Study 095-002 [redacted] Efficacy Results – Patients Having Qualifying Examination up to Day 11

Endpoint	Number of Patients with Events (%)		
	Org31540/SR90107A	Enoxaparin	p-value
Total VTE	45/361 (12.5%)	101/363 (27.8%)	2.7×10^{-7}
Total DVT	45/361 (12.5%)	98/363 (27.0%)	1×10^{-6}
Proximal DVT	9/368 (2.4%)	20/372 (5.4%)	0.057
Distal DVT only	35/372 (9.4%)	78/366 (21.3%)	9×10^{-6}
Total PE	1/361 (0.3%)	4/363 (1.1%)	0.37
Fatal PE	0/361 (0.0%)	1/363 (0.3%)	
Non-fatal PE	1/361 (0.3%)	3/363 (0.8%)	

Table based on tables in Medical Officer's Review (M. Lu), pp. 166 and 167

Events in the operated leg were several-fold more common than in the non-operated leg. In this study Org31540/SR90107A was highly statistically significantly superior to enoxaparin with regard to the primary efficacy endpoint, VTE. However, again the result is carried predominantly by difference in DVT, particularly, distal DVT, though there is a strong trend favoring Org31540/SR90107A for fewer proximal DVT and a trend favoring Org31540/SR90107A for fewer PE in the few PE events that occurred. Results were similar across demographic parameters and across features of surgery, except for use of cement. Results for Org31540/SR90107A were much stronger in the U.S.A. than in Canada as shown below.

Study 095-002 [redacted] Incidence of VTE by Country

	Number of Patients (%)		p-value
	Org31540/SR90107A	Enoxaparin	
U.S.A.	32/289 (11.1%)	85/286 (29.7%)	2.6×10^{-8}
Canada	13/72 (18.1%)	16/77 (20.8%)	0.69

Based on information and tables in Medical Officer's review (M. Lu), pp. 170 and 171

There were few deaths in this study, 1 in the Org31540/SR90107A group and 2 (1 due to PE) in the enoxaparin group up to 11 days; up to Day 49 there were 2 deaths (1 due to PE) in the Org31540/SR90107A group and 3 (1 due to PE) in the enoxparin group. Symptomatic VTE were uncommon. Up to Day 11 three DVT in the Org31540/SR90107A group and 4 DVT in the enoxaparin group were symptomatic. These symptomatic DVT accounted for 6.7% (3/45) of Org31540/SR90107A DVT and 4.1% (4/98) of enoxaparin DVT. All PE were symptomatic. Patients were followed up to Day 49 for symptomatic VTE and experienced additional events as summarized in the following table. Numbers of additional events were comparable in the two groups.

Study 095-002 ——— Additional VTE Occurring from Day 11 – Day 49

	Number of Patients with Events (%)	
	Org31540/SR90107A	Enoxaparin
VTE	2/517 (0.4%)	3/517 (0.6%)
DVT	1/517 (0.2%)	2/517 (0.4%)
Non-fatal PE	1/517 (0.2%)	0/517 (0.0%)
Fatal PE	1/517 (0.2%)	1/517 (0.2%)

Based on table in Medical Officer's Review (M. Lu), p. 170

Study 095001 ——— Study 095001 was a multicenter, randomized, open-label, dose ranging study of Org31540/SR90107A (0.75 mg, 1.5 mg, 6.0 mg and 8.0 mg) once daily subcutaneously started post-operatively 6 hrs after incision closure in patients undergoing elective total knee replacement. Treatments were given for 5 to 10 days and mandatory bilateral venography was performed at Day 11. Primary efficacy endpoint was incidence of DVT during the treatment perios and secondary efficacy endpoints included VTE and PE. Evalautions were as for Study 9501.

A total of 318 patients were randomized at 19 U.S.A. sites and 316 received study drug. The 6.0 mg and 8.0 mg doses were terminated prematurely because of unacceptable rate of major bleeding (>3%). The 0.75 mg dose was terminated prematurely because of unacceptable rate of DVT. Patients ranged in age from 34 to 90 years (median, about 70 years) and 63.8% of patients were females. Seventy-two percent of patients had data available for efficacy evaluation. Mean days of exposure ranged from 5.7 to 6.1 days. Efficacy results for the efficacy evaluable population are summarized in the following table.

Study 095-002 ——— Efficacy Results – Patients Having Examination During Study Period

Endpoint	Number of Patients (%)				
	Org31540/SR90107A				
	0.75 mg	1.5 mg	3.0 mg	6.0 mg	8.0 mg
Total VTE	14/35 (40.0%)	21/74 (28.4%)	12/67 (17.9%)	5[a]/30 (16.7%)	4/22 (18.2%)
Total DVT	14/35 (40.0%)	21/74 (28.4%)	12/67 (17.9%)	4/30 (13.8%)	4/22 (18.2%)
Proximal DVT	0/35 (0.0%)	0/74 (0.0%)	0/67 (0.0%)	2/29 (6.9%)	0/22 (0.0%)
Distal DVT only	13/35 (21.5%)	19/74 (25.7%)	12/67 (17.9%)	2/29 (6.9%)	4/22 (18.2%)

[a] one patient had PE

based on sponsor's tables

There was a statistically significant dose response relationship within the Org31540/SR90107A range evaluated in this study.

Safety:
The safety database for Org31540/SR90107A includes over 5900 subjects and patients who have been exposed to Org31540/SR90107A in clinical studies in the U.S.A., Europe,

Canada, Australia, Argentina, South Africa and Japan. Over 3600 of these have received Org31540/SR90107A in studies for orthopedic indications. Most of the exposure has been at a dose of 2.5 mg daily administered subcutanously for 5 to 9 days. Doses of 6.0 mg daily and 8.0 mg daily were found to cause unacceptable major bleeding (>3% Of patients) in dose finding studies in hip replacement and knee replacement surgery.

In the Phase I/II trials for orthopedic indications, a total of 3595 patients received Org31540/SR90107A 2.5 mg. These patients ranged in age from 17 to 97 years (median, 70 years; Mean, 68.0 years). Sixty percent of patients were female; 96% of patients were Caucasian; 83% of patients had creatinine clearance ≥50 ml/min and fewer than 3% of patients had creatinine clearance <30 ml/min. About 10% of patients had history of cancer, 5% had history of myocardial infarction, 3% had history of stroke, and 4% had prior history of venous thromboembolic event. In these studies patients received Org31540/SR90107A for an average of 7 doses (maximum 11 doses). Important safety related events seen in the four pivotal orthopedic surgery trials are summarized in the following table.

Summary of Important Adverse Events Occurring in Pivotal Pivotal Orthopedic Efficacy Trials

Study/Treatment	Treated (N)	% of All Treated Patients								
		Bleeding			Deaths		Withdrawals Due to AEI			SAEs
		Major Bleeding	Any	Minor	Up to Day 11	Up to end of Followup	Total	Bleeding	Non-bleeding	
EFC2698										
Org31540/SR90107A	831	2.2%	6.3%	4.1%	0.3%	0.5%	3.6%	1.3%	2.3%	4.8%
Enoxaparin	842	2.3%	4.4%	2.1%	0.1%	0.3%	3.8%	0.4%	3.4%	4.2%
63118										
Org31540/SR90107A	1140	4.1%	8.0%	3.9%	0.0%	0.2%	1.6%	0.6%	1.1%	4.0%
Enoxaparin	1133	2.8%	6.2%	3.4%	0.2%	0.4%	1.3%	0.3%	1.5%	3.3%
EFC2442										
Org31540/SR90107A	1128	1.8%	3.3%	1.5%	0.3%	0.5%	2.9%	1.2%	1.7%	4.8%
Enoxaparin	1129	1.0%	3.1%	2.1%	0.1%	0.3%	3.1%	1.5%	1.6%	4.2%
095-002										
Org31540/SR90107A	517	2.1%			0.2%	0.4%	3.9%	1.4%	2.5%	7.4%
Enoxaparin	517	0.4%			0.4%	0.6%	2.5%	0.4%	2.1%	5.4%

Based on sponsor's tables

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Though there were no statistically significant differences between treatments for these adverse events, the Org31540/SR90107A groups tended to have numerically more serious events and major bleeding than did the enoxaparin groups. This may be due to sooner and longer exposure of patients to Org31540/SR90107A than to enoxaparin in the studies.

Incidence of bleeding with Org31540/SR90107A appeared similar across the three different types of surgery. Major bleeding occurred in 2.2% of hip fracture patients, 2.3% of total hip replacement patients and 2.1% of total knee replacement patients. The bleeding tended to occur early in the treatment (over 60% of cases within the first 3 days). Where the first active post-operative injection was given < 4 hours after surgery, the bleeding rate tended to be higher (4.7%). Bleeding-related events (e.g., hematoma, post-operative hemorrhage, anemia) increased with increasing Org31540/SR90107A dose.

