l) increased wound drainage
m) fever
n) anemia
o) breathing abnormalities/hypoxia
p) pneumonia
q) paresis
r) gout
s) increased nitrogen protein
t) micturition problems
u) renal failure, acute
v) transient ischemic attack
w) arrhythmia
x) delirium

Laboratory abnormalities
Hemoglobin and hematocrit values declined post-operatively. Nine patients (5 fondaparinux patients, 4 enoxaparin) had a minimum platelet count below 100,000/cc[3]. The sponsor's table shows the patients who developed thrombocytopenia.

Reviewer's Comment: Most platelet counts improved on therapy.

Table (9.2.3) 1 - Patients experiencing thrombocytopenia - Characteristics of the events - All treated patients

Dose group	Patient	Description of the AE/SAE				Platelet count (Giga/L)'		
		Day of onset	Duration of the event (day)	Day of last injection	Serious	Last value before treatment	Minimum value	Value at date of resolution
Enoxaparin	240005	3	3	3	Yes			
	460010	3	4	11	No			
	500003	3	6	9	No			
	580009	3	4	10	No			
0.75 mg	50006	2	3	8	No			
	480002	2	5	7	No			
	550005	1	5	5	No			
1.5mg	720010	4	1	2	No			
3.0 mg	510013	3	5	7	No			
6.0 mg	70003	4	26	6	No			
	120039	1	4	6	No			
	210001	2	3	4	No			
	260003	1	7	3	No			
	310006	4	7	9	No			

*: Converted local value
1: Normal range: 130 - 400 Giga/L
2: one day after resolution
3: count at screening (Day -10)
4: 23 days before resolution (Day 29). No value avalaible after Day 6
PGM: [redacted] OUT: output/THROMB03 (08JUL99 - 15:35)

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Hepatic enzyme elevations were seen in the fondaparinux and enoxaparin treatment groups; however, the rate was the highest for the enoxaparin group.

Prolongation of APTT and PT did not occur during this trial.

B. Individual Study Safety reviews for Phase III studies for Thromboprophylaxis in Orthopedic Surgery

Trial-EFC2698 ———— (Phase III trial)- Multicenter, Randomized, double-blind, comparison study of fondaparinux 2.5 mg SC once daily compared with enoxaparin 40 mg SC once daily for thromboprophylaxis (hip fracture)

One thousand seven hundred and eleven patients were enrolled and randomized to either:
1) fondaprinux 2.5 mg SC once daily (post-operatively or pre-operatively) if surgery greater than 24-48 hours after hospital admission)
2) enoxaparin 40 mg SC once daily post-operatively

The preoperative doses were given 12± 2 hours prior to surgery. The postoperative fondaparinux dose was given 6±2 hours after surgery. The postoperative enoxaparin dose was given 12-24 hours after surgery.

The sponsor defined two safety evaluation periods. The first period was defined as Day 1 to Day 11. The second period was defined as Day 1 to Day 49.

Important eligibility criteria included that patients had to undergo surgery for fracture of the neck of the femur not more than 48 hours after admission.
Important exclusion criteria included:

1) Thrombocytopenia or history of previous thrombocytopenia (platelet less than 100,000/cc^3)
2) Acute bacterial endocarditis
3) Hemorrhagic stroke or recent brain, spinal or ophthalmological surgery (within less than 3 months)
4) Planned indwelling intrathecal or epidural catheters for more than 6 hours after the end of surgery
5) Creatinine > 2.0 mg/dL
6) Patients with multiple trauma affecting more than 1 organ system
7) More than 24 hours time elapse between trauma (causing hip fracture) and admission to hospital

Safety Variables
The major bleeding endpoint was recorded between the first injection of the drug and Day 11. Other safety variables included: minor bleeding, transfusion requirements, AEs, SAEs, deaths and changes in laboratory parameters. Adverse events were recorded from baseline assessment up to Day 42 ± 7. Unless considered clinically significant, post-operative events reported frequently after surgery (e.g., post-operative pain, serous drainage) were not reported as AEs.

The sponsor defined bleeding as follows:

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)
- Reoperation due to bleeding/hematoma at the operative site
- Clinically overt bleeding leading to a fall in hemoglobin ≥2 g/dL (1.6 mmol/L) and/or a transfusion ≥2 units of packed red blood cells (PRBCs) or whole blood AND for which the combined calculated index was ≥2[1].

The definition of minor bleeding was clinically overt bleeding not meeting the criteria for major bleeding and considered more than expected in the clinical context.

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Deaths
An autopsy report was required to adjudicate death. Deaths were recorded as fatal PE, hemorrhagic death, and death not associated with VTE or bleeding.

Antiplatelet antibodies
An assessment of antiplatelet antibodies was performed through sampling at screening and on Day 9. Additional samples were collected if patients experienced thrombotic events (DVT, PE, MI, and stroke), unusual bleeding, thrombocytopenia, or in case of suspicion of these events, repeat sampling after 3 days.

Thrombocytopenia
A significant reduction in platelet count was defined as a platelet count < 100,000/cc^3 or a decrease > 40% from any previous count from Day 5 onwards.

Safety Results
Eighteen patients were excluded from the safety analyses because they experienced a bleeding event prior to first injection (7 fondaparinux, 11 enoxaparin).

Bleeding
The sponsor's table below shows the number of patients having an adjudicated bleed up to Day 11.

Reviewer's Comment: There was no statistically significant difference between the treatment groups for major, minor, or any bleed up to Day 11. Minor bleeding was the major contributor to the differences seen between treatment groups. Three fondaparinux patients were discontinued from treatment due to minor bleeding. Similar results were seen for up to Day 49.

Table (8.1.1) 1 - Number (%) of Patients with Adjudicated Bleeding Events From First Injection to Day 11 - All Treated Patients

Patients With		Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)
Major bleeding	n (%) 95% CI	18 (2.2 %) [1.3; 3.4]	19 (2.3 %) [1.4; 3.5]
Minor bleeding only	n (%) 95% CI	34 (4.1 %) [2.8; 5.7]	18 (2.1 %) [1.3; 3.4]
Any bleeding	n (%) 95% CI	52 (6.3 %) [4.7; 8.1]	37 (4.4 %) [3.1; 6.0]

PGM: [redacted] OUT: output/ITBLD101 (07JUN00 - 17:31)
Ref: Appendix 14.2.3.1.1

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Major Bleeding Categories
The sponsor's tables below show the major bleeding events up to Day 11 and Day 49.

Reviewer's Comment: Event rates were similar for the major bleeding subcategories between the two treatment groups. Major bleeding at the surgical site led to reoperation in 3 fondaparinux patients compared with 2 enoxaparin patients. The fondaparinux patient who experienced an intracranial bleed was receiving warfarin at the time. The intracranial bleed occurred on the fourteenth day following the last fondaparinux dose.

Table (8.1.2) 1 - Number (%) of Patients With Adjudicated Major Bleeding Events From First Injection to Day 11 by Adjudication Criterion - All Treated Patients

Patients With	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)
Any major bleeding	18 (2.2%)	19 (2.3%)
Fatal bleeding	0 (0.0%)	1 (0.1%)
Non-fatal critical bleeding	0 (0.0%)	0 (0.0%)
Other non-fatal major bleeding	18 (2.2%)	18 (2.1%)
At surgical site	14 (1.7%)	13 (1.5%)
At non-surgical site only	4 (0.5%)	5 (0.6%)

PGM: [redacted] OUT: output/ITBLD104 (29JUN00 - 14:11)
Ref: Appendix 14.2.3.1.3

Table (8.1.2) 2 - Number (%) of Patients With Adjudicated Major Bleeding Events From First Injection to Day 49 by Adjudication Criterion - All Treated Patients

Patients With	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)
Any major bleeding	21 (2.5%)	28 (3.3%)
Fatal bleeding	0 (0.0%)	2 (0.2%)
Non-fatal critical bleeding	1 (0.1%)	0 (0.0%)
Intracranial	1 (0.1%)	0 (0.0%)
Other non-fatal major bleeding	20 (2.4%)	26 (3.1%)
At surgical site	14 (1.7%)	17 (2.0%)
At non-surgical site only	6 (0.7%)	9 (1.1%)

PGM: [redacted] OUT: output/ITBLD105 (29JUN00 - 14:11)
Ref: Appendix 14.2.3.1.3

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The sponsor analyzed the main safety endpoint using a number of covariates (e.g., country, age, sex, obesity, type of anesthesia, type of fracture, type of surgery, use of cement, duration of surgery, baseline creatinine, previous antithrombin medication, drug-drug and drug-disease interactions). No statistically significant interaction was demonstrated for any covariate and major bleeding.

Transfusions
Similar numbers of patients were transfused in both treatment groups.

Table (8.2.2) 1 - Number (%) of Transfused Patients up to Day 49 - All Treated Patients

Transfused Patients	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)
Pre-operatively*	12 (1.4%)	17 (2.0%)
Intra-operatively	95 (11.4%)	117 (13.9%)
Post-operatively up to Day 11	388 (46.7%)	371 (44.1%)
Up to Day 11*	421 (50.7%)	422 (50.1%)
Up to Day 49*	430 (51.7%)	432 (51.3%)

PGM: [redacted] OUT: output/CTITB01 (12SEP00 - 16:05)
* Excluding transfusions performed before the day of randomization
Ref: Appendix 14.2.3.2.5

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Adverse Events

The sponsor's table below shows the number of patients with one adverse event from first injection to Day 11.

Reviewer's Comment: There is no statistically significant difference between the treatment groups for any adverse event. Most differences were minimal between the treatment groups. Similar results were seen for AEs reported up to Day 49.

Table (9.1.1) 1 - Overview of Patients With at Least One Adverse Event From First Injection to Day 11 - All Treated Patients

From First Injection to Day 11	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)
Patients with any AE[a]	415(49.9 %)	420(49.9 %)
Patients with any drug-related AE[a,b]	74 (8.9 %)	64 (7.6 %)
Patients with any AE[a] of severe intensity[c]	48 (5.8 %)	57 (6.8 %)
Patients with SAEs[d]	58 (7.0 %)	52 (6.2 %)
Patients with drug-related SAEs[b]	10 (1.2 %)	6 (0.7 %)
Deaths	11 (1.3 %)	16 (1.9 %)
Patients permanently discontinued study drug for any AE[a,e,f]	26 (3.1 %)	31 (3.7 %)
Patients permanently discontinued study drug for events not considered in AE analysis[g,f]	3 (0.4 %)	4[h] (0.5 %)

PGM: [redacted] OUT: output/ITae1 (22AUG00 - 11:45)

[a] Including SAEs
[b] Relationship to study drug judged as likely or difficult to assess by the Investigator, or missing
[c] Including missing intensity
[d] Including SAEs leading to death
[e] AEs started after the first study drug administration
[f] According to the 'end of treatment' form. Three (3) additional patients (1 in the Org31540/SR90107A group and 2 in the enoxaparin group) permanently discontinued study drug for an AE whereas the primary reason reported on the 'end of treatment' form was not an AE/SAE (see Appendix 14.2.4.2.15)
[g] Events started before the first study drug administration
[h] Note that 3 of these 4 patients also experienced AEs started after the first study drug administration and leading to study drug discontinuation

Ref: Appendix 14.2.4.1.1

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The sponsor's table below shows the number of patients with adverse events occurring from first injection to Day 11 with an incidence ≥ 2%.

Reviewer's Comment: Statistically significant differences for adverse events in favor of enoxaparin included: platelet, bleeding, and clotting disorders ($p<0.05$) and skin and appendage disorders ($p<0.007$).

