGM: [redacted] OUT: output/MBLCAT01 (26OCT99 - 10:42)

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Reviewer's Comment: Permanent treatment discontinuation due to major bleeding occurred in all treatment groups.

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Major Bleeding Rate Leading to Permanent Treatment Discontinuation for DRI 2643

Study Drug	*Number of Patients (Rate)*
Enoxaparin	*5/9 (55%)*
Fondaparinux 0.75 mg	*0/0*
Fondaparinux 1.5 mg	*0/1 (0%)*
Fondaparinux 3.0 mg	*2/8 (25%)*
Fondaparinux 6.0 mg	*9/12 (75%)*
Fondaparinux 8.0 mg	*7/9 (77.8%)*

Reviewer's Table

Blood loss
In general, mean intraoperative blood loss increased with increasing fondaparinux dose. Fondaparinux doses 0.75-mg and 1.5-mg had a lower mean intraoperative blood loss (567 mL and 558 mL) than enoxaparin (594mL). The greatest blood loss occurred in the first four days. The sponsor's table below shows the number of patients and mean blood loss for the trial.

Reviewer's Comment: Few patients had blood loss in the follow up phase (Day 11 to Day 42).

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Table (8.2.1) 1 - Summary of blood loss (mL) throughout the study by dose group - All treated patients

Blood loss (mL)		Org31540/SR90107A					Enoxaparin
		0.75 mg	1.5 mg	3.0 mg	6.0 mg	8.0 mg	
Intraoperatively on Day 1	N	172	182	168	70	50	245
	Median	500	500	500	500	500	500
	Mean	567.0	558.0	615.6	628.1	609.5	594.4
	SD	345.7	397.7	450.4	474.6	405.9	455.5
	Min	[					]
	Max						
Postoperatively[1] on Day 1	N	112	112	110	41	23	162
	Median	350	275	275	250	292	300
	Mean	371.0	306.2	320.0	322.6	291.4	339.3
	SD	231.9	212.6	228.0	252.0	137.5	206.5
	Min	[					]
	Max						
Day 2 - Day 10 period	N	111	109	105	43	22	168
	Median	250	165	190	190	116	200
	Mean	282.3	215.2	238.6	238.4	226.6	248.0
	SD	238.2	179.0	208.9	243.7	257.7	220.0
	Min	[					]
	Max						
Day 11 - Day 42 period	N	2	2	2	1	0	3
	Median	725	695	150	760	.	215
	Mean	725.0	695.0	150.0	760.0	.	203.3
	SD	106.1	431.3	70.7	.	.	103.0
	Min	[					]
	Max						

1: between the end of surgery and 24 hours
Ref: Appendices 13.2.3.2.4.1 and 13.2.3.2.8.1
PGM: _____ OUT: output/REPBLS01 (08OCT99 - 10:40)

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Blood Transfusion Rates

The sponsor's table below shows blood transfusion rates during the trial.

Reviewer's Comment: The majority of transfusions occurred during the treatment period. Increasing transfusion rate was observed with increasing fondaparinux dose.

Table (8.2.2) 1 - Number (%) of patients transfused with whole blood or packed red blood cells by dose group - All treated patients

Period for transfusion	Org31540/SR90107A					Enoxaparin (N=260)
	0.75 mg (N=184)	1.5 mg (N=188)	3.0 mg (N=177)	6.0 mg (N=72)	8.0 mg (N=52)	
Day 1 - Day 10	85 (46.2)	101 (53.7)	100 (56.5)	46 (63.9)	35 (67.3)	138 (53.1)
Day 1 - Day 42	89 (48.4)	102 (54.3)	100 (56.5)	46 (63.9)	35 (67.3)	139 (53.5)

Ref: Appendix 13.2.3.2.12.1
PGM: _____ OUT: output/TRFSUP01 (08OCT99 - 11:46)

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Reviewer's Comment: The two major reasons for transfusion for the fondaparinux and enoxaparin treatment groups were an abnormal laboratory value (42.9%) followed by autologous reinfusion (15.9%).

Adverse events

The sponsor's text below defines the term serious adverse events used during the trial.