About 65% of treated patients experienced at least 1 adverse event. The most common classes of adverse events during treatment were: body as a whole- general disorders (25.9% of patients), gastrointestinal events (24.5%); red blood cell disorders (19.7%), central and peripheral nervous system disorders (14.7%) and; platelet, bleeding and clotting disorders (12.4% of patients). The most common individual events are summarized in the following table. The frequency of these events was similar in Org31540/SR90107A- and enoxaparin -treated patients, except for anemia which tended to be higher in the Org31540/SR90107A-treated patients (19.6%) than in the enoxaparin-treated patients (16.9%):

Most Frequent Adverse Events in Patients Receiving Org31540/SR90107A 2.5 mg in Orthopedic Trials

Event	Number of Patients (%) (N=3616)
Any event	2359 (65.2%)
Anemia	707 (19.6%)
Fever	491 (13.6%)
Nausea	409 (11.3%)
Constipation	309 (8.5%)
Vomiting	212 (5.9%)
Insomnia	179 (5.0%)

Based on data in sponsor's tables

Among non-bleeding AEs, none were clearly dose-related. There was a suggestion of some dose- relationship of constipation, atrial fibrillation, urinary retention, and hyperglycemia.rinary retentdizziness and hepatic and biliary disorders (e.g., increased transaminases). There was more anemia and more post-operative hemorrhage with Org31540/SR90107A than with enoxaparin.

Patients with significant renal failure (serum creatinine >2.0g/dl) were excluded from these clinical trials by entry criteria. Patients with creatinine clearance <30ml/min accounted for about 5% of the study population; about 32% of patients had creatinine clearance 30-50ml/min. Among the patients who received Org31540/SR90107A in the

clinical trials, patients with decreased creatinine clearance had higher rates of bleeding than did patients with normal renal function as shown in the following table. This is consistent with the decreased renal clearance and increased half-life of the drug seen in pharmacokinetic studies.

Major Bleeding Adverse Events in Orthopedic Trials (Up to Day 11) by Weight and Renal Function

	Number of Patients with Major Bleeding (%)
Creatinine clearance (ml/min):	
Missing	1/155 (0.6%)
<30	4/83 (4.8%)
30-50	19/504 (3.8%)
50-80	31/1288 (2.4%)
≥80	25/1565 (1.6%)
Weight (kg):	
Missing	1/37 (2.7%)
<50	7/130 (5.4%)
50-100	63/3030 (2.1%)
≥100	9/398 (2.3%)

From sponsor's table

About 3.0% of patients receiving Org31540/SR90107A and 3.2% of patients receiving enoxaparin experienced decrease in platelet counts to less than 100 x 10^9/L. Six Org31540/SR90107A-treated patients and 1 enoxaparin-treated patient had decreases to <50 x 10^9/L. About 4.3% of Org31540/SR90107A patients and 3.3% of enoxaparin patients developed antiplatelet antibodies after beginning active study drug. This suggests that patients receiving fondaparinux may have some risk of developing platelet-associated complications (e.g., drug-induced thrombocytopenia and thrombosis) as occurs with heparin and low molecular weight heparins.

About 20-27% of patients treated with Org31540/SR90107A and 26-31% of patients treated with enoxaparin showed significant elevations in hepatic transaminases during the studies. This is consistent with the transient and apparently clinically no-significant transaminase elevations seen with heparin and low molecular weight heparins. Serum bilirubin appeared to increase with increasing Org31540/SR90107A dose (1.7% with dose <2.5mg to 2.8% with doses >2.5mg). About 2.1% of patients receiving Org31540/SR90107A 2.5mg and 1.5% of patients receiving enoxaparin showed elevation in total bilirubin >2.0g/dl.

Safety update (covering period 5/11/00-2/28/01) included 1 case of torsade des pointes with unclear causality. This is the only such case known for this drug.

Discussion:
Efficacy: Efficacy results from the four pivotal trials for orthopedic indications are summarized in the following table:

Summary Table of Efficacy Results

Study	N				% of treated pts missing efficacy data	% of Primary Efficacy Population							
	Randomized	Treated	Treated and appropriate surgery	Primary Efficacy Population		Total VTE	Total DVT	Proximal DVT[+]	Distal DVT only[+]	Total PE	Fatal PE	Non-Fatal PE	Symptomatic DVT
EFC2698 [hip fracture]	1711												
Org31540/SR90107A	849	831	831	626	24.7%	8.3%	7.8%	0.9%	6.7%	0.5%	0.5%	0.0%	0.1%
Enoxaparin	862	842	840	624	25.9%	19.1%	18.6%	4.3%	15.0%	0.5%	0.3%	0.2%	0.1%
p-value						2.6×10^{-8}	1×10^{-8}	0.0001	2×10^{-6}				
63118 [hip replacement]	2309*												
Org31540/SR90107A	1155	1140	1129	908	20.4%	4.1%	4.0%	0.7%	3.3%	0.2%	0.0%	0.2%	0.3%
Enoxaparin	1154	1133	1123	919	18.9%	9.2%	9.0%	2.5%	7.3%	0.2%	0.0%	0.2%	0.1%
p-value								0.0021	0.0001				
EFC2442 [hip replacement]	2275												
Org31540/SR90107A	1138	1128	1126	787	30.2%	6.1%	5.6%	1.7%	4.3%	0.6%	0.0%	0.6%	0.9%
Enoxaparin	1137	1129	1128	797	29.4%	8.3%	8.2%	1.2%	6.8%	0.1%	0.1%	0.0%	0.1%
p-value						0.099	0.047	0.42	0.037	0.122			0.0062
095-002 [knee replacement]	1049												
Org31540/SR90107A	526	517	517	361	30.2%	12.5%	12.5%	2.4%	9.4%	0.3%	0.0%	0.3%	0.6%
Enoxaparin	523	517	517	363	29.8%	27.8%	27.0%	5.4%	21.3%	1.1%	0.3%	0.8%	0.8%
p-value						2.7×10^{-7}	1×10^{-6}	0.057	9×10^{-6}	0.37			

* does not include 15 patients at a center that had study irregularities

+ N includes all patients who were evaluable for proximal and/or distal DVT

reviewer's table based on data in sponsor's tables

The sponsor has provided one adequate and well-controlled study for prophylaxis of deep vein thrombosis which may lead to pulmonary embolus in each of the following indications: hip fracture surgery (Study EFC2698), total hip replacement surgery (Study 63118), and total knee replacement surgery (Study 095-002). Each study in addition to being internally consistent and having a robust primary efficacy result for the studied indication is supported also by the studies for the other two indications. The one unsuccessful study in total hip replacement (Study EFC2442) though not statistically convincing and having some internal inconsistency in efficacy result across countries, was nevertheless, generally consistent with a treatment effect of Org31540/SR90107A.

To date no products have been approved for the broad indication being requested by the sponsor. Other products approved for uses similar to those being proposed by the sponsor include the low molecular weight heparins (enoxaparin for hip and knee replacement; dalteparin for hip replacement, and ardeparin for knee replacement [ardeparin not currently marketed]) and danaproid for hip replacement. No drug has been approved for use in hip fracture surgery. The approval of these products has been based on studies for use of the drug in each of the target populations. While it is reasonable that an anticoagulant drug will have a physiologic anticoagulant effect in all of these populations, the benefit/risk relationship of the drug may not be the same across these populations. Therefore, studies in each of the target population have been required. In the current application the sponsor has provided one study demonstrating safety and effectiveness of Org31540/SR90107A in hip fracture surgery, one study demonstrating safety and effectiveness of Org31540/SR90107A in knee replacement surgery, one study demonstrating safety and effectiveness of Org31540/SR90107A in hip replacement surgery and one failed study in hip replacement surgery. Evidence for safety and effectiveness of Org31540/SR90107A in the U.S. population comes mainly from one study in knee replacement surgery.

The sponsor's p-values for the between treatment efficacy comparisons imply a degree of precision and level of certainty that may be misleading. All of these studies had a considerable proportion of patients missing data for the primary efficacy assessment. Experience has shown that for these indications where the efficacy assessment involves a highly invasive test such as venography, the percentage of patients missing efficacy data is substantial and probably cannot be reduced much below 20%. The proportions of patients in the two treatment groups and the comparability of the characteristics of the randomized and efficacy evaluable populations for the two treatment groups are reassuring that the studies were well-designed and conducted and allow a valid comparison of the two treatments. However, we cannot be reasonably sure that the event rates seen in the efficacy evaluable patients are the same as would be seen in the non-evaluable patients. The reasons for non-evaluable venograms are varied but may include factors that may affect the thrombosis itself (e.g., small veins, obesity). These factors may be difficult to discern. Note that in all these studies the rates of clinically symptomatic DVT were very low. Also, note that the time to first dose in these studies was shorter and the number of daily doses received by the patient were generally more

for the Org31540/SR90107A patients than for the enoxaparin patients. This may have biased the results in favor of Org31540/SR90107A. Care should be taken in the description of the studies in the Clinical Trials section of the labeling to not overstate the degree of precision and level of certainty we these studies provide about the quantitative clinical benefit of Org31540/SR90107A relative to enoxaparin in these settings.