Table (9.1.2) 1 - Number (%) of Patients With Adverse Events Occurring From First Injection to Day 11 for all WHO Organ-Classes and Preferred Term With Incidence >2.0% in Any Treatment Group - All Treated Patients

WHO Organ-Class Preferred Term	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)
Any event	415 (49.9 %)	420 (49.9 %)
Gastro-intestinal system disorders		
Total	132 (15.9 %)	142 (16.9 %)
Constipation	46 (5.5 %)	66 (7.8 %)
Nausea	45 (5.4 %)	46 (5.5 %)
Vomiting	36 (4.3 %)	34 (4.0 %)
Diarrhoea	22 (2.6 %)	21 (2.5 %)
Body as a whole - General disorders		
Total	101 (12.2 %)	91 (10.8 %)
Fever	64 (7.7 %)	54 (6.4 %)
Wound drainage increased	15 (1.8 %)	17 (2.0 %)
Urinary system disorders		
Total	77 (9.3 %)	79 (9.4 %)
Urinary tract infection	57 (6.9 %)	58 (6.9 %)
Red blood cell disorders		
Total	74 (8.9 %)	74 (8.8 %)
Anaemia	74 (8.9 %)	73 (8.7 %)
Platelet, bleeding and clotting disorders		
Total	85 (10.2 %)	62 (7.4 %)
Post-operative haemorrhage	24 (2.9 %)	13 (1.5 %)
Haematoma	16 (1.9 %)	19 (2.3 %)
Central and peripheral nervous system disorders		
Total	65 (7.8 %)	69 (8.2 %)
Confusion	32 (3.9 %)	35 (4.2 %)
Respiratory system disorders		
Total	56 (6.7 %)	55 (6.5 %)
Pneumonia	14 (1.7 %)	28 (3.3 %)
Skin and appendage disorders		
Total	56 (6.7 %)	31 (3.7 %)
Cardiovascular disorders, general		
Total	34 (4.1 %)	42 (5.0 %)
Cardiac failure	10 (1.2 %)	17 (2.0 %)
Liver and biliary system disorders		
Total	26 (3.1 %)	42 (5.0 %)
Hepatic enzymes increased	9 (1.1 %)	19 (2.3 %)
Metabolic and nutritional disorders		
Total	38 (4.6 %)	30 (3.6 %)
Hypokalaemia	25 (3.0 %)	19 (2.3 %)

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Table(9.1.2) 1 - *continued* - Number (%) of Patients With Adverse Events Occurring From First Injection to Day 11 for all WHO Organ-Classes and Preferred Term With Incidence >2.0% in Any Treatment Group - All Treated Patients

WHO Organ-Class Preferred Term	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)
Psychiatric disorders		
Total	24 (2.9 %)	42 (5.0 %)
Insomnia	6 (0.7 %)	19 (2.3 %)
Resistance mechanism disorders		
Total	20 (2.4 %)	14 (1.7 %)
Secondary terms		
Total	15 (1.8 %)	19 (2.3 %)
Heart rate and rhythm disorders		
Total	16 (1.9 %)	10 (1.2 %)
Myo/endo/pericardial and valve disorders		
Total	9 (1.1 %)	12 (1.4 %)
Musculo-skeletal system disorders		
Total	7 (0.8 %)	12 (1.4 %)
Vascular (extracardiac) disorders		
Total	8 (1.0 %)	9 (1.1 %)
Autonomic nervous system disorders		
Total	5 (0.6 %)	4 (0.5 %)
Vision disorders		
Total	5 (0.6 %)	4 (0.5 %)
Reproductive disorders, male		
Total	1 (0.1 %)	5 (0.6 %)
Reproductive disorders, female		
Total	3 (0.4 %)	2 (0.2 %)
Neoplasm		
Total	2 (0.2 %)	2 (0.2 %)
Application site disorders		
Total	1 (0.1 %)	2 (0.2 %)
Collagen disorders		
Total	0 (0.0 %)	2 (0.2 %)
Endocrine disorders		
Total	1 (0.1 %)	0 (0.0 %)
Hearing and vestibular disorders		
Total	1 (0.1 %)	0 (0.0 %)
White cell and RES disorders		
Total	1 (0.1 %)	0 (0.0 %)

PGM: ——— OUT: output/AE_AT11 (06JUL00 - 15:54)
RES = reticuloendothelial system
NOTE: Sorted by WHO organ-class in decreasing order of incidence
Ref: Appendix 14.2.4.1.3

Deaths
The sponsor's table below shows the number of deaths up to Day 49.

Reviewer's Comment: There was no statistically significant difference between treatment groups for total deaths. Adjudicated deaths were similar between treatment groups in the following categories: fatal PE, hemorrhagic death, and death not due to VTE or bleeding.

Table (9.2.1) 1 - Number (%) of Deaths From First Injection - All Treated Patients

Patients With	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)
SAE between first injection and Day 11		
Leading to death between first injection and Day 11	11 (1.3 %)	16 (1.9 %)
Leading to death between Day 12 and Day 49	6 (0.7 %)	4 (0.5 %)
SAE from Day 12		
Leading to death between Day 12 and Day 49	21 (2.5 %)	22 (2.6 %)
Leading to death after the end of the study	2 (0.2 %)	2 (0.2 %)
Total deaths between first injection and Day 49	38 (4.6 %)	42 (5.0 %)
Total deaths reported	40 (4.8 %)	44 (5.2 %)

PGM: [redacted] OUT: output/DEATH1 (24AUG00 - 11:24)
NOTE: Deaths before the first study drug administration or deaths due to AEs which occurred after Day 49 were not counted in this table
Ref: Appendix 14.2.4.2.1

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This reviewer's assessment of the cause of death was consistent with that of the Central Adjudication Committee.

Serious Adverse Events
The sponsor's table below shows the number of patients experiencing serious adverse events.

Reviewer's Comment: There were no statistically significant differences between treatment groups.

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Table (9.2.2) 1 - Number (%) of Patients With Serious Adverse Events Occurring From First Injection to Day 11 by WHO Organ-Class and Preferred Term - All Treated Patients

WHO Organ-Class Preferred Term	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)
Any event	58 (7.0 %)	52 (6.2 %)
Cardiovascular disorders, general		
Total	7 (0.8 %)	13 (1.5 %)
Cardiac failure	4 (0.5 %)	11 (1.3 %)
Cardiac failure left	1 (0.1 %)	2 (0.2 %)
Fluid overload	1 (0.1 %)	0 (0.0 %)
Hypotension	1 (0.1 %)	0 (0.0 %)
Platelet, bleeding and clotting disorders		
Total	14 (1.7 %)	4 (0.5 %)
Post-operative haemorrhage	7 (0.8 %)	0 (0.0 %)
Haematoma	3 (0.4 %)	3 (0.4 %)
Haemorrhage nos	2 (0.2 %)	0 (0.0 %)
Dissem. intravasc. coagulation	1 (0.1 %)	0 (0.0 %)
Gastro-intestinal haemorrhage	0 (0.0 %)	1 (0.1 %)
Melaena	1 (0.1 %)	0 (0.0 %)
Respiratory system disorders		
Total	11 (1.3 %)	6 (0.7 %)
Pneumonia	6 (0.7 %)	2 (0.2 %)
Respiratory insufficiency	3 (0.4 %)	3 (0.4 %)
Dyspnoea	1 (0.1 %)	1 (0.1 %)
Bronchospasm	1 (0.1 %)	0 (0.0 %)
Respiratory depression	1 (0.1 %)	0 (0.0 %)
Secondary terms		
Total	4 (0.5 %)	8 (1.0 %)
Surgical site reaction	3 (0.4 %)	5 (0.6 %)
Inflicted injury	1 (0.1 %)	3 (0.4 %)
Vascular (extracardiac) disorders		
Total	5 (0.6 %)	7 (0.8 %)
Cerebrovascular disorder	4 (0.5 %)	7 (0.8 %)
Transient ischaemic attack	1 (0.1 %)	0 (0.0 %)
Myo/endo/pericardial and valve disorders		
Total	5 (0.6 %)	6 (0.7 %)
Myocardial infarction	5 (0.6 %)	5 (0.6 %)
Angina pectoris	0 (0.0 %)	1 (0.1 %)

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Table (9.2.2) 1 - *continued* - Number (%) of Patients With Serious Adverse Events Occurring From First Injection to Day 11 by WHO Organ-Class and Preferred Term - All Treated Patients

WHO Organ-Class **Preferred Term**	**Org31540/SR90107A** **2.5 mg o.d.** **(N = 831)**	**Enoxaparin** **40 mg o.d.** **(N = 842)**
Gastro-intestinal system disorders		
Total	4 (0.5 %)	3 (0.4 %)
Ileus paralytic	1 (0.1 %)	2 (0.2 %)
Intestinal perforation	2 (0.2 %)	0 (0.0 %)
Gastritis	0 (0.0 %)	1 (0.1 %)
Ileus	0 (0.0 %)	1 (0.1 %)
Intestinal obstruction	1 (0.1 %)	0 (0.0 %)
Oesophagitis	0 (0.0 %)	1 (0.1 %)
Body as a whole - General disorders		
Total	5 (0.6 %)	0 (0.0 %)
Death	3 (0.4 %)	0 (0.0 %)
Allergic reaction	1 (0.1 %)	0 (0.0 %)
Oedema peripheral	1 (0.1 %)	0 (0.0 %)
Central and peripheral nervous system disorders		
Total	2 (0.2 %)	2 (0.2 %)
Coma	1 (0.1 %)	1 (0.1 %)
Confusion	1 (0.1 %)	0 (0.0 %)
Convulsions	0 (0.0 %)	1 (0.1 %)
Liver and biliary system disorders		
Total	2 (0.2 %)	1 (0.1 %)
Cholelithiasis	1 (0.1 %)	0 (0.0 %)
Hepatic failure	1 (0.1 %)	0 (0.0 %)
Hepatic function abnormal	0 (0.0 %)	1 (0.1 %)
Neoplasm		
Total	1 (0.1 %)	2 (0.2 %)
Basal cell carcinoma	0 (0.0 %)	1 (0.1 %)
Neoplasm malignant	0 (0.0 %)	1 (0.1 %)
Pulmonary carcinoma	1 (0.1 %)	0 (0.0 %)
Red blood cell disorders		
Total	1 (0.1 %)	2 (0.2 %)
Anaemia	1 (0.1 %)	2 (0.2 %)
Urinary system disorders		
Total	1 (0.1 %)	2 (0.2 %)
Renal failure acute	0 (0.0 %)	2 (0.2 %)
Renal tubular disorder	1 (0.1 %)	0 (0.0 %)
Heart rate and rhythm disorders		
Total	2 (0.2 %)	0 (0.0 %)
Fibrillation atrial	2 (0.2 %)	0 (0.0 %)

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Table (9.2.2) 1 - *continued* - Number (%) of Patients With Serious Adverse Events Occurring From First Injection to Day 11 by WHO Organ-Class and Preferred Term - All Treated Patients

WHO Organ-Class Preferred Term	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)
Metabolic and nutritional disorders		
Total	1 (0.1 %)	1 (0.1 %)
Dehydration	0 (0.0 %)	1 (0.1 %)
Diabetes mellitus aggravated	1 (0.1 %)	0 (0.0 %)
Psychiatric disorders		
Total	1 (0.1 %)	1 (0.1 %)
Delirium	1 (0.1 %)	0 (0.0 %)
Psychosis	0 (0.0 %)	1 (0.1 %)
Resistance mechanism disorders		
Total	2 (0.2 %)	0 (0.0 %)
Sepsis	2 (0.2 %)	0 (0.0 %)
Application site disorders		
Total	0 (0.0 %)	1 (0.1 %)
Cellulitis	0 (0.0 %)	1 (0.1 %)
Autonomic nervous system disorders		
Total	1 (0.1 %)	0 (0.0 %)
Syncope	1 (0.1 %)	0 (0.0 %)
Reproductive disorders, female		
Total	0 (0.0 %)	1 (0.1 %)
Breast neoplasm malignant female	0 (0.0 %)	1 (0.1 %)

PGM: [redacted] OUT: output/AE_ST1 (06JUL00 - 15:55)
Dissem. intravasc. = Disseminated intravascular
Ref: Appendix 14.2.4.2.5

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Thrombocytopenia

Investigators coded ten patients (5 fondaparinux and 5 enoxaparin) as having thrombocytopenia from the first injection to Day 11. Six patients (3 fondaparinux and 3 enoxaparin) had a baseline value lower than 150,000/cc^3. In all cases except one in the fondaparinux treatment group, the onset of thrombocytopenia occurred within the first 3 days of therapy. ELISA tests for antiplatelet antibodies were negative except for one fondaparinux patient (#29010002). One patient in each treatment group developed a DVT (#29010002 and 2080010). No patient who developed thrombocytopenia died during the trial or follow up period. The sponsor's table is presented below.

Reviewer's Comment: For most thrombocytopenic patients, the treatment was continued with resolution of thrombocytopenia.

The constellation of thrombocytopenia, VTE, and positive ELISA results in a fondaparinux patient is suspicious for HIT/HITTS; however, the thrombocytopenia resolved on continued study medication.

Table (9.2.3.1) 1 - Patients Experiencing a Decrease in Platelet count According to the Investigator's Judgment - Characteristics of the Events

		Description of the AE/SAE					Platelet Count (10^9/L)		
Treatment Group	Patient	Day of Onset[a]	Duration of the Event (Days)	Day of Last Injection[a]	Serious	Action Taken on Study Drug	Last Value Before Treatment	Minimum Value	Value at Date of Resolution[c]
Org31540/SR90107A	2080007	2/2	6	8/8	No	No change			
	12070108	6/6	4	7/7	No	Drug permanently discontinued			
	12080109	3/2	3	7/6	No	No change			
	29010002	2/1	3	8/7	No	No change			
	29030002	1/1	5	2/2	No	Drug permanently discontinued			
Enoxaparin	2080010	2/2	3	6/6	No	No change			
	10020007	3/3	2	2/2	No	Drug permanently discontinued			
	12080116	2/1	5	4/3	No	Drug permanently discontinued			
	12140103	2/2	4	3/3	No	Drug permanently discontinued			
	26030053	1/2	3	6/7	No	No change			

PGM: ——— OUT: output/out=ITDEATH (04SEP00 - 11:41)

NOTE: Normal range: 150-400 x 10^9/L

[a] Expressed as days since surgery/since start of study drug (active or placebo)

[b] Platelet count was ——— on the first day of study drug administration (time of blood sampling was not recorded)

[c] Resolution date of the AE reported by the Investigator

Ref: Appendix 14.2.4.2.17

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Permanent Discontinuations
There were no statistically significant differences between treatment groups for patients who discontinued. The most frequent reason for discontinuation was platelet, bleeding, and clotting disorder (12 fondaparinux patients (1.4%), 6 enoxaparin patients (0.7%)).

Laboratory Parameters
There were no statistically significant differences between treatment groups for mean change from baseline for hemoglobin or hematocrit, platelet counts, biochemistry, and liver function tests. The following sponsor's tables show the results for selected parameters.