Any AE was considered serious if it met at least one of the following conditions:

- Resulted in death or was life threatening
- Necessitated or prolonged hospitalization
- Resulted in disability or was incapacitating
- Congenital anomaly

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The sponsor's table below shows the numbers of patients who experienced AEs during the treatment and follow up periods of the trial.

Reviewer's Comment: Drug related AEs and SAEs rates increased with increasing fondaparinux dose.

Table (9.1.1) 1 - Overview of patients with at least one adverse event (non-treatment or treatment emergent) during the [Day 1 - Day 42] period - All treated patients

	Org31540/SR90107A					
	0.75 mg (N=184)	1.5 mg (N=188)	3.0 mg (N=177)	6.0 mg (N=72)	8.0 mg (N=52)	Enoxaparin (N=260)
Patients with any AEs	183 (99.5 %)	186 (98.9 %)	176 (99.4 %)	71 (98.6 %)	52 (100.0 %)	257 (98.8 %)
Patients with any drug-related AEs[a]	36 (19.6 %)	37 (19.7 %)	41 (23.2 %)	25 (34.7 %)	21 (40.4 %)	57 (21.9 %)
Patients with any AEs of severe intensity	39 (21.2 %)	27 (14.4 %)	39 (22.0 %)	19 (26.4 %)	12 (23.1 %)	56 (21.5 %)
Patients with SAEs[b]	23 (12.5 %)	12 (6.4 %)	19 (10.7 %)	19 (26.4 %)	10 (19.2 %)	26 (10.0 %)
Patients with drug-related SAEs[a]	0 (0.0 %)	0 (0.0 %)	3 (1.7 %)	7 (9.7 %)	6 (11.5 %)	4 (1.5 %)
Deaths[c]	3 (1.6 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (0.4 %)

a: relationship to study drug judged as likely or unknown by the investigator
b: including SAE leading to death
c: two additional patients (one in the 0.75 mg group and one in the enoxaparin group) died after the end of the study due to SAE which began during the study
PGM: [redacted] OUT: output/SAFETY14 (19OCT99 - 16:10)

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The two sponsor's tables below show the treatment emergent adverse event rates during the treatment and follow up periods.

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Table (9.1.1) 3 - Overview of patients with at least one treatment emergent adverse event during the treatment period - All treated patients

	Org31540/SR90107A					Enoxaparin
	0.75 mg (N=184)	1.5 mg (N=188)	3.0 mg (N=177)	6.0 mg (N=72)	8.0 mg (N=52)	(N=260)
Patients with any AEs	182 (98.9 %)	181 (96.3 %)	174 (98.3 %)	71 (98.6 %)	51 (98.1 %)	247 (95.0 %)
Patients with drug-related AEs[a]	33 (17.9 %)	36 (19.1 %)	39 (22.0 %)	23 (31.9 %)	20 (38.5 %)	52 (20.0 %)
Patients with any AE of severe intensity	21 (11.4 %)	11 (5.9 %)	19 (10.7 %)	8 (11.1 %)	6 (11.5 %)	20 (7.7 %)
Patients with SAEs[b]	12 (6.5 %)	6 (3.2 %)	12 (6.8 %)	12 (16.7 %)	7 (13.5 %)	11 (4.2 %)
Patients with drug-related SAEs[a]	0 (0.0 %)	0 (0.0 %)	3 (1.7 %)	5 (6.9 %)	5 (9.6 %)	2 (0.8 %)
Patients permanently discontinued for any AE	7 (3.8 %)	8 (4.3 %)	7 (4.0 %)	10 (13.9 %)	9 (17.3 %)	18 (6.9 %)
Patients permanently discontinued for SAE	6 (3.3 %)	1 (0.5 %)	2 (1.1 %)	8 (11.1 %)	5 (9.6 %)	6 (2.3 %)

a: relationship to study drug judged as likely or unknown by the investigator
b: including SAE leading to death
Ref: Appendices 13.2.4.1.4.1, 13.2.4.1.5.1, 13.2.4.2.2.1, 13.2.4.2.3.1 and 13.2.4.1.8.2
PGM: [redacted] OUT: output/SAFETY12 (19OCT99 - 16:07)

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Table (9.1.1) 4 - Overview of patients with at least one treatment emergent adverse event during the follow-up period - All treated patients