These indications generally affect more elderly patients and there is limited applicability to the pediatric population. Therefore, a waiver for pediatric studies for these indications has been granted.

The information available regarding use of Org31540/SR90107A in races other than Caucasians is extremely limited. While there is no reason to expect that the effect of Org31540/SR90107A in other races should be different from that in the populations studied in this application,

Safety:
The safety profile of Org31540/SR90107A mainly reflects its pharmacologic action as an anticoagulant, with bleeding adverse events being the most common and most severe.

Patients with significant renal failure (serum creatinine >2.0 g/dL) were excluded from the clinical efficacy trials. Because Org31540/SR90107A is cleared almost exclusively by the kidney

In the trials renal failure and low weight were associated with more major bleeding.

There is no antidote for fondaparinux and its half-life is long (15-20 hrs). Resolution of anticoagulant-related toxicity is dependent on renal clearance of the drug form the body. There appears to be minimal metabolism of the drug.

This drug may provide a potential benefit in that while Org31540/SR90107A may not be devoid of antigenic potential, it may be expected to have a lower incidence of adverse events such as drug-induced thrombocytopenia.

Conclusions and Recommendations:
The sponsor has provided substantial evidence that fondaparinux sodium is effective for thromboprophylaxis in the populations studied. The adverse event profile of the drug in the clinical trials that have been done is acceptable for marketing of the product with appropriate labeling.

Fondaparinux sodium (Arixtra) is approvable for the following indications:

Prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism:

- In patients undergoing hip fracture surgery;

- In patients undergoing hip replacement surgery; and
- In patients undergoing knee replacement surgery.

The dose should be 2.5 mg daily administered subcutaneously beginning 6 hours after surgery and continuing for up to 9 days.

Efficacy concerns that should be reflected in the labeling include:

- Uncertainty as to whether or not fondaparinux is superior to enoxaparin for the indications hip replacement surgery and knee replacement surgery. It should be noted that: (1) a significant percentage of patients (>20%) had missing efficacy data (mainly because of no or inadequate venogram), consequently, either an outcome result must be assumed for these patients or they must be excluded from analysis; (2) only a small proportion of venographically demonstrated DVT were symptomatic, (3) in the clinical trials fondaparinux-treated patients on average received their active dose sooner after surgery and received more active doses than did the enoxaparin treated patients.

- Lack of appropriate representation of racial diversity of U.S.A. population in the patient population studied in the clinical trials.

Safety concerns that should be reflected in the labeling include:

- Risk of bleeding adverse events that may occur in all patients
- Enhanced risk of bleeding with significantly impaired renal function (Because of this increased risk and the specific exclusion of these patients from the clinical trials, these patients should not be included in the population for which fondaparinux is indicated at this time)
- Enhanced risk of bleeding in patients with low weight (<50kg).
- Include Black Box Warning regarding increased risk of spinal/epidural hematomas in patients undergoing neuraxial anesthesia or spinal puncture
- Possible risk of drug-induced platelet toxicity, as for heparin and low molecular weight heparins. The current database is not sufficiently large to completely evaluate this risk.
- Serious and severe adverse events
- There is no antidote for fondaparinux, so resolution of overdosage is dependent on clearance.

The sponsor should be asked to commit to the following post-marketing studies:

Additional recommendations including labeling as expressed in the Medical Officer's Efficacy Review (M. Lu) and Medical Officer's Safety Review (A.Farrell) should be addressed by the sponsor.

Requests and labeling recommendations from other disciplines including CMC, Microbiology, Pharmacology/Toxicology, Clinical Pharmacology and Biopharmaceutics and DCRH should be addressed by the sponsor.

cc:
NDA 21-345
HFD-180/Division File
HFD-180/KOliver
HFD-180/MLu
HFD-180/AFarrell
HFD-180/KRobie-Suh
HFD-715/TPermutt
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/s/

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MEDICAL OFFICER

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Division of Gastrointestinal and Coagulation Drug Products

Medical Officer's Safety Review

NDA:	21345, BM
Sponsor:	Fonda BV
Drug Product:	Arixtra™ (fondaparinux sodium, Org31540/SR90107A)
Date submitted:	February 15, 2001, June 18, 2001
Date assigned:	March 15, 2001, June 19, 2001
Review Completed:	July 13, 2001
Reviewer:	Ann T. Farrell MD

Table of Contents for Safety Review

Reviewer's Table

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Table of Abbreviations

	List of Abbreviations
Ab	Antibody
AE	Adverse event
ALT	Alanine aminotransferase
APTT or APTT	Activated partial thromboplastin time
ASA	Acetyl salicylic acid
AST	Aspartate aminotransferase
ATIII	Antithrombin III
AUC	Area Under the Curve
AV	Arteriovenous
AVC	Abrupt Vessel Closure
b.i.d.	Twice a day
BUN	Blood urea nitrogen
CIAC	Central Independent Adjudication Committee
CRF	Case report form
CT	Computed tomography
DL	Deciliter(s)
DMC	Data Monitoring Committee
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
Fxa	Activated Factor Xa
Hct	Hematocrit
Hgb	Hemoglobin
HIT	Heparin-Induced Thrombocytopenia
HITTS	Heparin-Induced Thrombocytopenia and Thrombosis
ILFD	Intra-luminal filling defect
IRB	Institutional Review Board
ITT	Intent-to-treat
IU	International unit
IV	Intravenous
Kg	Kilogram
L	Liter
LFT	Liver function test
LMWH	Low molecular weight heparin
MI	myocardial infarction
Mg	milligram
ML	milliliter
Mmol	millimole(s)
NSAID	Nonsteroidal anti-inflammatory drug
o.d.	Once a day
PDR	Physicians' Desk Reference
PE	Pulmonary embolism
PK/PD	Pharmacokinetic/Pharmacodynamic
PRBC	Packed red blood cell
PT	Prothromobin time
RH	Relative humidity
RTPA	Recombinant Tissue Plasminogen Activator
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SGOT	Serum glutamate oxaloacetate transaminase
SGPT	Serum glutamate pyruvate transaminase
SRA	Serotonin Release Assay
THR	Total hip replacement
UFH	Unfractionated heparin
US	Ultrasound
ULN	Upper limit of normal
V/Q	Ventilation/perfusion
VTE	Venous thromboembolic event
WHO	World Health Organization
WHO-ART	World Health Organization-adverse reaction terminology dictionary

Reviewer's Table

Executive Summary

I. Recommendations

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.

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)

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. This safety review discusses the fondaparinux NDA pre-clinical and clinical safety database, reviews the sponsor's proposed labeling, and recommends further drug development study. This review does not include the safety update.

A. Recommendation on Approvability

For fondaparinux, the benefit/risk analysis weighs the risk reduction of a thromboembolic event after major orthopedic surgery with the bleeding risk and must include adverse reactions specific to the pentasaccharide.

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

The application is approvable from a clinical safety perspective in the studied populations. The reader is referred to Dr. Min Lu's Medical Officer Efficacy review of this NDA for approvability from an efficacy perspective.

B. Safety Recommendations on Phase 4 Studies and/or Risk Management Steps

Risk Management
1. The sponsor should revise the label as recommended in Appendix F.

Phase 4 Commitments
2. The sponsor should collect safety information on the use of the drug in hepatic impairment patients.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program- See Dr. Min Lu's Medical Officer Efficacy Review

B. Efficacy-See Dr. Min Lu's Medical Officer Efficacy Review

C. Safety

Major safety concerns identified in pre-clinical and clinical phase I, II, III testing of this anticoagulant drug included a long-half-life, renal excretion, bleeding risk, thrombocytopenia, heparin antibodies, and skin reactions.

Over 5900 subjects and patients have been exposed to fondaparinux in clinical studies. More than 3600 patients enrolled and were treated with fondaparinux in the phase II and III clinical orthopedic trials. These patients had nearly normal renal function (serum creatinine < 2.0mg/dL) and most were treated for 5-9 days (maximum 11 days) with fondaparinux 2.5 mg daily. Study safety data collection continued up to Day 49. The major safety adverse event (AE) observed was

bleeding. The overall bleeding rate associated with fondaparinux was higher compared with enoxaparin (5.7% and 4.8% respectively). Patients with body weight less than 50 kg, older patients > 65 years of age, and those with reduced renal function had increased bleeding and AE rates. Overall, there were no statistically significant differences for serious adverse events (SAEs) or adverse events (AEs) between fondaparinux and enoxaparin. During the treatment period, the most frequent SAE category was platelet, bleeding, and clotting disorders (fondaparinux 1% and enoxaparin 0.7%).