Reviewer's Comment: A greater number of fondaparinux patients had hematocrit values less than 24%, and a greater than a 6% decrease in hematocrit, or both, compared with enoxaparin.

Table (9.3.1.2) 1 - Number (%) of Patients With an Hematocrit Value <24% and/or a Decrease ≥6.0% Compared to First Post-operative Values - All Treated Patients

Hematocrit	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)
Values <24.0%[a]	101/814 (12.4%)	89/820 (10.9%)
Decrease ≥6.0%[b]	242/812 (29.8%)	213/825 (25.8%)
Both	55/808 (6.8%)	43/820 (5.2%)

PGM: [redacted] OUT: EFC2698/output/SAFRNG02 (30OCT00 - 11:23)
[a] After first post-operative injection
[b] From first post-operative value
Ref: Appendix 14.2.4.3.9

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The sponsor's table below shows the number of patients with platelet counts less than 100,000/cc^3.

Reviewer's Comment: There was no statistically significant difference between treatment groups for platelet counts less than 100,000/cc^3.

Table (9.3.1.3) 1 - Number (%) of Patients With a Platelet Count Included in the [50 x 10^9/L-100 x 10^9/L[Range or <50 x 10^9/L After the First Study Drug Injection - All Treated Patients

Platelet Counts	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)
[50 x 10^9/L- 100 x 10^9/L[[b]	37/822 (4.5%)	44/831 (5.3%)
<50 x 10^9/L[c]	3/822 (0.4%)	0/831 (0.0%)

PGM: [redacted] OUT: EFC2698/output/SAFRNG03 (30OCT00 - 11:23)
[a] After the first study drug injection
[b] With baseline value ≥100 x 10^9/L or missing
[c] With baseline value ≥50 x 10^9/L or missing
Ref: Appendix 14.2.4.3.9

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The sponsor's table below shows the number of patients who had a positive ELISA test for heparin specific IgG antibodies after starting study treatment.

Reviewer's Comment: A greater percentage of fondaparinux patients became ELISA or SRA positive after having a negative or missing result at baseline. Review of patients who became ELISA positive revealed that:

1) *2 fondaparinux patients had received prior heparin exposure,*
2) *1 fondaparinux patient received heparin during the study, and*
3) *3 enoxaparin patients received heparin during the study.*

Thus the majority of patients who became ELISA positive did not have documented exposure to heparin prior to or during the trial.

Table (9.3.1.4) 1 - Number (%) of Patients With ELISA and SRA Tests (Among Positive ELISA Tests) Which Became Positive After Beginning of Active Study Drug - All Treated Patients with Antiplatelet Antibodies Evaluation

Test	Org31540/SR90107A 2.5 mg o.d.	Enoxaparin 40 mg o.d.
Positive ELISA test[a]	38/749 (5.1%)	29/750 (3.9%)
Positive SRA test[b]	13/38 (34.2%)	6/29 (20.7%)

PGM: [redacted] OUT: output/BIOAB01 (30OCT00 - 10:48)

[a] Patients with switch to positive ELISA test after beginning of active study drug from negative (or missing) ELISA test at baseline

[b] Out of patients with switch to positive ELISA test, patients with switch to positive SRA test from negative (or missing) SRA test at baseline

Ref: Appendix 14.2.4.3.15

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The sponsor's table below shows the number of ELISA positive patients who developed either a VTE or a platelet count below 100,000/cc[3].

Reviewer's Comment: These results suggest fondaparinux patients may develop HIT /HITTS. Only one patient in each treatment group had documented prior or during trial exposure to heparin. Two ELISA positive fondaparinux patients died during the follow up period. Patient #4020007 died of sepsis and multiple complications on Day 30 and patient #33040032 died of bronchopneumonia on Day 25.

Table (9.3.1.4) 2 - Number (%) of Patients With Antiplatelet Antibodies (Positive ELISA Test) Associated With a VTE or a Platelet Count Below 100 x 10^9/L - All Treated Patients With Antiplatelet Antibodies Evaluation

Patients With Antiplatelet Antibodies Associated With	Org31540/SR90107A 2.5 mg o.d. (N = 38)	Enoxaparin 40 mg o.d. (N = 29)
VTE	7 (18.4 %)	4 (13.8 %)
Platelet count <100 x 10^9/L	0 (0.0 %)	1 (3.4 %)

PGM: [redacted] OUT: output/BIOAB02 (30OCT00 - 10:48)

Ref : Appendix 14.2.4.3.16

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Pharmacokinetic evaluation of main efficacy and safety endpoints

The sponsor evaluated the relationship between plasma drug levels and development of either a VTE or adjudicated major bleeding. The sponsor concluded that no relationship existed between plasma drug levels and development of an endpoint.

Reviewer's Comment: The evaluation included only a subset of the total fondaparinux patients (17%).

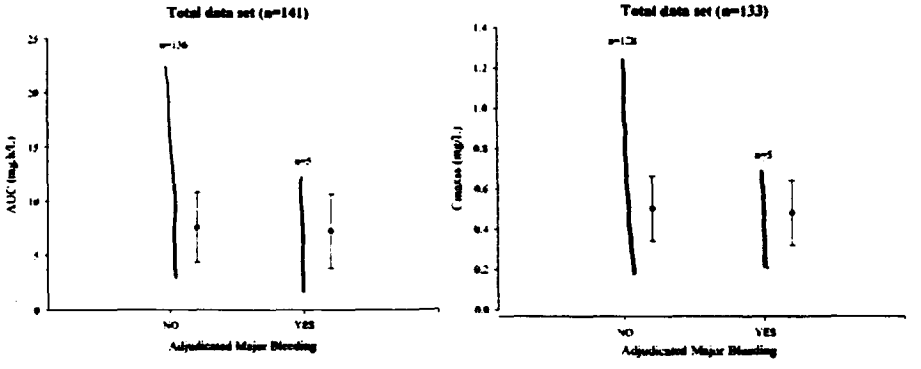

Figure (10.3) 1 - Individual and Mean (SD) Plasma Exposure (AUC) (Left) and C_{max} at Steady State (C_{maxSS}) (Right) as a Function of Occurrence of Adjudicated Major Bleeding - Total Data Set

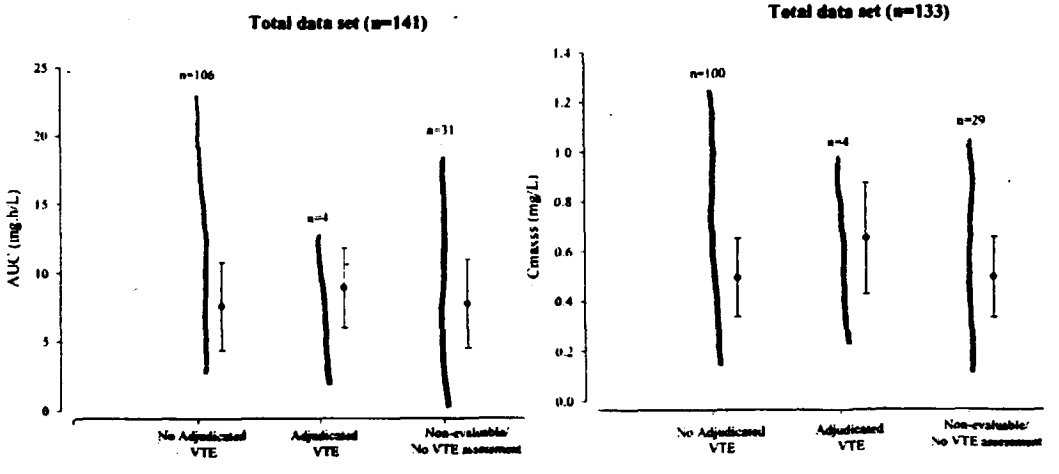

Figure (10.3) 2 - Individual and Mean (SD) Plasma Exposure (AUC) (Left) and C_{max} at Steady State (C_{maxSS}) (Right) as a Function of Occurrence of Adjudicated VTE - Total Data Set

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Trial- 095002 - [redacted] (knee replacement) –Multicenter, randomized, double-blind comparison of subcutaneous Org31540/SR90107A with enoxaparin in the prevention of deep vein thrombosis and symptomatic pulmonary embolism after elective major knee surgery or a revision

The sponsor's exclusion criteria and safety analyses were the same as the ——— study.

Dosing
The patients were randomized to either:
1) fondaparinux 2.5 mg SC once daily for 7-9 days
2) enoxaparin 30 mg SC twice daily for 7- 9 days

The protocol stipulated that the fondaparinux dose would be given 6± 2 hours after surgery and the enoxaparin dose would be given 12-24 hours after surgery.

Bleeding
Fifteen patients were excluded from the safety analyses because they did not receive any injection of study drug.

The sponsor's tables below show the number of patients who had an adjudicated bleed up to Day 11 and Day 49.

Reviewer's Comment: There was a statistically significant difference between the treatment groups for major bleeding in favor of enoxaparin up to Day 11 (p=0.006) and up to Day 49 (p=0.02). There was no statistically significant difference between the treatment groups for minor or any bleed up to Day 11 and up to Day 49. Only one enoxaparin patient experienced a major bleed. The major bleeding rate for enoxaparin is lower than that observed in other orthopedic surgery trials.

Table (8.1.1) 1 - Number (%) of patients with adjudicated bleeding events from the first injection to Day 11 - All treated patients

Patients with		Org31540/SR90107A 2.5 mg o.d. (N = 517)	Enoxaparin 30 mg b.i.d. (N = 517)
Major bleeding	n (%) 95% CI	11 (2.1%) [1.1; 3.8]	1 (0.2%) [0.0; 1.1]
Minor bleeding only	n (%) 95% CI	14 (2.7%) [1.5; 4.5]	19 (3.7%) [2.2; 5.7]
Any bleeding	n (%) 95% CI	25 (4.8%) [3.2; 7.1]	20 (3.9%) [2.4; 5.9]

Ref: Appendix 14.2.3.1.1

Table (8.1.1) 2 - Number (%) of patients with adjudicated bleeding events from the first injection to Day 49 - All treated patients

Patients with		Org31540/SR90107A 2.5 mg o.d. (N = 517)	Enoxaparin 30 mg b.i.d. (N = 517)
Major bleeding	n (%) 95% CI	11 (2.1%) [1.1; 3.8]	2 (0.4%) [0.0; 1.4]
Minor bleeding only	n (%) 95% CI	16 (3.1%) [1.8; 5.0]	19 (3.7%) [2.2; 5.7]
Any bleeding	n (%) 95% CI	27 (5.2%) [3.5; 7.5]	21 (4.1%) [2.5; 6.1]

Ref: Appendix 14.2.3.1.1

Major Bleeding Categories
The sponsor's tables below show the major bleeding events up to Day 11 and up to Day 49.

Reviewer's Comment: Major bleeding at the surgical site led to reoperation in 2 fondaparinux patients compared with 1 enoxaparin patient.

Table (8.1.2) 1 - Number (%) of patients with adjudicated major bleeding events from the first injection to Day 11 by adjudication criterion - All treated patients

Patients with	Org31540/SR90107A 2.5 mg o.d. (N = 517) n (%)	Enoxaparin 30 mg b.i.d. (N = 517) n (%)
Any major bleeding	11 (2.1)	1 (0.2)
Fatal bleeding	0 (0.0)	0 (0.0)
Non-fatal critical bleeding	0 (0.0)	0 (0.0)
Other non-fatal major bleeding	11 (2.1)	1 (0.2)
At surgical site	9 (1.7)	1 (0.2)
At non-surgical site only	2 (0.4)	0 (0.0)

Ref: Appendix 14.2.3.1.3

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The sponsor analyzed the main safety endpoint using a number of covariates (e.g., country, age, sex, obesity, type of anesthesia, type of fracture, type of surgery, use of cement, duration of surgery, baseline creatinine, previous antithrombin medication, and drug-drug interactions). No statistically significant interaction was demonstrated for any covariate and major bleeding.

Transfusions
Similar numbers of patients were transfused in both treatment groups.

Table (8.2.2) 1 - Number (%) of patients transfused up to Day 49 - All treated patients

	Org31540/SR90107A 2.5 mg o.d. (N = 517) n (%)			Enoxaparin 30 mg b.i.d. (N = 517) n (%)		
Transfused patients	Autologous	Homologous	Total	Autologous	Homologous	Total
Intra-operatively	21 (4.1)	3 (0.6)	24 (4.6)	25 (4.8)	3 (0.6)	28 (5.4)
Post-operatively up to Day 11	150 (29.0)	101 (19.5)	222 (42.9)	138 (26.7)	76 (14.7)	197 (38.1)
Post-operatively up to Day 49	150 (29.0)	103 (19.9)	224 (43.3)	138 (26.7)	77 (14.9)	197 (38.1)

Ref: Appendix 14.2.3.2.6

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Adverse Events

The sponsor's table below shows the number of patients with one adverse event from first injection to Day 11.

Reviewer's Comment: There was no statistically significant difference between the treatment groups for any adverse event. A two percent difference between the treatment groups in favor of enoxaparin occurred in the Patients with SAEs category. Similar results were seen up to Day 49.