	Org31540/SR90107A					Enoxaparin
	0.75 mg (N=184)	1.5 mg (N=188)	3.0 mg (N=177)	6.0 mg (N=72)	8.0 mg (N=52)	(N=260)
Patients with any AEs	61 (33.2 %)	72 (38.3 %)	54 (30.5 %)	28 (38.9 %)	18 (34.6 %)	81 (31.2 %)
Patients with any AEs of severe intensity	10 (5.4 %)	4 (2.1 %)	7 (4.0 %)	4 (5.6 %)	3 (5.8 %)	10 (3.8 %)
Patients with SAEs[a]	13 (7.1 %)	7 (3.7 %)	8 (4.5 %)	8 (11.1 %)	3 (5.8 %)	16 (6.2 %)
Deaths	3 (1.6 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (0.4 %)
Patients with any drug-related AEs[b]	3 (1.6 %)	1 (0.5 %)	1 (0.6 %)	2 (2.8 %)	2 (3.8 %)	2 (0.8 %)
Patients with drug-related SAEs[b]	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	2 (2.8 %)	1 (1.9 %)	2 (0.8 %)

a: including SAE leading to death
b: relationship to study drug judged as likely or unknown by the investigator
PGM: [redacted] OUT: output/SAFETY13 (08JUL99 - 15:24)

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The adverse events listed below were seen with greater frequency in the fondaparinux treatment groups compared with enoxaparin:

1) Fever
2) Constipation
3) Nausea
4) Vomiting
5) Dyspepsia
6) Urinary Retention
7) Anemia
8) Skin disorder
9) Post-operative pain
10) Anxiety

11) Dyspnea
12) Micturition disorder
13) Male reproductive disorder
14) Hearing and Vestibular Disorder

Deaths
The table below lists the six deaths that occurred. Four patients died during the follow up period and two patients died after the end of the study.

Reviewer's Comment: None of the fondaparinux patients had autopsies. The one enoxaparin patient, listed as having a fatal PE, had an autopsy, which demonstrated multiple small emboli present in both lungs. Patient 60017 had negative bilateral doppler ultrasounds on Day 17 and was later diagnosed with bilateral pneumonia and sepsis. Despite treatment with antibiotics, he died on Day 39. Patient 110101 experienced a myocardial infarction on Day 3, which was followed by additional unstable angina and CABG surgery. Following surgery, the patient deteriorated further with infection and heart failure and eventually died on Day 65. Patient 290002 experienced a myocardial infarction on Day 3, which was followed by progressive renal failure, pulmonary edema, and hypertension. Aggressive measures to treat the patient's hypertension and pulmonary edema were stopped and comfort measures only were undertaken. Patient 400002 developed dyspnea and ventricular ectopy on Day 5. Subsequently the patient had a MI and developed small bowel infarction.

Table (9.2.1) 1 - List of patients who died - Characteristics of the serious adverse events

Treatment group	Patient	Day of onset*	Serious adverse event (Verbatim)	Day of death*	Day of last injection*	Relationship to study drug	Adjudication result
Enoxaparin	490020	43	Adenocarcinoma-peritoneal fluid	79	9	No	Not adjudicated because after Day 42
	500009	18	Death attributed to pulmonary embolism	18	10	Unlikely	Fatal PE
0.75 mg	60017	17	Difficulty breathing	39	5	No	Death not associated with VTE or bleeding
	110101	3	Myocardial infarction	65	6	No	Not adjudicated because after Day 42
	290002	4	Post operative myocardial infarction	7	4	No	Death not associated with VTE or bleeding
	400002	5	Small bowel infarction secondary to myocardial infarction	28	5	No	Death not associated with VTE or bleeding

* Day 1 = day of surgery
Ref: Appendix 13.2.4.2.6.1
PGM: [redacted] OUT: output/DTHRPT01 (20OCT99 - 13:53)

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Serious Adverse Events

Serious adverse events for fondaparinux requiring treatment during this trial included:
a) post-operative hemorrhage
b) hemorrhage/hematoma
c) coagulation disorder
d) surgical site reaction
e) myocardial infarction/ischemia/unstable angina
f) cardiac failure
g) hypotension
h) dysphagia
i) ileus
j) intestinal necrosis
k) intestinal obstruction