The table below shows AEs seen with greater frequency for the fondaparinux patients compared with the enoxaparin patients. Statistically significant differences were noted for anemia and post-operative hemorrhage in favor of enoxaparin.

Reviewer's Comment: The statistically significant differences seen for anemia and post-operative hemorrhage may have been due to the timing of study drug administration during the clinical trials. In most trials, fondaparinux was administered approximately 6 hours after surgery, whereas, enoxaparin was administered approximately 12-24 hours after surgery.

Adverse Events Seen with Greater Frequency for Fondaparinux Compared with Enoxaparin in Phase II/III Clinical Orthopedic Trials

Adverse Event	Fondaparinux 2.5 mg daily (N=3616)	Enoxaparin (40 mg QD or 30 mg BID) (N=3956)	P value (Fisher's exact)
Anemia	707 (19.6%)	694 (17.6%)	0.03
Hypokalemia	152 (4.2%)	164 (4.1%)	0.91
Hypotension	126 (3.5%)	125 (3.1%)	0.44
Urinary tract infection	136 (3.8%)	135 (3.4%)	0.23
Bullous eruption	90 (2.5%)	86 (2.2%)	0.40
Urinary retention	85 (2.4%)	91 (2.3%)	0.76
Hematoma	73 (2%)	74 (1.9%)	0.62
Post-operative Hemorrhage	53 (1.5%)	36 (0.9%)	0.03

Reviewer's Table

Overall, thrombocytopenia was seen with nearly equal frequency for both fondaparinux and enoxaparin patients. (2.9% and 3.1% respectively). Overall, the rates of positive ELISA test for heparin antibodies were fondaparinux 4.3% and enoxaparin 3.3%. Serotonin release tests were performed only in ELISA positive patients. Among ELISA positive patients, the rates of positive serotonin release test were fondaparinux 16.5% and enoxaparin 11.4%. Overall, the frequency of patients having both thrombocytopenia and a positive ELISA test was 2.9% for both treatment groups. Overall, the frequency of patients having both a venous thromboembolism (VTE) and positive ELISA test was for fondaparinux 6.7% and enoxaparin 9.8%.

These results suggest that fondaparinux may be associated with heparin induced thrombocytopenia (HIT) and thrombosis (HITTS). Heparin induced thrombocytopenia and thrombosis is a clinical diagnosis based on the presence of VTE and thrombocytopenia in a patient with recent or ongoing exposure to heparin or a low molecular weight heparin (e.g., enoxaparin). Laboratory testing for ELISA antibodies and serotonin release supports the clinical diagnosis. In every phase III orthopedic clinical trial, the same adverse events (thrombocytopenia, VTE, positive ELISA, and positive serotonin tests) are observed.

The following issues preclude making a definitive statement that fondaparinux causes HIT/HITTS

1) the increased risk of a thromboembolic phenomenon after orthopedic surgery/immbolization
2) the incomplete information regarding prior heparin exposure in trial patients
3) the changing definition of HIT/HITTS
4) the trial design
5) incomplete characterization of the heparin antibody formed including any cross reactivity with fondaparinux

Risk management options include informing healthcare providers and the public via the labeling about the fact that both thrombocytopenia and heparin antibodies have been associated with fondaparinux treatment.

Drug-drug interaction studies were performed. Aspirin, warfarin, piroxicam, and digoxin did not influence fondaparinux steady state pharmacokinetics/pharmacodynamics (anti-Xa activity). Co-administration did not affect warfarin pharmacodynamics (PT, APTT, FVII, and FVIIa), aspirin (arachidonic acid and collagen induced platelet aggregation, and bleeding time), piroxicam (collagen induced platelet aggregation and bleeding time) or digoxin pharmacokinetics.

Fondaparinux risk management steps include revisions of the sponsor's proposed labeling and recommendations for additional information listed in the Executive Summary.

Fondaparinux is not approved in any country therefore no post-marketing information is available.

D. Dosing

Fondaparinux is an indirect thrombin generation inhibitor with nearly complete bioavailability (107%) after subcutaneous (SC) injection compared with IV administration. Fondaparinux half-life is approximately 17 hours. After injection, t_{max} occurs at 1.7 $\pm$ 0.4 hours. The major elimination mechanism is renal excretion. The sponsor proposes fondaparinux at the dose of 2.5mg administered subcutaneously once daily. 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 and 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 additional details, the reader is referred to the individual trial efficacy and safety reviews. The final dose ranging trial (DRI2643) in hip replacement patients 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 0.75 mg 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 30 mg BID (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 daily subcutaneously would provide the optimal benefit/risk (VTE prophylaxis/hemorrhage) ratio for comparison trials with enoxaparin. The 2.5 mg dose was chosen to reduce the major bleeding rate observed with higher fondaparinux doses. This dose was studied in the major clinical orthopedic trials. Trial results support the use of fondaparinux 2.5 mg administered subcutaneously daily.

E. 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.

Gender
No known gender identified pharmacologic differences exist for fondaparinux. 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.

Race
The sponsor's data and comments concerning ethnicity are:

1) The sponsor's covariate analyses for each study suggested there was no race drug interaction.
2) The sponsor stated that there were too few non-Caucasians to allow any conclusion of race effect on bleeding and AE.
3) The sponsor compared plasma clearance in Black patients with Caucasian patients and found no significant differences.
4) Several PK/PD studies with healthy Japanese volunteers suggested 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.

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

Reviewer's Comment: This reviewer does not recommend additional studies in elderly patients.

Renal impairment
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.

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 secondary hemostasis. This reviewer recommends the sponsor collect information on fondaparinux use 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 for the proposed indications.

Pediatric Development 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.

Clinical Review

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.

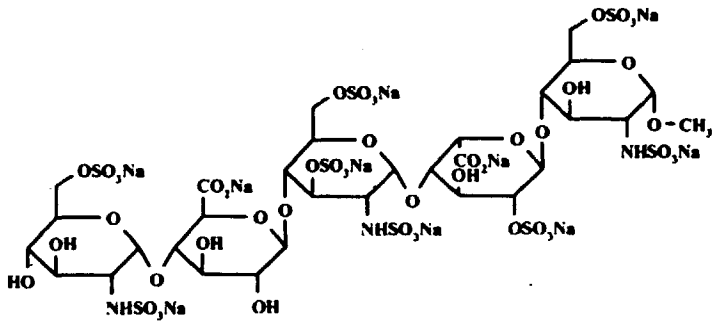
This safety review discusses the fondaparinux NDA pre-clinical and clinical safety database, reviews the sponsor's proposed labeling, and recommends further drug development study. This review does not include the safety update.

I. Introduction and Background - See Dr. Min Lu's Medical Officer Efficacy Review

II. Clinically Relevant Findings from Chemistry, Toxicology, Microbiology and Biopharmaceutics Reviews

Chemistry

Drug Substance
The chemical structure is reproduced below.



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The drug substance appears as a white to almost white powder.

The sponsor's table below lists the drug substance characteristics.

APPEARS THIS WAY
ON ORIGINAL

Drug Manufacture

The manufacturing process involves more than [redacted] chemical steps, for further details see the Agency's Chemistry, Manufacturing, and Control Review of this NDA.
The active substance is hygroscopic and stored in a glass container. Stability testing suggested that no significant degradation or content change is observed at 25°C/60% relative humidity (RH) or 30°C/60% RH after 12 months or at 40°C/75% RH after 6 months.

Drug Product
The sponsor's table below shows the drug product composition for the commercial injection (2.5mg/0.5 mL in pre-filled syringe). Bioequivalence studies have been conducted with the clinical trial formulation and the commercial formulation. For further details, see the Agency's Office of Biopharmaceutics Review.

Table (4.2.1) 1 - Composition of the Medicinal Product (Formula 2B2)

Ingredients	Quantity Per Unit	Function	Reference to Standards
Active substance			
Org31540/SR90107A	2.5 mg	Active substance	In-house monograph
Excipients			
Sodium chloride	[redacted]	[redacted]	USP
Water for injection	[redacted]	[redacted]	USP
[redacted]	[redacted]	[redacted]	NF

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The solution [redacted]

The primary container/closure system is a 1 mL pre-filled, fixed needle, single dose syringe. This system consists of a barrel with a needle, a needle shield, and a stopper. A secondary container closure system is designed to prevent needle stick injuries

Stability studies have been conducted with the prefilled syringes. The pre-filled syringes were photostable and stability results did not differ from those conducted with the drug substance. For details, see the Agency's Chemistry, Manufacturing, and Control Review.
The sponsor recommends storage at 25°C and states that the drug product has a shelf-life of two years.

Pharmacology

Fondaparinux is a synthetic pentasaccharide with indirect antithrombin activity, which results from fondaparinux binding to antithrombin III (ATIII). This binding results in the neutralization of Factor Xa (FXa), thus inhibiting thrombin formation and thrombus development.