Table (9.1.1) 1 - Overview of patients with at least 1 adverse event from the first injection to Day 11 - All treated patients

From first injection to Day 11	Org31540/SR90107A 2.5 mg o.d. (N = 517) n (%)	Enoxaparin 30 mg b.i.d. (N = 517) n (%)
Patients with any AE[a]	424 (82.0)	419 (81.0)
Patients with any drug-related AE[a,b]	59 (11.4)	52 (10.1)
Patients with any AE[a] of severe intensity[c]	17 (3.3)	17 (3.3)
Patients with SAE[d]	38 (7.4)	28 (5.4)
Patients with drug-related SAE[b]	6 (1.2)	3 (0.6)
Death	1 (0.2)	2 (0.4)
Patients permanently discontinued study drug for any AE[e,h]	20 (3.9)	12 (2.3)
Patients permanently discontinued study for events not considered in the AE analysis[f,h]	0 (0.0)	2 (0.4)[g]

[a] Including SAEs
[b] Relationship to study drug judged as likely or as difficult to assess by the Investigator, or missing
[c] Including missing intensity
[d] Including SAEs leading to death
[e] AEs that started after the first study drug administration
[f] Events started before the first study drug administration;
[g] Including 1 patient (02220105) who discontinued solely due to an AE that was present before first study drug injection and 1 patient (02210186) who discontinued due to an AE described as present before the first study drug injection and after the first study drug injection
[h] According to the primary reason on the End of Treatment Form. No additional patients discontinued permanently from study drug for an AE reported on the AE/SAE form (see Appendix 14.2.4.2.15).
Ref: Appendix 14.2.4.1.1

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The sponsor's table below shows the number of patients with adverse events occurring from first injection to Day 11 with an incidence ≥ 2%.

Reviewer's Comment: Statistically significant differences for adverse events in favor of enoxaparin included: platelet, bleeding, and clotting disorders ($p<0.05$) and skin and appendage disorders ($p<0.007$).

Table (9.1.2) 1 - Number (%) of patients with adverse events from the first injection to Day by WHO organ class and preferred term with incidence >2.0 % in any treatment group - A treated patients

WHO organ class **Preferred term**	**Org31540/SR90107A** **2.5 mg o.d.** **(N = 517)** **n (%)**	**Enoxaparin** **30 mg b.i.d.** **(N = 517)** **n (%)**
Any event	424 (82.0)	419 (81.0)
Gastro-intestinal system disorders		
Total	185 (35.8)	182 (35.2)
Nausea	101 (19.5)	98 (19.0)
Constipation	67 (13.0)	59 (11.4)
Vomiting	41 (7.9)	40 (7.7)
Dyspepsia	32 (6.2)	28 (5.4)
Abdominal pain	8 (1.5)	11 (2.1)
Body as a whole - general disorders		
Total	165 (31.9)	189 (36.6)
Fever	134 (25.9)	157 (30.4)
Leg pain	14 (2.7)	9 (1.7)
Pain	11 (2.1)	9 (1.7)
Centr & periph nervous system disorders		
Total	135 (26.1)	120 (23.2)
Urinary retention	36 (7.0)	29 (5.6)
Confusion	33 (6.4)	29 (5.6)
Dizziness	26 (5.0)	21 (4.1)
Hypertonia	24 (4.6)	19 (3.7)
Headache	16 (3.1)	24 (4.6)
Red blood cell disorders		
Total	136 (26.3)	110 (21.3)
Anaemia	135 (26.1)	109 (21.1)
Skin and appendages disorders		
Total	118 (22.8)	102 (19.7)
Rash erythematous	41 (7.9)	36 (7.0)
Pruritus	35 (6.8)	29 (5.6)
Bullous eruption	28 (5.4)	18 (3.5)
Rash	19 (3.7)	17 (3.3)
Sweating increased	12 (2.3)	5 (1.0)
Cardiovascular disorders, general		
Total	104 (20.1)	100 (19.3)
Oedema	70 (13.5)	63 (12.2)
Hypertension	15 (2.9)	13 (2.5)
Hypotension	12 (2.3)	13 (2.5)

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Table (9.1.2) 1 - *continued* - Number (%) of patients with adverse events from the first injection to Day 11 by WHO organ class and preferred term with incidence >2.0 % in any treatment group - All treated patients

WHO organ class **Preferred term**	**Org31540/SR90107A** **2.5 mg o.d.** **(N = 517)** **n (%)**	**Enoxaparin** **30 mg b.i.d.** **(N = 517)** **n (%)**
Platelet, bleeding & clotting disorders		
Total	89 (17.2)	83 (16.1)
Purpura	46 (8.9)	49 (9.5)
Post-operative haemorrhage	15 (2.9)	13 (2.5)
Haematoma	11 (2.1)	7 (1.4)
Metabolic and nutritional disorders		
Total	55 (10.6)	68 (13.2)
Hypokalaemia	33 (6.4)	50 (9.7)
Hyponatraemia	11 (2.1)	9 (1.7)
Respiratory system disorders		
Total	51 (9.9)	70 (13.5)
Dyspnoea	11 (2.1)	16 (3.1)
Hypoxia	7 (1.4)	13 (2.5)
Bronchospasm	7 (1.4)	12 (2.3)
Psychiatric disorders		
Total	64 (12.4)	47 (9.1)
Insomnia	26 (5.0)	19 (3.7)
Anxiety	13 (2.5)	7 (1.4)
Urinary system disorders		
Total	56 (10.8)	55 (10.6)
Urinary tract infection	19 (3.7)	19 (3.7)
Micturition disorder	14 (2.7)	17 (3.3)
Secondary terms		
Total	20 (3.9)	23 (4.4)
Heart rate and rhythm disorders		
Total	23 (4.4)	19 (3.7)
Tachycardia	16 (3.1)	9 (1.7)

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Table (9.1.2) 1 - *continued* - Number (%) of patients with adverse events from the first injection to Day 11 by WHO organ class and preferred term with incidence >2.0 % in any treatment group - All treated patients

WHO organ class Preferred term	Org31540/SR90107A 2.5 mg o.d. (N = 517) n (%)	Enoxaparin 30 mg b.i.d. (N = 517) n (%)
Musculo-skeletal system disorders		
Total	18 (3.5)	17 (3.3)
Resistance mechanism disorders		
Total	21 (4.1)	7 (1.4)
Autonomic nervous system disorders		
Total	12 (2.3)	12 (2.3)
Application site disorders		
Total	14 (2.7)	5 (1.0)
Cellulitis	11 (2.1)	4 (0.8)
Liver and biliary system disorders		
Total	6 (1.2)	10 (1.9)
Vision disorders		
Total	5 (1.0)	5 (1.0)
Myo-, endo-, pericardial & valve disorders		
Total	2 (0.4)	4 (0.8)
Vascular (extracardiac) disorders		
Total	2 (0.4)	3 (0.6)
Endocrine disorders		
Total	0 (0.0)	1 (0.2)
Neoplasm		
Total	1 (0.2)	0 (0.0)
Reproductive disorders, male		
Total	0 (0.0)	1 (0.2)
White cell and RES disorders		
Total	1 (0.2)	0 (0.0)

Ref: Appendix 14.2.4.1.3

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Deaths

The sponsor's table below shows the number of deaths up to Day 49.

Reviewer's Comment: There was no statistically significant difference between treatment groups for total deaths or death categories.

Table (9.2.1) 1 - Number (%) of patients who died from first injection - All treated patients

Patients with	Org31540/SR90107A 2.5 mg o.d. (N = 517) n (%)	Enoxaparin 30 mg b.i.d. (N = 517) n (%)
SAE between first injection and Day 11		
Leading to death between first injection and Day 11	1 (0.2)	2 (0.4)
SAE between Day 12 and Day 49		
Leading to death between Day 12 and Day 49	1 (0.2)	1 (0.2)
Total deaths between first injection and Day 49	2 (0.4)	3 (0.6)
Total deaths reported	2 (0.4)	3 (0.6)

NOTE: Deaths before the first study drug administration or deaths due to AE that occurred after Day 49 were not reported.
Ref: Appendix 14.2.4.2.1

Table (9.2.1) 2 - Number (%) of patients who died between the first injection and Day 49 by adjudication criterion - All treated patients

Adjudication criterion	Org31540/SR90107A 2.5 mg o.d. (N = 517) n (%)	Enoxaparin 30 mg b.i.d. (N = 517) n (%)
Fatal PE	1 (0.2)	1 (0.2)
Death not associated with VTE or bleeding	1 (0.2)	2 (0.4)
Total	2 (0.4)	3 (0.6)

Ref: Appendix 14.2.4.2.2

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This reviewer's assessment of the causes of death was consistent with that of the Central Adjudication Committee.

Serious Adverse Events
The sponsor's table below shows the number of patients experiencing serious adverse events.

Reviewer's Comment: There was no statistically significant difference for SAEs between treatment groups.

Table (9.2.2) 1 - Number (%) of patients with serious adverse events from the first injectic
Day 11 by WHO organ class and preferred term - All treated patients

WHO organ class Preferred term	Org31540/SR90107A 2.5 mg o.d. (N = 517) n (%)	Enoxaparin 30 mg b.i.d. (N = 517) n (%)
Any event	38 (7.4)	28 (5.4)
Body as a whole - general disorders		
Total	6 (1.2)	2 (0.4)
Fever	3 (0.6)	1 (0.2)
Pain	1 (0.2)	1 (0.2)
Abdomen enlarged	0 (0.0)	1 (0.2)
Chest pain	1 (0.2)	0 (0.0)
Leg pain	1 (0.2)	0 (0.0)
Heart rate and rhythm disorders		
Total	4 (0.8)	4 (0.8)
Tachycardia supraventricular	2 (0.4)	1 (0.2)
Arrhythmia	1 (0.2)	1 (0.2)
Fibrillation atrial	1 (0.2)	1 (0.2)
Tachycardia ventricular	0 (0.0)	1 (0.2)
Respiratory system disorders		
Total	5 (1.0)	3 (0.6)
Hypoxia	0 (0.0)	3 (0.6)
Pneumonia	2 (0.4)	0 (0.0)
Bronchitis	1 (0.2)	0 (0.0)
Pulmonary oedema	1 (0.2)	0 (0.0)
Respiratory depression	1 (0.2)	0 (0.0)
Platelet, bleeding & clotting disorders		
Total	4 (0.8)	3 (0.6)
Haematoma	1 (0.2)	2 (0.4)
Coagulation disorder	1 (0.2)	0 (0.0)
Haemarthrosis	1 (0.2)	0 (0.0)
Haematemesis	0 (0.0)	1 (0.2)
Thrombophlebitis deep	1 (0.2)	0 (0.0)
Red blood cells disorders		
Total	5 (1.0)	2 (0.4)
Anaemia	5 (1.0)	2 (0.4)
Gastro-intestinal system disorders		
Total	2 (0.4)	4 (0.8)
Ileus	1 (0.2)	3 (0.6)
Nausea	1 (0.2)	1 (0.2)
Oesophagitis	0 (0.0)	1 (0.2)
Centr & periph nervous system disorders		
Total	2 (0.4)	3 (0.6)
Neuropathy	0 (0.0)	2 (0.4)
Convulsions	1 (0.2)	0 (0.0)
Dizziness	1 (0.2)	0 (0.0)
Gait abnormal	0 (0.0)	1 (0.2)
Hypoaesthesia	0 (0.0)	1 (0.2)

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Table (9.2.2) 1 - *continued* -Number (%) of patients with serious adverse events from the first injection to Day 11 by WHO organ class and preferred term - All treated patients

WHO organ class Preferred term	Org31540/SR90107A 2.5 mg o.d. (N = 517) n (%)	Enoxaparin 30 mg b.i.d. (N = 517) n (%)
Resistance mechanism disorders		
Total	4 (0.8)	1 (0.2)
Post-operative wound infection	3 (0.6)	0 (0.0)
Infection	0 (0.0)	1 (0.2)
Moniliasis	1 (0.2)	0 (0.0)
Application site disorders		
Total	2 (0.4)	2 (0.4)
Cellulitis	2 (0.4)	2 (0.4)
Cardiovascular disorders, general		
Total	1 (0.2)	1 (0.2)
Cardiac failure	0 (0.0)	1 (0.2)
Hypotension postural	1 (0.2)	0 (0.0)
Musculo-skeletal system disorders		
Total	1 (0.2)	1 (0.2)
Arthropathy	0 (0.0)	1 (0.2)
Bone disorder	1 (0.2)	0 (0.0)
Myo-, endo-, pericardial & valve disorders		
Total	1 (0.2)	1 (0.2)
Myocardial infarction	1 (0.2)	1 (0.2)
Secondary terms		
Total	1 (0.2)	1 (0.2)
Spinal cord compression	1 (0.2)	0 (0.0)
Surgical site reaction	0 (0.0)	1 (0.2)
Vascular (extracardiac) disorders		
Total	0 (0.0)	2 (0.4)
Vascular disorder	0 (0.0)	2 (0.4)
Psychiatric disorders		
Total	1 (0.2)	0 (0.0)
Withdrawal syndrome	1 (0.2)	0 (0.0)
Urinary system disorders		
Total	1 (0.2)	0 (0.0)
Renal tubular necrosis	1 (0.2)	0 (0.0)

Ref: Appendix 14.2.4.2.5

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Thrombocytopenia

Investigators coded nine patients (6 fondaparinux and 3 enoxaparin) as having thrombocytopenia from first injection to Day 11. Eight patients (7 fondaparinux and 1 enoxaparin) had a baseline value lower than 150,000/cc^3. All cases had the onset of thrombocytopenia occur within the first 4 days. ELISA tests for antiplatelet antibodies were unknown for 5 and negative for 4 patients. One patient in each treatment group developed a DVT (#03910474 and 07011092). No patient who developed thrombocytopenia died during the trial or follow up period. The sponsor's table is presented below.