In vitro studies

Mechanism of action

[redacted] studies demonstrated that fondaparinux induced a conformational change in ATIII at physiologic pH and ionic strength with 1:1 stoichiometry. Enzymatic studies suggested that fondaparinux enhanced ATIII activity by approximately 300 times. Linear correlation has been observed with increasing fondaparinux concentrations and increases in anti-FXa activity and ATIII mediated inhibition. Studies have demonstrated an inhibition of FXa and thrombin generation in plasma assays. Studies have demonstrated no change in PT and APTT values at pharmacologically active concentrations.

Arterial Thrombosis Studies

Single dose IV and SC studies demonstrated that fondaparinux dose-dependently inhibited thrombus formation in a rat AV shunt model and this inhibition correlated with the degree of anti-FXa activity. Fondaparinux was not as successful inhibiting arterial thrombus formation compared with venous in this model.

Safety Pharmacology

Single doses of up to 30 mg/kg administered to rats did not induce any neurotrophic, psychotrophic, or neurobehavioral effects. Single doses of up to 10 mg/kg administered to mice did not induce any noticeable effects in the conditioned taste aversion or ambulation tests. Single doses of 3.6mg/kg given to anesthetized Beagle dogs at 3.6 mg/kg IV caused no noticeable changes in cardiovascular hemodynamic, electrocardiogram (EKG), hematologic parameters, and respiratory function. In vitro testing of fondaparinux did not demonstrate prolongation of action potential duration in piglet Purkinjie fibers.

In vitro testing demonstrated that fondaparinux slightly inhibits thrombin-induced platelet aggregation but not adenosine diphosphate (ADP) or collagen induced aggregation. In vitro testing suggested that fondaparinux did not interact with platelet factor 4 (PF4) and did not cross react with heparin induced antibodies.

Animal Drug-Drug Interaction Studies

Fondaparinux given with recombinant tissue plasminogen activator (rTPA) or streptokinase was associated with increased thrombolysis. Fondaparinux given with aspirin 100mg/kg or ticlopidine 50mg/kg resulted in greater inhibition of thrombus formation on stents than ASA or ticlopidine alone.

Animal Biopharmaceutics

The sponsor performed combined animal pharmacokinetic/toxicologic studies. The sponsor's table below shows comparative species data after a single subcutaneous injection. Fondaparinux was rapidly absorbed from the injection site with peak plasma levels occurring after 1-2 hours. At doses > 0.4 mg/kg, increases in AUC in rats and rabbits were less dose proportional.

Table (5.3.2) 1 - Plasma Pharmacokinetic Parameters in Male Animals and Humans Following a Single Administration of Org31540/SR90107A (Definitive Studies) [Mean]

		C_{max} (µg/mL)	t_{max} (h)	$t_{½}$ (h)	$AUC_{0-\infty}$ (µg·h/mL)	CL (mL/h/kg)	Vd (mL/kg)
Rat IV	0.4 mg/kg	na	na	1.1	4.0	90	100
	2 mg/kg	na	na	1.2	9.4	190	190
	10 mg/kg	na	na	1.1	27.8	310	210
Macaque SC	10 mg/kg	11.3	1-2	5.7	114	80	662
Human SC	mg (0.035 mg/kg)[a]	0.34	1.7	17.2	6.65	4.82[b]	117[c]

na = not applicable
[a] Based on average human bodyweight of 70 kg.
[b] Converted from units of mL/min in the original report.
[c] Converted from units of L in the original report.
Ref: Rat [SDGRR4528], Macaque [ABS0300], Human [BDR3780]

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Distribution and Protein Binding

Radioactively labeled fondaparinux was given to rats via a single SC injection. After initial distribution, the highest concentrations were seen in the bladder and blood. Levels fell over 24 hours and by 48 hours radioactivity was cleared from most tissues except for kidney cortex and cartilage.

Radioactively labeled fondaparinux given to pregnant and lactating rats demonstrated slight transmittal to the fetus and minimal concentration in breast milk.

At low concentrations approximately 92-93% of fondaparinux is protein bound. At higher concentrations approximately 70% is protein bound. The sponsor's table below shows the binding relationship observed between fondaparinux and antithrombin III.

Binding fractions in human plasma and purified antithrombin

concentration (ng/mL)	500	1000	2000	3000	5000	7500	10000	30000	50000
binding fraction in human plasma (%)	98.6	98.4	97.0	95.3	91.1	87.5	85.1	80.3	80.7
binding fraction with antithrombin (%)	97.4	96.4	94.0	90.7	72.2	52.1	42.4	28.7	27.2

binding fraction (%) = 100 x (bound concentration/total concentration)

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Metabolism
No evidence of in vitro or in vivo metabolism was detected. Two-week repeat dose studies did not demonstrate any effect on liver cytochrome P450 activity.

Excretion
The major pathway for excretion in rats and macaques was urine. Approximately 91-95% of radioactivity was recovered in rat urine and approximately 81-82% of radioactivity was recovered in macaque urine. In both species renal excretion was rapid with the majority of drug excreted in the first 24 hours and only 6-8% recovered after 24 hours. Fecal excretion accounted for less than 8% in the rat and less than 0.5% in the macaque.

Toxicity
Single dose, repeat dose, reproductive, genetic, antigenecity studies were conducted. The sponsor conducted both preliminary and single dose animal studies under Standard Operating Procedures but not always under Good Laboratory Practices. Results obtained suggested the highest dose for the initial single dose studies was 40 mg/kg and for the repeat dose toxicology studies 10 mg/kg/day. After one treatment related death in a 3 month chronic toxicity study at 10 mg/kg/day, the sponsor considered it unethical to increase the dose testing further. This dose was associated with mortality in other pre-clincal studies. The sponsor's table below outlines the comparative exposure information between species.

Table (5.4.8) 1 - Summary of Animal and Human Exposure Data

	Route	Dose	Systemic Plasma Exposure	
			AUC (μg·h/mL)[a]	Exposure Ratio
Human [BDR3780]	SC	2.5 mg/d	6.65	
Rat [SDGRR4528]	IV	10 mg/kg/d	34.6[b]	5.2
Rabbit [TER0302]	SC	10 mg/kg/d	84.1	12.6
Macaque [ABS0300]	SC	10 mg/kg/d	105[b]	15.8

[a] $AUC_{0\text{-}inf}$ in human and rat; $AUC_{0\text{-}24}$ in rabbit and macaque
[b] Mean of male and female exposure

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Single Dose Toxicity Studies

Single dose toxicity studies conducted in mice, rats, and monkeys demonstrated injection site hematoma formation and minor changes in weight. No mortality was seen. For details, see the Agency's Pharmacology/Toxicology Review of this NDA.

Repeated Dose Toxicity Studies

The majority of adverse events were injection site hematomas, or handling site hematomas, or self-induced trauma hematomas. One female rat died from handling trauma, which resulted in nape hemorrhage. Monkeys experienced more frequent and severe adverse reactions compared with rats. Six of fifteen monkeys died or were prematurely sacrificed. These deaths resulted from severe anemia, hemorrhage, and handling trauma.

After the last IV and SC injection, activated partial thromboplastin times (APTT) and prothrombin times (PT) remained prolonged for 1 hr (IV) and 2 hrs (SC). Mild PT elevations were noted at doses at 0.4mg/kg/day and moderate elevations were noted at 10 mg/kg/day compared with control.

Reproductive and development toxicity
The reproductive and development toxicity studies used SC administration. Rat placenta levels were ten percent of maternal plasma levels and detectable at 0.5 hrs following administration. Negligible levels were noted in the female rat and fetus at 24 hours following administration. Approximately 0.06% of the administered dose was excreted during provoked milk collection over a 24-hour period.

Adverse effects seen during the reproduction studies were mainly due to injection site hemorrhage and anemia for the parents. No significant effects on fertility, parturition, and lactation were noted. One of 132 fetuses/liveborn rabbits had a meningocele. One of 10 rat fetuses had both malrotation of hind paw and gastroschisis. One of more than 100 rabbit offspring/fetuses had congenital abnormalities, which were malformation of the spine and gastroschisis.

Genetic testing

Fondaparinux was not mutagenic in the following tests:.

1) in vitro Ames test
2) mouse lymphoma cell forward mutation
3) human lymphocyte chromosomal aberration
4) in vivo rat micronucleus test

Fondaparinux has not been tested for carcinogenic potential in long term animal studies.

Additional In vitro testing

The sponsor performed three in vitro tests because thrombocytopenia and heparin antibodies had been noted in clinical trials.
Reviewer's Comment: The studies (1 and 2) reported below did not demonstrate significant serotonin release with fondaparinux or SR 90107A; however, this assay method is known to be relatively insensitive. The third study did not demonstrate significant binding of Org 31540/SR 90107A to platelet factor 4.