Table (9.2.3.1) 1 - Patients experiencing a decrease in platelet count according to the Investigator's judgment - Characteristics of the events - All treated patients

Treatment group	Patient	Description of the AE/SAE					Platelet count (10^9/L)		
		Day of onset[a]	Duration of the event (day)	Day of last injection[a]	Serious	Action taken on study drug	Last value before treatment	Minimum value	Value at date of resolution[b]
Org31540/ SR90107A	01110276	4	5	9	No	No change	[redacted]		
	03910474	4	2	3	No	Drug permanently discontinued			
	03910602	2	4	4	No	Drug permanently discontinued			
	06010360	2	5	7	No	No change			
	08411213[c]	1	2	6	No	No change			
	08510961	2	5	1	No	Drug permanently discontinued			
Enoxaparin	03610244	2	4	6	No	No change			
	06410562	3	1	6	No	No change			
	07011092	3	1	6	No	No change			

NOTE: Normal range: 150-400 x 10^9/L

[a] Expressed as days since surgery/since start of study drug (active or placebo)

[b] Resolution date as reported by the Investigator on the AE Form

[c] The last reported platelet count was on Day 4 ([redacted]) and did not lead to treatment discontinuation; results of antiplatelet antibody testing were not available.

Ref: Appendix 14.2.4.2.17

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Permanent Discontinuations
There were no statistically significant differences between treatment groups for patients who discontinued. The most frequent reason for discontinuation was platelet, bleeding, and clotting disorder (7 fondaparinux patients (1.4%), 3 enoxaparin patients (0.6%)).

Laboratory Parameters
There were no statistically significant differences between treatment groups for mean change from baseline for hemoglobin or hematocrit, platelet counts, biochemistry, and liver function tests. The sponsor's tables show the results for selected parameters.

Reviewer's Comment: A greater number and percentage of fondaparinux patients had hematocrit values less than 24%, experienced greater than a 6% decrease in hematocrit, or both compared with enoxaparin.

Table (9.3.1.2) 1 - Number (%) of patients with a hematocrit value <24.0% and/or a decrease ≥6.0% compared to baseline values - All treated patients

Hematocrit	Org31540/SR90107A 2.5 mg o.d. n/N (%)	Enoxaparin 30 mg b.i.d. n/N (%)
Values[a] <24.0%	90/516 (17.4)	77/517 (14.9)
Decrease[b] ≥6.0%	364/516 (70.5)	342/517 (66.2)
Both	77/516 (14.9)	57/517 (11.0)

[a] After first injection
[b] From first post-operative value
Ref: Appendix 14.2.4.3.9

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The sponsor's table below shows the number of patients with platelet counts less than 100,000/cc^3.

Table (9.3.1.3) 1 - Number (%) of patients with a platelet count included in the [50x10^9/L-100x10^9/L[range or < 50x10^9/L after first study drug injection - All treated patients

Platelet count	Org31540/SR90107A 2.5 mg o.d. n/N (%)	Enoxaparin 30 mg b.i.d. n/N (%)
[50x10^9/L - 100x10^9/L[[b]	14/516 (2.7)	9/517 (1.7)
<50x10^9/L[c]	0/516 (0.0)	0/517 (0.0)

[a] After first injection
[b] With baseline value ≥100x10^9/L or missing.
[c] With baseline value ≥50x10^9/L or missing.
Ref: Appendix 14.2.4.3.9

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The sponsor's table below shows the number of patients who had a positive ELISA test for heparin specific IgG antibodies after study drug treatment.

Reviewer's Comment: A greater percentage of enoxaparin patients became ELISA positive after having a negative or missing result at baseline and developed a positive SRA compared with fondaparinux. Review of patients who became ELISA positive revealed that only one patient had received heparin during the study.

Thus the majority of patients who became ELISA positive did not have documented exposure to heparin prior to or during the trial.
One ELISA positive fondaparinux patient developed a DVT; no ELISA positive enoxaparin patient developed a DVT. No ELISA positive patient died during the trial or follow up period.

Table (9.3.1.4) 1 - Number (%) of patients with ELISA and Serotonin Release Assay (SRA) tests (among positive ELISA tests) which became positive after beginning active study drug - All treated patients with antiplatelet antibodies evaluation

Test	Org31540/SR90107A 2.5 mg o.d. n/N (%)	Enoxaparin 30 mg b.i.d. n/N (%)
Positive ELISA test[a]	11/388 (2.8)	19/365 (5.2)
Positive SRA test[b]	2/11 (18.2)	1/19 (5.3)

[a] Patients with switch to positive ELISA test after beginning of active study drug from negative (or missing) ELISA test at baseline
[b] Among patients with switch to positive ELISA test, patients with switch to positive SRA test from negative (or missing) SRA test at baseline
Ref: Appendix 14.2.4.3.15

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The sponsor's table below shows the changes in AST and ALT.

Reviewer's Comment: There were greater percentages of fondaparinux patients than enoxaparin patients who had an increase in AST and ALT levels to greater than 3 times the upper limit of normal.

Table (9.3.2.1) 1 - Number (%) of patients with no increase or with an increase in AST and/or ALT values above 1 or 3 times the upper limit of normal compared to baseline values - All treated patients

Parameter		Org31540/SR90107A 2.5 mg o.d. n/N (%)	Enoxaparin 30 mg b.i.d. n/N (%)
AST	No increase[a]	375/462 (81.2)	325/441 (73.7)
	Increase]ULN - 3ULN][b]	78/462 (16.9)	113/441 (25.6)
	Increase >3ULN[c]	9/462 (1.9)	3/441 (0.7)
ALT	No increase[a]	381/450 (84.7)	361/431 (83.8)
	Increase]ULN - 3ULN][b]	60/450 (13.3)	67/431 (15.5)
	Increase >3ULN[c]	9/450 (2.0)	3/431 (0.7)

Note: ULN = upper limit of normal range
[a] No increase: values remained in the same range (i.e., ≤ULN,]ULN - 3ULN] or >3ULN) after the beginning of treatment compared to the baseline values, or values decreased
[b] Increase]ULN - 3ULN]: values increased from baseline at least once to a value >ULN but remained ≤3ULN
[c] Increase >3ULN: values increased from baseline at least once to a value >3ULN
Ref: Appendix 14.2.4.3.10

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Trial- ——————— (hip replacement)-Multicenter, randomized, double-blind comparison of fondaparinux 2.5 mg SC once daily compared with enoxaparin 30 mg SC BID given post-operatively for 7-9 days for thromboprophylaxis in hip replacement surgery

Enrollment and Dosing
Two thousand two hundred and seventy five patients were randomized to either:

1) fondaparinux 2.5 mg SC starting 6 ± 2 hours after surgery
2) enoxaparin 30 mg SC BID starting 12-24 hours after surgery

The sponsor's exclusion criteria and safety analyses were the same as the ——————— study.

Safety Results
Eighteen patients were excluded from the safety analyses because they did not receive any injection of study drug.

Bleeding
The sponsor's table below shows the number of patients with an adjudicated bleed up to Day 11.

Reviewer's Comment: There was no statistically significant difference between the treatment groups for major, minor, or any bleed up to Day 11. Higher major and any bleeding rates up to Day 11 were seen in the fondaparinux treatment groups. Similar results were seen for up to Day 49.

Table (8.1.1) 1 - Number (%) of Patients with Adjudicated Bleeding Events From First Injection to Day 11 - All Treated Patients

Patients with		Org31540/SR90107A 2.5 mg o.d. (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)
Major bleeding	n (%) 95% CI	20 (1.8%) [1.1;2.7]	11 (1.0%) [0.5;1.7]
Minor bleeding only	n (%) 95% CI	17 (1.5%) [0.9;2.4]	24 (2.1%) [1.4;3.1]
Any bleeding	n (%) 95% CI	37 (3.3%) [2.3;4.5]	35 (3.1%) [2.2;4.3]

PGM: ——————— OUT: output/TBLD101 (13SEP00 - 20:51)

Ref: Appendix 14.2.3.1.1

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Center 1216 (Australia) had a high incidence of bleeding and the investigator terminated this site. Twenty-one patients were randomized at the site with 7 bleeding events reported (5 major and 2 minor). All 5 major bleeding events were in the fondaparinux treatment group. The sponsor suggested that a single surgeon who operated on 6 of the 7 patients might have been responsible. The auditor noted that this surgeon prescribed standing orders for heparin flushes 5 times a day for up to 5 days and enoxaparin. The auditor believed that these flushes and enoxaparin might have been given in addition to study drug.

The sponsor's tables below show the major bleeding events up to Day 11 and up to Day 49.

Reviewer's Comment: Event rates were similar for the major bleeding subcategories between the two treatment groups. Major bleeding at the surgical site led to reoperation in 2 fondaparinux patients compared with 3 enoxaparin patients. One enoxaparin patient experienced a

retroperitoneal bleed. The gastrointestinal tract was the most frequent non-surgical site for major bleeding.

Table (8.1.2) 1 - Number (%) of Patients With Adjudicated Major Event Bleeding Events From First Injection to Day 11 by Adjudication Criterion - All Treated Patients

Patients With	Org31540/SR90107A 2.5 mg o.d. (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)
Any major bleeding	20 (1.8%)	11 (1.0%)
Fatal bleeding	0 (0.0%)	0 (0.0%)
Non-fatal critical bleeding	0 (0.0%)	1 (0.1%)
- Retroperitoneal	0 (0.0%)	1 (0.1%)
Other non-fatal major bleeding	20 (1.8%)	10 (0.9%)
-At surgical site	14 (1.2%)	7 (0.6%)
-At non-surgical site only	6 (0.5%)	3 (0.3%)

PGM: [redacted] OUT: outputs\TBLD104 (29SEP00 - 14:36)

Ref: Appendix 14.2.3.1.3

Table (8.1.2) 2 - Number (%) of Patients With Adjudicated Major Bleeding Events From First Injection to Day 49 by Adjudication Criterion - All Treated Patients

Patients With	Org31540/SR90107A 2.5 mg o.d. (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)
Any major bleeding	22 (2.0%)	13 (1.2%)
Fatal bleeding	0 (0.0%)	0 (0.0%)
Non-fatal critical bleeding	0 (0.0%)	1 (0.1%)
- Retroperitoneal	0 (0.0%)	1 (0.1%)
Other non-fatal major bleeding	22 (2.0%)	12 (1.1%)
-At surgical site	16 (1.4%)	8 (0.7%)
-At non-surgical site only	6 (0.5%)	4 (0.4%)

PGM: [redacted] OUT: outputs\TBLD105 (29SEP00 - 14:36)

Ref: Appendix 14.2.3.1.3

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The sponsor analyzed the main safety endpoint using a number of covariates (e.g., country, age, sex, race, obesity, type of anesthesia, type of surgery, use of cement, duration of surgery, baseline creatinine, and drug-drug interactions). No statistically significant interaction was demonstrated for any covariate and major bleeding.

Transfusions
Similar numbers of patients were transfused in both treatment groups.

Table (8.2.2) 1 - Number (%) of Transfused Patients Up to Day 49 - All Treated Patients

Transfused Patients	Org31540/SR90107A 2.5 mg o.d. (N=1128)			Enoxaparin 30 mg b.i.d. (N=1129)		
	Autologous	Homologous	Total	Autologous	Homologous	Total
Intra-operatively	108 (9.6%)	51 (4.5%)	154 (13.7%)	112 (9.9%)	63 (5.6%)	172 (15.2%)
Post-operatively up to Day 11	348 (30.9%)	304 (27.0%)	593 (52.6%)	348 (30.8%)	254 (22.5%)	555 (49.2%)
Post-operatively up to Day 49	348 (30.9%)	312 (27.7%)	597 (52.9%)	348 (30.8%)	261 (23.1%)	559 (49.5%)

PGM: [redacted] OUT: EFC2342/output/CRJTB101 (14SEP00 - 17:24)

Ref: Appendices 14.2.3.2.6 and 14.2.3.2.7

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Adverse Events

The sponsor's table below shows the number of patients with one adverse event from first injection to Day 11.

Reviewer's Comment: There was no statistically significant difference between the treatment groups for any adverse event. Similar results were seen up to Day 49.

Table (9.1.1) 1 - Overview of Patients With at Least One Adverse Event From First Injection to Day 11 - All Treated Patients

From First Injection to Day 11	Org31540/SR90107A 2.5 mg o.d (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)
Patients with any AE[a]	854 (75.7%)	860 (76.2%)
Patients with any drug-related AE[a,b]	144 (12.8%)	138 (12.2%)
Patients with any AE[a] of severe intensity[c]	53 (4.7%)	45 (4.0%)
Patients with SAE[d]	54 (4.8%)	47 (4.2%)
Patients with drug-related SAE[b]	6 (0.5%)	6 (0.5%)
Deaths	3 (0.3%)	1 (0.1%)
Patients permanently discontinued study drug for any AE[a,e]	33 (2.9%)	33 (2.9%)
Patients permanently discontinued study drug for events not considered in AE analysis[f]	0 (0.0%)	2 (0.2%)

PGM: [redacted] OUT: output/ITae1 (30OCT00 - 10:28)

[a] Including SAEs.
[b] Relationship to study drug judged as likely or difficult to assess by the Investigator or missing.
[c] Including missing intensity.
[d] Including SAEs leading to death.
[e] AEs started after the first study drug administration.
[f] Events started before the first study drug administration.

Ref: Appendix 14.2.4.1.1

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The sponsor's table below shows the number of patients with adverse events occurring from first injection to Day 11 with an incidence $\geq$ 2%.

Reviewer's Comment: Statistically significant differences for adverse events in favor of enoxaparin included: oedema ($p < 0.02$) and anemia ($p < 0.02$).

Table (9.1.2) 1 - Number (%) of Patients With Adverse Events From First Injection to Day 11 for All WHO Organ Classes and Preferred Term With Incidence >2% in Any Treatment Group - All Treated Patients

WHO Organ Class **Preferred Term**	**Org31540/SR90107A 2.5 mg o.d. (N=1128)**	**Enoxaparin 30 mg b.i.d. (N=1129)**
Any event	854 (75.7%)	860 (76.2%)
Body as a whole - general disorders		
Total	430 (38.1%)	414 (36.7%)
Fever	228 (20.2%)	238 (21.1%)
Oedema	96 (8.5%)	64 (5.7%)
Wound drainage increased	64 (5.7%)	56 (5.0%)
Oedema peripheral	61 (5.4%)	55 (4.9%)
Pain	37 (3.3%)	41 (3.6%)
Gastro-intestinal system disorders		
Total	318 (28.2%)	338 (29.9%)
Nausea	142 (12.6%)	168 (14.9%)
Constipation	113 (10.0%)	103 (9.1%)
Vomiting	69 (6.1%)	88 (7.8%)
Dyspepsia	33 (2.9%)	40 (3.5%)
Diarrhoea	34 (3.0%)	34 (3.0%)
Red blood cell disorders		
Total	274 (24.3%)	227 (20.1%)
Anaemia	272 (24.1%)	225 (19.9%)
Skin and appendages disorders		
Total	228 (20.2%)	249 (22.1%)
Bullous eruption	62 (5.5%)	57 (5.0%)
Pruritus	56 (5.0%)	59 (5.2%)
Rash	46 (4.1%)	61 (5.4%)
Rash erythematous	50 (4.4%)	50 (4.4%)
Central and peripheral nervous system disorders		
Total	212 (18.8%)	239 (21.2%)
Dizziness	58 (5.1%)	67 (5.9%)
Urinary retention	49 (4.3%)	55 (4.9%)
Confusion	34 (3.0%)	44 (3.9%)
Headache	29 (2.6%)	33 (2.9%)
Hypertonia	28 (2.5%)	29 (2.6%)
Platelet, bleeding and clotting disorders		
Total	134 (11.9%)	118 (10.5%)
Purpura	70 (6.2%)	56 (5.0%)
Respiratory system disorders		
Total	109 (9.7%)	105 (9.3%)

(continued)

WHO Organ Class Preferred Term	Org31540/SR90107A 2.5 mg o.d. (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)
Metabolic and nutritional disorders		
Total	87 (7.7%)	95 (8.4%)
Hypokalaemia	56 (5.0%)	62 (5.5%)
Urinary system disorders		
Total	85 (7.5%)	74 (6.6%)
Urinary tract infection	34 (3.0%)	29 (2.6%)
Psychiatric disorders		
Total	79 (7.0%)	77 (6.8%)
Insomnia	28 (2.5%)	31 (2.7%)
Cardiovascular disorders, general		
Total	67 (5.9%)	52 (4.6%)
Hypotension	41 (3.6%)	29 (2.6%)
Liver and biliary system disorders		
Total	38 (3.4%)	69 (6.1%)
SGOT increased	17 (1.5%)	37 (3.3%)
SGPT increased	17 (1.5%)	32 (2.8%)
Musculo-skeletal system disorders		
Total	49 (4.3%)	51 (4.5%)
Secondary terms		
Total	42 (3.7%)	38 (3.4%)
Heart rate and rhythm disorders		
Total	31 (2.7%)	48 (4.3%)
Tachycardia	17 (1.5%)	29 (2.6%)
Resistance mechanism disorders		
Total	41 (3.6%)	26 (2.3%)
Autonomic nervous system disorders		
Total	18 (1.6%)	23 (2.0%)

PGM: [redacted] OUT: output/AE_AT11 (30OCT00 - 11:23)

Ref: Appendix 14.2.4.1.3

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Deaths
The sponsor's table below shows the number of deaths up to Day 49.

Reviewer's Comment: There was no statistically significant difference between treatment groups for total deaths. Adjudicated deaths were similar between treatment groups in the fatal PE category.

Table (9.2.1) 1 - Number (%) of Deaths From First Injection - All Treated Patients

Patients with	Org31540/SR90107A 2.5 mg o.d. (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)
SAE between first injection and Day 11:		
Leading to death between first injection and Day 11	3 (0.3%)	1 (0.1%)
Leading to death between Day 12 and Day 49	0 (0.0%)	1 (0.1%)
SAE from Day 12:		
Leading to death between Day 12 and Day 49	3 (0.3%)	1 (0.1%)
Leading to death after the end of the study	0 (0.0%)	1 (0.1%)
Total deaths between first injection and Day 49	6 (0.5%)	3 (0.3%)
Total deaths reported	6 (0.5%)	4 (0.4%)

PGM: [redacted] OUT: output/DEATH1 (18SEP00 - 11:23)

NOTE: Deaths before first study drug administration or deaths due to AE which occurred after Day 49 were not counted in this table.

Ref: Appendix 14.2.4.2.1

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This reviewer's assessment of the causes of death was consistent with that of the Central Adjudication Committee.

Serious Adverse Events

The sponsor's table below shows the number of patients experiencing serious adverse events up to Day 11.

Reviewer's Comment: There were no statistically significant differences between treatment groups. Serious adverse events were higher for the fondaparinux treatment group compared with enoxaparin up to Day 49 (8.6% and 7.4%, respectively).

Table (9.2.2) 1 - Number (%) of Patients With Serious Adverse Events Occurring From First Injection to Day 11 by WHO Organ Class and Preferred Term - All Treated Patients

WHO Organ Class Preferred Term	Org31540/SR90107A 2.5 mg o.d. (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)
Any event	54 (4.8%)	47 (4.2%)
Secondary terms		
Total	7 (0.6%)	13 (1.2%)
Surgical site reaction	3 (0.3%)	11 (1.0%)
Inflicted injury	4 (0.4%)	1 (0.1%)
Post-operative pain	0 (0.0%)	1 (0.1%)
Gastro-intestinal system disorders		
Total	12 (1.1%)	5 (0.4%)
Ileus	5 (0.4%)	1 (0.1%)
Intestinal obstruction	2 (0.2%)	0 (0.0%)
Vomiting	2 (0.2%)	0 (0.0%)
Diarrhoea	1 (0.1%)	0 (0.0%)
Diarrhoea, clostridium difficile	0 (0.0%)	1 (0.1%)
Enterocolitis	0 (0.0%)	1 (0.1%)
Gastritis	1 (0.1%)	0 (0.0%)
Haemorrhoids	1 (0.1%)	0 (0.0%)
Ileus paralytic	0 (0.0%)	1 (0.1%)
Intestinal perforation	0 (0.0%)	1 (0.1%)
Megacolon congenital	1 (0.1%)	0 (0.0%)
Platelet, bleeding and clotting disorders		
Total	12 (1.1%)	5 (0.4%)
Haematoma	5 (0.4%)	1 (0.1%)
Haematuria	2 (0.2%)	1 (0.1%)
Post-operative haemorrhage	1 (0.1%)	2 (0.2%)
Melaena	1 (0.1%)	1 (0.1%)
GI haemorrhage	1 (0.1%)	0 (0.0%)
Haemorrhage NOS	1 (0.1%)	0 (0.0%)
Haemorrhage rectum	1 (0.1%)	0 (0.0%)
Heart rate and rhythm disorders		
Total	5 (0.4%)	5 (0.4%)
Tachycardia	2 (0.2%)	2 (0.2%)
Cardiac arrest	2 (0.2%)	0 (0.0%)
Fibrillation atrial	0 (0.0%)	2 (0.2%)
Sick sinus syndrome	1 (0.1%)	0 (0.0%)
Tachycardia supraventricular	0 (0.0%)	1 (0.1%)
Body as a whole - general disorders		
Total	4 (0.4%)	5 (0.4%)
Chest pain	1 (0.1%)	1 (0.1%)
Fever	2 (0.2%)	0 (0.0%)
Asthenia	0 (0.0%)	1 (0.1%)
Death	1 (0.1%)	0 (0.0%)
Hypovolaemia	0 (0.0%)	1 (0.1%)
Oedema peripheral	0 (0.0%)	1 (0.1%)
Pain	0 (0.0%)	1 (0.1%)

(continued)

WHO Organ Class Preferred Term	Org31540/SR90107A 2.5 mg o.d. (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)
Respiratory system disorders		
Total	4 (0.4%)	4 (0.4%)
Pneumonia	3 (0.3%)	2 (0.2%)
Atelectasis	0 (0.0%)	1 (0.1%)
Dyspnoea	1 (0.1%)	0 (0.0%)
Pneumonitis	0 (0.0%)	1 (0.1%)
Myo, endo, pericardial and valve disorders		
Total	3 (0.3%)	3 (0.3%)
Angina pectoris	1 (0.1%)	2 (0.2%)
Myocardial infarction	2 (0.2%)	1 (0.1%)
Central and peripheral nervous system disorders		
Total	2 (0.2%)	3 (0.3%)
Confusion	1 (0.1%)	1 (0.1%)
Coma	0 (0.0%)	1 (0.1%)
Encephalopathy	1 (0.1%)	0 (0.0%)
Hypoaesthesia	0 (0.0%)	1 (0.1%)
Urinary system disorders		
Total	3 (0.3%)	2 (0.2%)
Renal failure acute	1 (0.1%)	1 (0.1%)
Micturition disorder	1 (0.1%)	0 (0.0%)
Renal tubular necrosis	1 (0.1%)	0 (0.0%)
Urinary tract infection	0 (0.0%)	1 (0.1%)
Application site disorders		
Total	1 (0.1%)	1 (0.1%)
Cellulitis	1 (0.1%)	1 (0.1%)
Metabolic and nutritional disorders		
Total	1 (0.1%)	1 (0.1%)
Dehydration	1 (0.1%)	0 (0.0%)
Hyperglycaemia	0 (0.0%)	1 (0.1%)
Resistance mechanism disorders		
Total	2 (0.2%)	0 (0.0%)
Post-operative wound infection	2 (0.2%)	0 (0.0%)
Cardiovascular disorders, general		
Total	1 (0.1%)	0 (0.0%)
Hypertension	1 (0.1%)	0 (0.0%)
Musculo-skeletal system disorders		
Total	1 (0.1%)	0 (0.0%)
Arthritis	1 (0.1%)	0 (0.0%)
Psychiatric disorders		
Total	0 (0.0%)	1 (0.1%)
Delirium	0 (0.0%)	1 (0.1%)
Red blood cell disorders		
Total	1 (0.1%)	0 (0.0%)
Anaemia	1 (0.1%)	0 (0.0%)

(continued)

WHO Organ Class Preferred Term	Org31540/SR90107A 2.5 mg o.d. (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)
Skin and appendages disorders		
Total	1 (0.1%)	0 (0.0%)
Skin ulceration	1 (0.1%)	0 (0.0%)
Vascular (extracardiac) disorders		
Total	0 (0.0%)	1 (0.1%)
Transient ischaemic attack	0 (0.0%)	1 (0.1%)

PGM: [redacted] OUT: output/AE_ST1 (14SEP00 - 2:26)

NOS = not otherwise specified
Ref: Appendix 14.2.4.2.5

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Thrombocytopenia
Investigators coded sixteen patients (8 fondaparinux and 8 enoxaparin) as having thrombocytopenia from the first injection to Day 11. Nine patients (4 fondaparinux and 5 enoxaparin) had a baseline value lower than 150,000/cc^3. All cases had the onset of thrombocytopenia occur within the first 5 days. Three fondaparinux patients had their treatment discontinued; no enoxaparin patient had treatment discontinued. ELISA tests for antiplatelet antibodies were negative. No patient developed a DVT. No patient who developed thrombocytopenia died during the trial or follow up period. The sponsor's table is presented below.