Study #1-

Title: Comparison of cross-reactivity for induction of heparin induced thrombocytopenia (HIT) between heparin and Org 31540/SR 90107A

Date of Report: May 18, 1995

This study evaluated ^{14}C-serotonin release from three healthy volunteers' platelets exposed to heparin or Org 31540/90107A. The platelets were incubated with HIT patients' sera. The sponsor's results are shown below.

RESULTS

Table 1 : Effect of Org31540/SR90107A and heparin on cross-reactivity with HIT serum in the serotonin release assay. The results are expressed in percentage release of serotonin.

	Concentration (µg/ml)	SRA assay run			
		Sera A/B/C EA 1157	Sera A/B EA 1159	Sera A EA 1186	mean
heparin	0.625-1.25				95
	625				0
Org 31540/SR 90107A	0.14				14
	1.43				8
	14.3				15
Control values	0.9% NaCl				4

Sera A = serum of patient A
Sera A/B = mixture of serum of patient A and B
Sera A/B/C = mixture of serum of patient A, B and C
EA 1157, EA 1159 and EA 1186: codes of the experiments.

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The sponsor concluded that fondaparinux does not cross-react with heparin antibodies because with fondaparinux the percent serotonin release was less than 20% in contrast with heparin which had approximately 95% release.

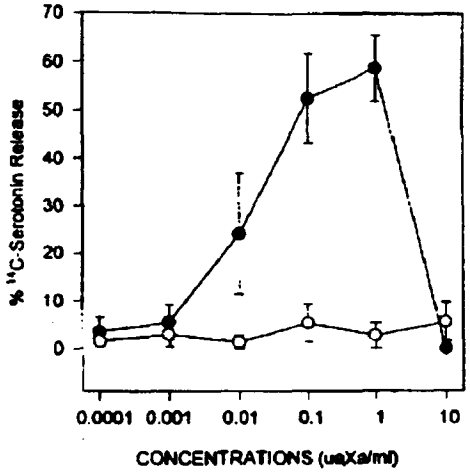
Study #2-

Title: Cross-reactivity of SR 90107A with serum from HIT patients

Date of Report: February 18, 1997

This study evaluated ^{14}C-serotonin release from three healthy volunteers' platelets exposed to heparin or SR 90107A. The platelets were incubated with HIT patients' sera. The sponsor's results are shown below.

Figure (5.1) Release of ^{14}C-Serotonin from platelets from healthy donors in serum from patients with Heparin-Induced Thrombocytopenia (HIT) in the presence of SR 90107A (open circle) and heparin (close circle).



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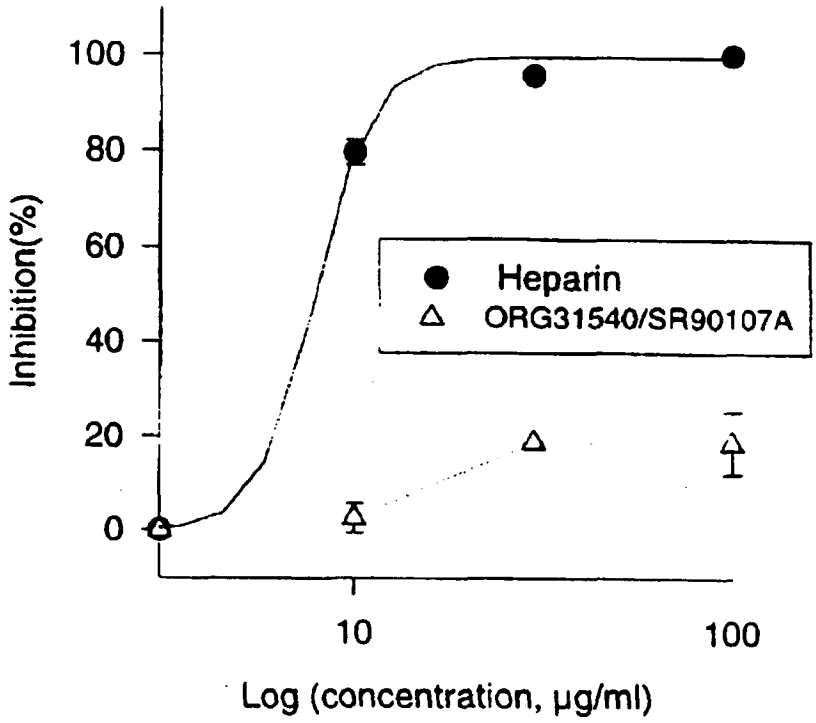
The sponsor concluded that SR 90107A did not cross react with HIT antibodies based on serotonin release.

Study #3-

Title: Interaction of Org 31540/SR 90107A with platelet factor 4 (PF4)

Date of Report: October 5, 1999

This study evaluated competitive inhibition of ^{3}H-heparin binding to platelet factor 4 by unlabeled heparin or Org 31540/90107A. The sponsor's results are shown below.



Sponsor's graph volume 3.8 p. 7 of 18

The sponsor concluded that Org 31540/SR90107A does not bind to PF4 and is not expected to induce HIT.

III. Human Pharmacokinetics and Pharmacodynamics

In healthy volunteer studies, the 2.5-mg SC injection resulted in 107% bioavailability after SC injection compared with IV administration. After SC injection, t_{max} was 1.7 ± 0.4 hours. The volume of distribution in human subjects ranged from ——— The plasma $t_{1/2}$ elimination ranged from —— hours, the plasma clearance from ——— mL/min, and the renal clearance from ——— mL/min. In vitro studies did not reveal evidence of fondaparinux liver metabolism. Within 72 hours of SC and IV dosing, 77% of fondaparinux was recovered from the urine. Steady state is achieved within 3 to 4 doses with daily SC injection. At steady state a 30% increase in C_{max} and AUC was observed compared with the first dose.

Drug-Drug studies
The table below outlines the basic information about the design of the drug-drug studies.

Study	Type	Study design	Usefulness
63108	Drug-drug	Three-way crossover design with two week washout; Concomitant administration of Warfarin or placebo with fondaparinux for 5 days	Concomitant administration
INT2767	Drug-drug	Part A- open label, tolerability, Part B- double-blind, randomized, crossover, Fondaparinux injection for 8 days, single dose of 975 mg aspirin D1 (everyone) and D4 (aspirin or placebo)	Short term concomitant administration
63109B	Drug-drug	Three- way crossover design, randomized, double-blinded interaction with Piroxicam	Short term concomitant administration
INT3933	Drug-drug	Open-label, crossover design with fondaparinux and digoxin or placebo (7 days)	Short term concomitant administration
INT3012	Potential antidote	Forced diuresis with lasix to improve clearance	Concomitant administration

Reviewer's Table

Aspirin, warfarin, piroxicam, and digoxin did not influence the fondaparinux steady state pharmacokinetics/pharmacodynamics (anti-Xa activity). Co-administration did not affect warfarin pharmacodynamics (PT, APTT, FVII, and FVIIa), aspirin (arachidonic acid and collagen induced platelet aggregation, and bleeding time), piroxicam (collagen induced platelet aggregation and bleeding time) or digoxin pharmacokinetics.

Body weight
In hip replacement patients, plasma clearance was increased by 9.3% for every 10 kg increase in body weight. Plasma clearance was low for patients weighing less than 50 kg.

Gender
Women had higher plasma concentrations compared with men. Gender differences were not present when normalized for body weight.

Age
Age was not a significant covariate for fondaparinux pharmacokinetic parameters. However, plasma clearance was slightly lower in patients > 75 years compared with patients < 65 years. Patients > 75 years undergoing hip replacement had a 13% higher fondaparinux concentration than patients < 65 years of age.

Race
No pharmacokinetic differences were noted between Caucasian subjects and Japanese subjects. No plasma clearance differences were noted Caucasian and Black patients.

Renal impairment
Renal impairment subjects and patients had reduced plasma and renal clearance. In hip replacement patients, fondaparinux concentrations were 58% higher in those with creatinine clearance < 50mL/min compared with those with creatinine clearance > 80mL/min. Chronic hemodialysis patients had $t_{1/2}$ from ——— hours during dialysis sessions and ——— hours post-dialysis sessions.

Hepatic Impairment
Hepatic Impairment studies were not performed.

Pharmacodynamic and Pharmacokinetic (PK/PD) studies

The table below illustrates the studies conducted and number of subjects.