Table (9.2.3.1) 1 - Patients Experiencing a Decrease in Platelet Count According to the Investigator's Judgment - Characteristics of the Events - All Treated Patients

		Description of the AE/SAE					Platelet Count (10^9/L)		
Treatment Group	Patient	Day of Onset*	Duration of the Event (day)	Day of Last Injection*	Serious	Action Taken on Study Drug	Last Value Before Treatment	Minimum Value	Value at Date of Resolution*
Org31540/ SR90107A	1210004	2/2	6	8/8	No	No change	[redacted]		
	1320008	3/3	1	5/5	No	No change			
	1350008	1/1	5	6/6	No	No change			
	1440006	4/4	1	3/3	No	Drug permanently discontinued			
	1840002	3/3	2	5/5	No	Drug permanently discontinued			
	1840009	3/3	4	3/3	No	Drug permanently discontinued			
	5120004*	2/2	3	6/6	No	No change			
	12050004	2/2	1	7/7	No	No change			
Enoxaparin	1220027	2/2	2	6/6	No	No change			
	1360007	2/2	4	6/6	No	No change			
	1600003	3/3	6	9/9	No	No change			
	5170004	2/2	4	7/7	No	No change			
	5200006	2/2	2	5/5	No	No change			
	5200018	3/3	1	7/7	No	No change			
	5220027	2/2	4	8/8	No	No change			
	5290023	4/4	1	6/6	No	No change			

PGM: [redacted] OUT: output/ITDILATH (13NOV00 - 10:42)

NOTE: Normal range: 150-400 x 10^9/L
* Expressed as days since surgery/since start of study drug (active or placebo).
* AE resolution date reported by the Investigator.
* Value measured the day after the day of resolution.
* Patient 5120004 had 2 consecutive episodes of thrombocytopenia which were counted as 1 event.
Ref: Appendix 14.2.4.2.17

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Permanent Discontinuations
There was no statistically significant difference between treatment groups for patients who discontinued (33 fondaparinux patients and 35 enoxaparin patients). The most frequent reason for discontinuation was platelet, bleeding, and clotting disorder (11 fondaparinux patients (1.0%), 12 enoxaparin patients (1.1%)).

Laboratory Parameters
There were no statistically significant differences between treatment groups for mean change from baseline for hemoglobin or hematocrit, platelet counts, biochemistry, and liver function tests. The sponsor's tables show the results for selected parameters.

Reviewer's Comment: A greater number and percentage of fondaparinux patients had hematocrit values less than 24%, experienced greater than a 6% decrease in hematocrit, or both compared with enoxaparin.

Table (9.3.1.2) 1 - Number (%) of Patients With a Hematocrit Value Below 24% and/or a Decrease Greater Than or Equal to 6.0% Compared to Baseline Values - All Treated Patients

Hematocrit	Org31540/SR90107A 2.5 mg o.d. (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)
Values <24.0%[a]	261/1125 (23.2%)	189/1127 (16.8%)
Decrease ≥6.0%[b]	557/1124 (49.6%)	530/1127 (47.0%)
Both	183/1124 (16.3%)	125/1127 (11.1%)

PGM: [redacted] OUT: output/SAFRNG02 (30OCT00 - 14:19)

[a] After first injection.
[b] From baseline value.
Ref: Appendix 14.2.4.3.9

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The sponsor's table below shows the number of patients with platelet counts less than 100,000/cc^3.

Table (9.3.1.3) 1 - Number (%) of Patients With a Platelet Count Included in the [50 x 10^9/L-100 x 10^9/L[Range or <50 x 10^9/L After First Study Drug Administration - All Treated Patients

Platelet counts	Org31540/SR90107A 2.5 mg o.d. (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)
[50 x 10^9/L - 100 x 10^9/L[[a,b]	23/1123 (2.0%)	29/1125 (2.6%)
<50 x 10^9/L[a,c]	0/1123 (0%)	1/1125 (0.1%)

PGM: [redacted] OUT: output/SAFRNG03 (30OCT00 - 14:19)

[a] After first study drug administration.
[b] With baseline value ≥100 x 10^9/L or missing.
[c] With baseline value ≥50 x 10^9/L or missing.
Ref: Appendix 14.2.4.3.9

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The sponsor's table below shows the number of patients who had a positive ELISA test for heparin specific IgG antibodies after starting study treatment.

Reviewer's Comment: A greater percentage of fondaparinux patients became ELISA positive after having a negative or missing result at baseline and developed a positive SRA compared with enoxaparin. The sponsor did not provide information on the number of patients who had documented exposure to heparin prior to or during the trial. No ELISA positive patient developed a VTE or had a platelet count less than 100,000/cc^3. No ELISA positive patient died during the trial or follow up period.

Table (9.3.1.4) 1 - Number (%) of Patients With ELISA and Serotonin Release Assay Tests (Among Positive ELISA Tests) Which Became Positive After Beginning of Active Study Drug - All Treated Patients With Antiplatelet Antibodies Evaluation

Test	Org31540/SR90107A 2.5 mg o.d.	Enoxaparin 30 mg b.i.d.
Positive ELISA test[a]	29 / 991 (2.9%)	21 / 985 (2.1%)
Positive SRA test[b]	1 / 29 (3.4%)	0 / 21 (0.0%)

PGM: [redacted] OUT: output/BIOAB01 (30OCT00 - 14:46)

[a] Patients with switch to positive ELISA test after beginning of active study drug from negative (or missing) ELISA test at baseline.

[b] Out of patients with switch to positive ELISA test, patients with switch to positive SRA test from negative (or missing) SRA test at baseline.

Ref: Appendix 14.2.4.3.15

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Pharmacokinetic evaluation of main efficacy and safety endpoints
The sponsor evaluated the relationship between plasma drug levels and development of either a VTE or adjudicated major bleeding. The sponsor concluded that no relationship existed between plasma drug levels and development of an endpoint.

Reviewer's Comment: The evaluation included only a subset of the total fondaparinux patients (2.9%). The results cannot be considered conclusive due to the small number of patients participating.

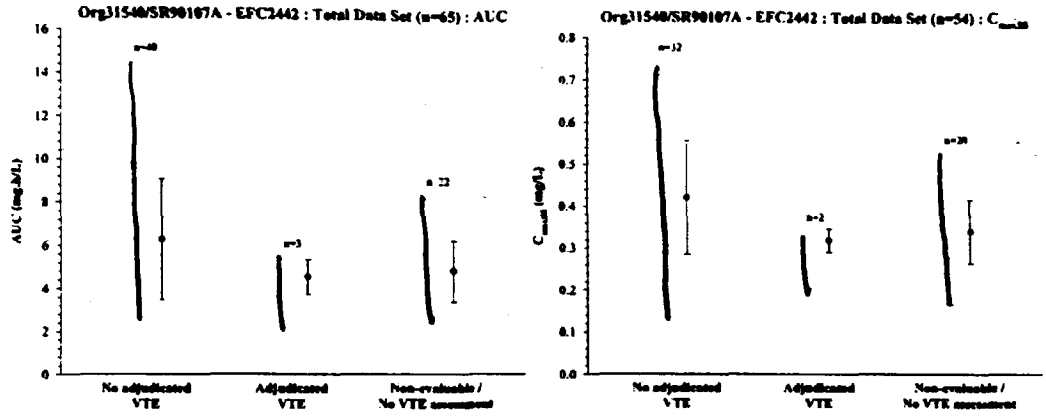

Figure (10.3) 1 - Individual and Mean (SD) AUC (left) and $C_{max,ss}$ (right) as a Function of Occurrence of VTEs

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Trial- [redacted] (hip replacement)- Multicenter, randomized, double-blind, comparison of post-operative fondaparinux 2.5 mg SC once daily compared with pre-operative enoxaparin 40 mg SC once daily for thromboprophylaxis in hip replacement

Enrollment and Dosing

Two thousand three hundred and nine patients were enrolled and randomized to either:

1) fondaparinux 2.5 mg started 6 ± 2 hours post-operatively

2) enoxaparin 40 mg started 12 ± 2 hours pre-operatively.

The sponsor's exclusion criteria and safety analyses were the same as the [redacted] study.

Safety Results
Thirty-six patients were excluded from the safety analyses because they did not receive any injection of study drug.

Bleeding
The sponsor's table below shows the number of patients with an adjudicated bleed up to Day 11.

Reviewer's Comment: There was no statistically significant difference between the treatment groups for major, minor, or any bleed up to Day 11. In all bleeding subcategories, a higher rate was seen in the fondaparinux treatment groups. Similar results were seen for up to Day 49.

Table (8.1.1) 1 - Number (%) of Patients With Adjudicated Bleeding Events From First Injection to Day 11 - All Treated Patients

Patients With		Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)
Major bleeding event	n (%)	47 (4.1 %)	32 (2.8 %)
	95% CI	[3.0;5.4]	[1.9;4.0]
Minor bleeding event only	n (%)	44 (3.9 %)	38 (3.4 %)
	95% CI	[2.8;5.1]	[2.4;4.6]
Any bleeding event	n (%)	91 (8.0 %)	70 (6.2 %)
	95% CI	[6.5;9.7]	[4.8;7.7]

Compound: Org31540/SR90107A (63118), SAS program: ——— /Date:13OCT2000 20:32
Ref: Appendix 14.2.3.1.1

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Major Bleeding Categories
The sponsor's tables below show the major bleeding events up to Day 11.

Reviewer's Comment: No statistically significant differences were observed between the treatment groups. Event rates were higher in the fondaparinux treatment group for the major bleeding subcategories. Major bleeding at the surgical site led to reoperation in 5 fondaparinux patients compared with 3 enoxaparin patients. Similar results were seen for adjudicated major bleeding to Day 49.

Table (8.1.2) 1 - Number (%) of Patients With Adjudicated Major Bleeding Events From First Injection to Day 11 by Adjudication Criterion - All Treated Patients

Patients With	Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)
Any major bleeding	47 (4.1 %)	32 (2.8 %)
Fatal bleeding	0 (0.0 %)	0 (0.0 %)
Non-fatal critical bleeding	0 (0.0%)	0 (0.0%)
Other non-fatal major bleeding	47 (4.1 %)	32 (2.8 %)
At surgical site	40 (3.5 %)	29 (2.6 %)
At non-surgical site only	7 (0.6 %)	3 (0.3 %)

Compound: Org31540/SR90107A (63118), SAS program: ——— Date:13OCT2000 20:43
Ref: Appendix 14.2.3.1.3

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The sponsor analyzed the main safety endpoint using a number of covariates (e.g., country, age, sex, race, obesity, type of anesthesia, type of fracture, type of surgery, use of cement, duration of surgery, baseline creatinine, previous antithrombin medication, and drug-drug interactions). No statistically significant interaction was demonstrated for any covariate and major bleeding.

Transfusions
A slightly higher percentage of patients in the fondaparinux treatment group were transfused post-operatively, up to Day 11, and up to Day 49.

Table (8.2.2) 1 - Number (%) of Transfused Patients up to Day 49 - All Treated Patients

Transfused Patients	Org31540/SR90107A 2.5 mg o.d. (N=1140)			Enoxaparin 40 mg o.d. (N=1133)		
	Auto-logous	Homo-logous	Total	Auto-logous	Homo-logous	Total
Intra-operatively	133 (11.7%)	369 (32.4%)	502 (44.0%)	133 (11.7%)	382 (33.7%)	515 (45.5%)
Post-operatively up to Day 11	106 (9.3%)	524 (46.0%)	630 (55.3%)	103 (9.1%)	484 (42.7%)	587 (51.8%)
Up to day 11	152 (13.3%)	562 (49.3%)	714 (62.6%)	146 (12.9%)	544 (48.0%)	690 (60.9%)
Up to day 49	152 (13.3%)	565 (49.6%)	717 (62.9%)	147 (13.0%)	550 (48.5%)	697 (61.5%)

Compound: Org31540/SR90107A (63118), SAS program: [redacted] Date:13OCT2000 20:49

n = All treated patients requiring transfusion (PRBC or Whole blood) at least once in the period considered

Ref: Appendix 14.2.3.2.6

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Adverse Events

The sponsor's table below shows the number of patients with one adverse event from first injection to Day 11.

Reviewer's Comment: There was no statistically significant difference between the treatment groups for any adverse event. Similar results were seen up to Day 49.

Table (9.1.1) 1 - Overview of Patients With at Least One Adverse Event From First Injection to Day 11 - All Treated Patients

From First Injection to Day 11	Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)
Patients with any AE[a]	666 (58.4 %)	660 (58.3 %)
Patients with any drug-related AE[a,b]	136 (11.9 %)	130 (11.5 %)
Patients with any AE[a] of severe intensity[c]	48 (4.2 %)	31 (2.7 %)
Patients with SAEs[d]	46 (4.0 %)	37 (3.3 %)
Patients with drug-related SAEs[b]	8 (0.7 %)	3 (0.3 %)
Deaths	0 (0.0 %)	2 (0.2 %)
Patients permanently discontinued study drug for any AE[a,e,f]	18 (1.6 %)	15 (1.3 %)

Compound: Org31540/SR90107A (63118), SAS program: [redacted] /Date:25OCT2000 17:32

[a] Including SAEs

[b] Relationship to study drug judged as likely or difficult to assess by the Investigator, or missing.

[c] Including missing intensity

[d] Including SAEs leading to death

[e] AEs started after the first study drug administration. Note that no patients discontinued study drug for events starting before the first study drug injection.

[f] According to the End Of Treatment form. Note that an additional 8 patients (3 in the Org31540/SR90107A group and 5 in the enoxaparin group) discontinued permanently from study drug for an AE whereas the primary reason reported on the End Of Treatment form was not an AE/SAE (see Appendix 14.2.4.2.15)

Ref: Appendix 14.2.4.1.1

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The sponsor's table below shows the number of patients with adverse events occurring from first injection to Day 11 with an incidence ≥ 2%.

Reviewer's Comment: No statistically significant difference for adverse events between treatment groups was found except for an increased SGPT in favor of fondaparinux (p<0.04).