Number of subjects participating in PK/PD studies conducted with fondaparinux

Study	Type	Subjects/Concomitant medication	Number of subjects
63106	Bioequivalence	Healthy volunteers	25
BDR3780	Bioequivalence	Healthy volunteers	16
P1653	Single dose	Healthy volunteers	54
63102	Single dose	Healthy volunteers (elderly)	31
TDU3085	Single dose	Healthy volunteers (Japanese)	40
TDU3166	Single dose	Healthy volunteers (Japanese)	9
63105	Single dose	Healthy volunteers	41
63103	Repeat dose	Healthy volunteers (elderly)	24
TDR3088	Repeat dose	Healthy volunteers (Japanese)	9
63107	Single dose	Renal impairment	20
63108	Drug-drug	Healthy volunteers/Warfarin	12
INT2767	Drug-drug	Healthy volunteers/Aspirin	20
63109B	Drug-drug	Healthy volunteers/Piroxicam	13
INT3933	Drug-drug	Healthy volunteers/Digoxin	26
INT3012	Potential antidote	Healthy volunteers/Forced diuresis	13

Reviewer's table

Adverse Events

Only one SAE occurred during the trials. One healthy volunteer receiving fondaparinux and digoxin (day 12) had 2nd degree Mobitz type I heart block requiring prolonged hospitalization. The majority of AEs did not require treatment. The most common reported side effects included headache, dizziness, malaise, abdominal discomfort, nausea, vomiting, epistaxis, hematoma/bruising, and diarrhea. Fewer patients experienced back pain, pharyngitis, occult blood, liver enzyme elevation, flushing, or pruritus. One subject had prolonged bleeding time 72 hours after infusion, which lasted for 8 days. This subject had a normal bleeding time pre-dose and 1 hour post-dose. The sponsor proposed no alternative explanation for the prolonged bleeding time. One subject had dysphonia, which lasted for less than six hours, twice (once with fondaparinux and placebo and once with fondaparinux plus aspirin).

IV. Description of Clinical Data and Sources- See Dr. Min Lu's review

V. Clinical Review Methods- See Dr. Min Lu's review

VI. Integrated review of Efficacy- See Dr. Min Lu's review

VII. Integrated Review of Safety

Reviewer's Conclusion: Major safety concerns identified in clinical phase I, II, III testing of this anticoagulant drug included bleeding risk, thrombocytopenia, heparin antibodies, and skin reactions. Over 5900 subjects and patients have been exposed to fondaparinux in clinical studies. More than 3600 patients were enrolled and treated with fondaparinux in the phase II and III clinical orthopedic trials. These patients had nearly normal renal function (serum creatinine < 2.0mg/dL) and most were treated for 5-9 days (maximum 11 days) with fondaparinux 2.5 mg daily. Study safety data collection continued up to Day 49. Study safety data collection continued up to Day 49. The major safety AE observed was bleeding. The overall bleeding rates associated

with fondaparinux compared with enoxaparin were 5.7% and 4.8%, respectively. Patients with body weight less than 50 kg, older patients > 65 years of age, and those with reduced renal function had increased bleeding and AE rates. There were no statistically significant differences for SAEs or AEs between fondaparinux and enoxaparin except for anemia and post-operative hemorrhage. The statistically significant differences seen may have been due to the timing of study drug administration during the clinical trials. Most trials post-operatively administered fondaparinux approximately 6 hours after surgery, whereas, most trials post-operatively administered enoxaparin approximately 12-24 hours after surgery. During the treatment period, the most frequent SAE category was platelet, bleeding, and clotting disorders (fondaparinux 1% and enoxaparin 0.7%).

The table below shows AEs seen with greater frequency for the fondaparinux patients compared with the enoxaparin patients. Statistically significant differences were noted for anemia and post-operative hemorrhage in favor of enoxaparin.

Adverse Events Seen with Greater Frequency for Fondaparinux compared with Enoxaparin in Phase II/III Clinical Orthopedic Trials

Adverse Event	*Fondaparinux 2.5 mg daily (N=3616)*	*Enoxaparin (40 mg QD or 30 mg BID) (N=3956)*	*P value (Fisher's exact)*
Anemia	*707 (19.6%)*	*694 (16.9%)*	*0.03*
Hypokalemia	*152 (4.2%)*	*164 (4.1%)*	*0.91*
Hypotension	*126 (4.2%)*	*125 (3.1%)*	*0.44*
Urinary tract infection	*136 (3.7%)*	*135 (3.4%)*	*0.23*
Bullous eruption	*90 (2.5%)*	*86 (2.2%)*	*0.40*
Urinary retention	*85 (2.4%)*	*91 (2.3%)*	*0.76*
Hematoma	*73 (2%)*	*74 (1.9%)*	*0.62*
Post-operative Hemorrhage	*53 (1.5%)*	*36 (0.9%)*	*0.03*

Reviewer's Table

Thrombocytopenia was seen with nearly equal frequency for both fondaparinux and enoxaparin patients. (2.9% and 3.1% respectively). Additional notable laboratory test results were positive ELISA test for heparin antibodies (fondaparinux 4.3% and enoxaparin 3.3% respectively) and positive serotonin release test (performed only in ELISA positive patients) (fondaparinux 16.5% and enoxaparin 11.4% respectively). The frequency of patients having both thrombocytopenia and a positive ELISA test was 2.9% for both treatment groups. The frequency of patients having both a venous thromboembolism (VTE) and positive ELISA test was 6.7% for fondaparinux and 9.8% for enoxaparin.

These results suggest that fondaparinux may be associated with HIT and HITTS. HIT and HITTS is a clinical diagnosis based on the presence of VTE and thrombocytopenia in a patient with recent or ongoing exposure to heparin or a low molecular weight heparin (e.g., enoxaparin). Laboratory testing for ELISA antibodies and serotonin release supports the clinical diagnosis. In every phase III orthopedic clinical trial, the same adverse events (thrombocytopenia, VTE, positive ELISA, and positive serotonin tests) are observed. The following issues preclude making a definitive statement that fondaparinux causes HIT/HITTS:

1) *the increased risk of a thromboembolic phenomenon after orthopedic surgery/immbolization*
2) *the incomplete information regarding prior heparin exposure in trial patients*
3) *the changing definition of HIT/HITTS*
4) *the trial design*
5) *incomplete characterization of the heparin antibody formed including any cross reactivity with fondaparinux*

Risk management options include informing healthcare providers and the public via the labeling about the fact that both thrombocytopenia and heparin antibodies have been associated with fondaparinux treatment.

Fondaparinux risk management steps include revisions of the sponsor's proposed labeling and recommendations for additional information listed in the Executive Summary.

This safety review is composed of several parts: an integrated safety review, individual reviews of studies/trials, and other safety information from studies for other indications. The separate study/trial reviews and other safety information are in the Appendices A, B, C, D, and E. Over 5900 patients, age 17-101, have participated in phase I, II and III studies and received fondaparinux. Numbers of treated subjects/patients are listed in the table below:

Numbers of fondaparinux treated subjects/patients in studies

Phase	Indication	Fondaparinux/patients subjects
I		293
II/III	Hip replacement	3159
II/III	Knee surgery	833
III	Hip fracture	831
	Other indications	863
Total		5979

Reviewer's table

The sponsor's table below shows the trials included in this review.

Table (3.2) 1 - List of Studies in the Org31540/SR90107A Integrated Summary of Safety Information

Phase I Studies	
Single Dose Administration	
P1653 (Completed)	Single rising SC doses in healthy young male volunteers
63102 (Completed)	Single rising SC doses in healthy male and female elderly volunteers
63105 (Completed)	Single dose to healthy male and female elderly volunteers
63106 (Completed)	Bioavailability after single SC dose in healthy elderly volunteers
BDR3780 (Completed)	Comparative bioequivalence actual form vs. marketed form
TDU3085 (Completed)	Single IV injection to healthy young male Japanese volunteers
TDU3166 (Completed)	Single ascending IV dose in healthy young male Japanese volunteers
TDU4089 (Report ongoing)	Single ascending SC dose in healthy young male Japanese volunteers
TDU4289 (Report ongoing)	Single SC dose in healthy male elderly Japanese volunteers
Multiple Dose Administration	
63103 (Completed)	Repeated, rising SC dose to healthy male and female elderly volunteers
TDR3088 (Completed)	Repeated IV dose to young healthy male Japanese volunteers
Interaction Studies	
63108 (Completed)	Healthy male volunteers (warfarin) - multiple dose
INT2767 (Completed)	Healthy male volunteers (aspirin) - multiple dose
63109 (Completed)	Healthy male volunteers (piroxicam) - multiple dose
INT3012 (Completed)	Healthy male volunteers (potential antidote) - single dose
INT3933 (Completed)	Healthy male volunteers (digoxin) - multiple dose
63114 (Completed)	*Ex vivo* model of arterial thrombosis in healthy volunteers
Renal Insufficiency	
63107 (Completed)	Renal disease
Prevention of VTE in Orthopedic Surgery	
Hip replacement	
ACT1840 (Completed)	Prevention of DVT after total hip replacement
ACT2545 (Completed)	Prevention of DVT after total hip replacement
DRI2643 [redacted] (Completed)	Prevention of VTE after total hip replacement
EFC2442 [redacted] (Completed)	Prevention of VTE after total hip replacement
63118 *EPHESUS* (Completed)	Prevention of VTE after total hip replacement
Hip fracture	
EFC2698 [redacted] (Completed)	Prevention of VTE in hip fracture surgery
Knee Replacement	
095-001 [redacted] (Completed)	Prevention of DVT after total knee replacement
095-002 [redacted] (Completed)	Prevention of VTE after total knee replacement
Other Indications	
Treatment of Venous Thromboembolism Events	
DRI2440 [redacted] (Completed)	Treatment of [redacted]
EFC2441 [redacted] (Ongoing)	Treatment of [redacted]
63123 [redacted] (Ongoing)	Treatment of [redacted]
Indications in [redacted]	
DRI3196 [redacted] (Completed)	[redacted]
ACT2445 (Completed)	Patients [redacted]
63119 [redacted] (Ongoing)	Dose ranging study [redacted]
Prevention of [redacted]	
63113 (Completed)	[redacted]