Table (9.1.2) 1 - Number (%) of Patients With Adverse Events Occurring From First Injection to Day 11 for All WHO Organ-Classes And Preferred Term With Incidence >2.0% in Any Treatment Group - All Treated Patients

WHO Organ Class Preferred Term	Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)
ANY EVENT	666 (58.4 %)	660 (58.3 %)
GASTRO-INTESTINAL SYSTEM DISORDERS		
TOTAL	252 (22.1 %)	249 (22.0 %)
NAUSEA	121 (10.6 %)	115 (10.2 %)
CONSTIPATION	83 (7.3 %)	102 (9.0 %)
VOMITING	66 (5.8 %)	55 (4.9 %)
DIARRHOEA	26 (2.3 %)	25 (2.2 %)
RED BLOOD CELL DISORDERS		
TOTAL	228 (20.0 %)	191 (16.9 %)
ANAEMIA	226 (19.8 %)	190 (16.8 %)
BODY AS A WHOLE - GENERAL DISORDERS		
TOTAL	178 (15.6 %)	171 (15.1 %)
WOUND DRAINAGE INCREASED	77 (6.8 %)	64 (5.6 %)
FEVER	65 (5.7 %)	67 (5.9 %)
PLATELET,BLEEDING & CLOTTING DISORDERS		
TOTAL	142 (12.5 %)	139 (12.3 %)
HAEMATOMA	57 (5.0 %)	45 (4.0 %)
HAEMORRHAGE NOS	44 (3.9 %)	54 (4.8 %)
POST-OPERATIVE HAEMORRHAGE	29 (2.5 %)	20 (1.8 %)
PSYCHIATRIC DISORDERS		
TOTAL	132 (11.6 %)	131 (11.6 %)
INSOMNIA	119 (10.4 %)	111 (9.8 %)
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS		
TOTAL	120 (10.5 %)	110 (9.7 %)
DIZZINESS	41 (3.6 %)	42 (3.7 %)
CARDIOVASCULAR DISORDERS, GENERAL		
TOTAL	112 (9.8 %)	99 (8.7 %)
HYPOTENSION	59 (5.2 %)	56 (4.9 %)
OEDEMA PERIPHERAL	32 (2.8 %)	23 (2.0 %)
URINARY SYSTEM DISORDERS		
TOTAL	58 (5.1 %)	54 (4.8 %)
URINARY TRACT INFECTION	26 (2.3 %)	22 (1.9 %)
SKIN AND APPENDAGES DISORDERS		
TOTAL	55 (4.8 %)	56 (4.9 %)
METABOLIC AND NUTRITIONAL DISORDERS		
TOTAL	58 (5.1 %)	38 (3.4 %)
HYPOKALAEMIA	38 (3.3 %)	27 (2.4 %)
RESPIRATORY SYSTEM DISORDERS		
TOTAL	47 (4.1 %)	41 (3.6 %)
MUSCULO-SKELETAL SYSTEM DISORDERS		
TOTAL	39 (3.4 %)	41 (3.6 %)

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Table (9.1.2) 1 - *continued* - Number (%) of Patients With Adverse Events Occurring From First Injection to Day 11 for all WHO Organ-Classes And Preferred Term With Incidence >2.0% in Any Treatment Group - All Treated Patients

WHO Organ Class Preferred Term	Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)
HEART RATE AND RHYTHM DISORDERS		
TOTAL	35 (3.1 %)	44 (3.9 %)
BRADYCARDIA	19 (1.7 %)	28 (2.5 %)
SECONDARY TERMS		
TOTAL	34 (3.0 %)	32 (2.8 %)
LIVER AND BILIARY SYSTEM DISORDERS		
TOTAL	29 (2.5 %)	31 (2.7 %)
SGPT INCREASED	13 (1.1 %)	27 (2.4 %)
RESISTANCE MECHANISM DISORDERS		
TOTAL	17 (1.5 %)	20 (1.8 %)
MYO ENDO PERICARDIAL & VALVE DISORDERS		
TOTAL	15 (1.3 %)	13 (1.1 %)
AUTONOMIC NERVOUS SYSTEM DISORDERS		
TOTAL	17 (1.5 %)	9 (0.8 %)
VISION DISORDERS		
TOTAL	4 (0.4 %)	5 (0.4 %)
REPRODUCTIVE DISORDERS, FEMALE		
TOTAL	3 (0.3 %)	5 (0.4 %)
COLLAGEN DISORDERS		
TOTAL	4 (0.4 %)	1 (0.1 %)
HEARING AND VESTIBULAR DISORDERS		
TOTAL	3 (0.3 %)	0 (0.0 %)
REPRODUCTIVE DISORDERS, MALE		
TOTAL	2 (0.2 %)	1 (0.1 %)
VASCULAR (EXTRACARDIAC) DISORDERS		
TOTAL	2 (0.2 %)	1 (0.1 %)
APPLICATION SITE DISORDERS		
TOTAL	1 (0.1 %)	0 (0.0 %)
FOETAL DISORDERS		
TOTAL	1 (0.1 %)	0 (0.0 %)

Compound: Org31540/SR90107A (63118), SAS program: [redacted] Date:23OCT2000 11:32
NOTE: Sorted by WHO organ class in decreasing order of incidence
Ref: Appendix 14.2.4.1.3

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Deaths

The sponsor's table below shows the number of deaths up to Day 49.

Reviewer's Comment: There was no statistically significant difference between treatment groups for total deaths. Fewer deaths were reported for fondaparinux treatment group. Adjudicated deaths are shown in the second table.

Table (9.2.1) 1 - Number (%) of Deaths From First Injection- All Treated Patients

Patients With:	Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)
SAE between first injection and Day 11:		
Leading to death between the first injection and Day 11	0 (0.0 %)	2 (0.2 %)
Leading to death between Day 12 and Day 49	1 (0.1 %)	0 (0.0 %)
SAE between Day 12 and Day 49:		
Leading to death between Day 12 and Day 49	1 (0.1 %)	2 (0.2 %)
Leading to death after Day 49	0 (0.0 %)	1 (0.1 %)
Total deaths between first injection and Day 49	2 (0.2 %)	4 (0.4 %)
Total deaths reported	2 (0.2 %)	5 (0.4 %)

Compound: Org31540/SR90107A (63118), SAS program: [redacted] Date:13OCT2000 23:03
NOTE: Deaths before the first study drug administration or deaths due to AEs which started after Day 49 were not reported.
Ref: Appendix 14.2.4.2.1

Table (9.2.1) 2 - Number (%) of Patients Who Died Between First Injection and Day 49 by Adjudication Criterion - All Treated Patients

Adjudication Criterion	Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)
Fatal PE	1 (0.1 %)	0 (0.0 %)
Hemorrhagic death	0 (0.0 %)	0 (0.0 %)
Death not associated with VTE or bleeding	1 (0.1 %)	4 (0.4 %)
Total	2 (0.2 %)	4 (0.4 %)

Compound: Org31540/SR90107A (63118), SAS program: [redacted] Date:13OCT2000 23:04
NOTE: One additional death after Day 49 was not associated with VTE or bleeding
Ref: Appendix 14.2.4.2.2

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Serious Adverse Events
The sponsor's table below shows the number of patients experiencing serious adverse events.

Reviewer's Comment: There were no statistically significant differences between treatment groups. The serious adverse event listed as "foetal disorder" is a hiatal hernia.

Table (9.2.2) 1 - Number (%) of Patients With Serious Adverse Events From First Injection to Day 11 by WHO Organ-Class and Preferred Term - All Treated Patients

WHO OrganClass Preferred Term	Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)
ANY EVENT	46 (4.0 %)	37 (3.3 %)
PLATELET,BLEEDING & CLOTTING DISORDERS		
TOTAL	10 (0.9 %)	7 (0.6 %)
HAEMATOMA	5 (0.4 %)	4 (0.4 %)
POST-OPERATIVE HAEMORRHAGE	4 (0.4 %)	1 (0.1 %)
HAEMORRHAGE NOS	1 (0.1 %)	1 (0.1 %)
GI HAEMORRHAGE	0 (0.0 %)	1 (0.1 %)
HAEMATURIA	1 (0.1 %)	0 (0.0 %)
PURPURA	0 (0.0 %)	1 (0.1 %)
SECONDARY TERMS		
TOTAL	8 (0.7 %)	6 (0.5 %)
SURGICAL SITE REACTION	6 (0.5 %)	6 (0.5 %)
POST-OPERATIVE PAIN	1 (0.1 %)	0 (0.0 %)
SPINAL CORD COMPRESSION *	1 (0.1 %)	0 (0.0 %)
BODY AS A WHOLE - GENERAL DISORDERS		
TOTAL	5 (0.4 %)	5 (0.4 %)
WOUND DRAINAGE INCREASED	1 (0.1 %)	2 (0.2 %)
FEVER	1 (0.1 %)	1 (0.1 %)
CHEST PAIN	0 (0.0 %)	1 (0.1 %)
DEATH	0 (0.0 %)	1 (0.1 %)
FATIGUE	1 (0.1 %)	0 (0.0 %)
LEG PAIN	1 (0.1 %)	0 (0.0 %)
PALLOR	1 (0.1 %)	0 (0.0 %)
RIGORS	1 (0.1 %)	0 (0.0 %)
MYO ENDO PERICARDIAL & VALVE DISORDERS		
TOTAL	2 (0.2 %)	6 (0.5)
MYOCARDIAL INFARCTION	2 (0.2 %)	5 (0.4)
ANGINA PECTORIS	0 (0.0 %)	2 (0.2)
MYOCARDIAL ISCHAEMIA	0 (0.0 %)	1 (0.1)
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS		
TOTAL	6 (0.5 %)	1 (0.1 %)
GAIT ABNORMAL	1 (0.1 %)	1 (0.1 %)
BRAIN STEM DISORDER	1 (0.1 %)	0 (0.0 %)
CONFUSION	1 (0.1 %)	0 (0.0 %)
CONVULSIONS GRAND MAL	1 (0.1 %)	0 (0.0 %)
PARAESTHESIA	1 (0.1 %)	0 (0.0 %)
PARESIS	1 (0.1 %)	0 (0.0 %)

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Table (9.2.2)1- *continued* - - Number (%) of Patients With Serious Adverse Events From First Injection to Day 11 by WHO Organ-Class and Preferred Term - All Treated Patients

WHO OrganClass Preferred Term	Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)
GASTRO-INTESTINAL SYSTEM DISORDERS		
TOTAL	3 (0.3 %)	3 (0.3 %)
COLITIS	0 (0.0 %)	1 (0.1 %)
DUODENAL ULCER	1 (0.1 %)	0 (0.0 %)
GASTRIC ULCER	1 (0.1 %)	0 (0.0 %)
ILEUS	1 (0.1 %)	0 (0.0 %)
ILEUS PARALYTIC	0 (0.0 %)	1 (0.1 %)
OESOPHAGITIS	1 (0.1 %)	0 (0.0 %)
PANCREATITIS	1 (0.1 %)	0 (0.0 %)
PEPTIC ULCER HAEMORRHAGIC	0 (0.0 %)	1 (0.1 %)
CARDIOVASCULAR DISORDERS, GENERAL		
TOTAL	2 (0.2 %)	3 (0.3 %)
OEDEMA PERIPHERAL	1 (0.1 %)	2 (0.2 %)
CARDIAC FAILURE	0 (0.0 %)	1 (0.1 %)
HYPOTENSION	1 (0.1 %)	0 (0.0 %)
HEART RATE AND RHYTHM DISORDERS		
TOTAL	2 (0.2 %)	3 (0.3 %)
CARDIAC ARREST	1 (0.1 %)	1 (0.1 %)
FIBRILLATION ATRIAL	1 (0.1 %)	1 (0.1 %)
TACHYCARDIA	0 (0.0 %)	1 (0.1 %)
MUSCULO-SKELETAL SYSTEM DISORDERS		
TOTAL	2 (0.2 %)	3 (0.3 %)
BONE DISORDER	2 (0.2 %)	1 (0.1 %)
ARTHROSIS	0 (0.0 %)	1 (0.1 %)
OSTEOSCLEROSIS	0 (0.0 %)	1 (0.1 %)
RED BLOOD CELL DISORDERS		
TOTAL	5 (0.4 %)	0 (0.0 %)
ANAEMIA	4 (0.4 %)	0 (0.0 %)
ANAEMIA HAEMOLYTIC	1 (0.1 %)	0 (0.0 %)
RESPIRATORY SYSTEM DISORDERS		
TOTAL	2 (0.2 %)	3 (0.3 %)
PNEUMONIA	1 (0.1 %)	1 (0.1 %)
CYANOSIS	1 (0.1 %)	0 (0.0 %)
DYSPNOEA	1 (0.1 %)	0 (0.0 %)
HYPOXIA	0 (0.0 %)	1 (0.1 %)
RESPIRATORY DEPRESSION	0 (0.0 %)	1 (0.1 %)
RESPIRATORY INSUFFICIENCY	1 (0.1 %)	0 (0.0 %)
RESISTANCE MECHANISM DISORDERS		
TOTAL	2 (0.2 %)	2 (0.2 %)
POST-OPERATIVE WOUND INFECTION	1 (0.1 %)	2 (0.2 %)
SEPSIS	1 (0.1 %)	0 (0.0 %)

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