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The safety information will be presented in the following four categories:

1) Phase II/III studies for thromboprophylaxis in orthopedic surgery
2) Phase I studies
3) Studies in other indications
4) Ongoing studies

Adverse Event Reporting

All protocols defined the adverse event collection period as starting after first study drug injection to end of study. The following phase II/III orthopedic trials had pre-operative randomization and dosing (ACT 1840, ACT 2545, 63118, and EFC2698). The following phase II/III orthopedic trials had post-operative randomization and dosing (DRI2643, EFC2442, 095001, and 095002). The end of study differed depending on the study phase. Adverse event reporting for the Phase I studies ended with closure of the study for each patient, usually a few days after study treatment ended. Adverse event reporting for the Japanese phase I studies ended approximately 11 days after the treatment ended. For studies in orthopedic surgery, adverse event reporting for phase II studies ended at study drug termination and for phase III trials ended 49 days after enrollment in a trial. For studies in other indications, the sponsor's text below shows the adverse event reporting time period.

Two periods were considered for studies DRI2440, DRI3196 and ACT2445:

- The treatment period corresponding to that used in the individual reports, i.e.
  - DRI2440: from first study drug injection up to end of treatment + 2 calendar days
  - DRI3196: from first study drug injection up to end of treatment + 72 hours
  - ACT2445: 48 hours after single administration
- The whole study period from the first injection up to the specified end in each individual report, i.e.,:
  - DRI2440: from first study drug injection up to Day 97
  - DRI3196: from first study drug injection up to Day 37
  - ACT2445: up to last available date by patient

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Study 63113 includes information only up to treatment end. For ongoing studies, adverse event information is reported only as of the cutoff date of May 11, 2000.

Adverse events were considered serious if the adverse event met the following criteria:

1) resulted in death or was life threatening
2) necessitated or prolonged hospitalization
3) resulted in persistent or significant disability/incapacity
4) congenital anomaly or birth defect

Non-fatal VTEs were not considered SAEs in Phase III trials and these events were not reported in the integrated summary of safety for the phase II trials.

An Independent Adjudication Committee blindly adjudicated deaths up to study end in the Phase II/III studies for the orthopedic indication and in the one completed study for treatment of VTE.

The adjudication committees determined the cause of death as due to:

1) VTE or
2) bleeding or
3) not VTE or bleeding

For all phase III studies and studies ACT1840 and 095001, only bleeding and death adverse events were adjudicated. In studies ACT 2545 and DRI2643, all adverse events were adjudicated.

The safety populations included all those subjects who had received at least one dose of study drug.

Bleeding
To adjudicate bleeding, the majority of studies used the Hamilton Criteria, which is provided below. One study (095001) did not and bleeding events were later readjudicated using the Hamilton criteria. Two early studies (ACT 1840 and ACT 2545) had similar bleeding criteria to allow pooling. The sponsor's text is below.

> An unusual bleeding was adjudicated as major according to the following: the complication should have been a clinically overt hemorrhage, in addition to one of the following criteria:
> - Fatal
> - Bleeding at critical site, e.g., intracranial, retroperitoneal, intra-ocular, pericardial, spinal or into adrenal gland
> - Reoperation at operative site
> - Hemoglobin and/or transfusion criteria: according to the Hamilton criteria, the bleeding index should be ≥2 (within 48 hours of the bleed, calculated as 'number of units transfused' + pre-bleed hemoglobin (g/dL) - post-bleed hemoglobin (g/dL)). In study ACT1840, bleeding associated hemoglobin decreases were considered but without pre-specified threshold. Bleeding associated transfusion criteria were not pre-specified in the 2 early studies (ACT1840 and ACT2545) but were taken into account by the Adjudication Committees
> - Treatment withdrawal was considered for major bleeding adjudication of the 2 early studies (ACT1840 and ACT2545)
>
> ***Adjudicated minor bleeding***
> In all studies, minor bleeding was clinically overt bleeding not meeting the criteria of major bleeding. Minor bleedings were adjudicated in all studies except in study ACT2545. In this study, any bleeding reported by the Investigators, classified in the platelet, bleeding and clotting disorders WHO organ class (1230) or coded as "injection site reaction" and not adjudicated as major was considered minor.

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Safety Demographics

Overall 4823 patients participated in the phase II/III trials. The population ranged in age from 17 to 97 years and in body weight from 30 to 169 kg. The population included 58.4% females, 41.6% males, 95.1% Caucasians, 3.4% Blacks, 0.3% Asian/Oriental, and 1.2% other races. Demographics were similar for fondaparinux and the comparator groups. The sponsor's table below lists the demographic characteristics for patients who received 2.5 mg fondaparinux in the phase II/III trials.

Reviewer's Comment: The percentage of non-Caucasians is low in comparison with the U.S. population. Except for the paucity of non-Caucasians, the population studied reflects the likely population to receive the drug once it is marketed.

Table (6.1.2.1) 1 - Demographic Characteristics - All Org31540/SR90107A 2.5 mg Treated Patients From First Active Injection in Orthopedic Surgery Studies

Parameter	Org31540/SR90107A 2.5 mg (N = 3595)
Age (years)	
N	3591
Median	70
Mean (SD)	68.0 (12.9)
Min-Max	17-97
Age (years) [n (%)]	
Missing	4
<65	1253 (34.9%)
[65,75[	1111 (30.9%)
≥75	1227 (34.2%)
Total	3591 (100.0%)
Height (cm)	
N	3512
Median	168
Mean (SD)	167.7 (9.9)
Min-Max	132-230
Weight (kg)	
N	3558
Median	75
Mean (SD)	77.3 (18.5)
Min-Max	30-169
Weight (kg) [n (%)]	
Missing	37
<50	130 (3.7%)
[50,100[	3030 (85.2%)
≥100	398 (11.2%)
Total	3558 (100.0%)
Creatinine clearance (mL/min) [n (%)]	
Missing	155
<30	83 (2.4%)
[30,50[	504 (14.7%)
[50,80[	1288 (37.4%)
≥80	1565 (45.5%)
Total	3440 (100.0%)
Gender [n (%)]	
Female	2166 (60.3%)
Male	1429 (39.7%)
Total	3595 (100.0%)
Race [n (%)]	
Missing	1
Asian/Oriental	11 (0.3%)
Black	91 (2.5%)
Caucasian	3458 (96.2%)
Other[a]	34 (0.9%)
Total	3594 (100.0%)

PGM: [redacted] OUT: output/OS611_A1
(20DEC00 - 11:56)

[a] Does not include Asian/Oriental, Black and Caucasian

Ref.: Appendix 2.2.12

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The sponsor's table below shows the numbers of patients with specific medical and surgical conditions.

Table (6.1.2.2) 1 - Number (%) of Patients With Specific Medical History - All Org31540/SR90107A 2.5 mg Treated Patients From First Active Injection in Orthopedic Surgery Studies

Specific Medical History	Org31540/SR90107A 2.5 mg
VTE	149/3595 (4.1%)
Stroke	117/3595 (3.3%)
Myocardial infarction	192/3595 (5.3%)
Cancer	372/3595 (10.3%)
Orthopedic surgery within the previous 12 months	
Any surgery	362/3595 (10.1%)
Hip replacement	143/3595 (4.0%)
Knee replacement	64/3595 (1.8%)
Other surgery	181/3594 (5.0%)

PGM: [redacted] OUT: output/OS612_A1
(16JAN01 - 14:34)
Ref.: Appendix 2.2.26

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The sponsor's table for exposure duration is listed below.

Reviewer's Comment: The majority of patients received between 5 and 9 days of study drug. No patient received study drug for longer than 11 days.

Table (7.1.2) 1 - Summary of Extent of Exposure to Active Study Drug - All Org31540/SR90107A 2.5 mg Treated Patients in Orthopedic Surgery Studies

	Org31540/SR90107A 2.5 mg (N = 3595)
Number of active injections	
Median	7
Mean (SD)	7.0 (1.6)
Min-Max	[redacted]
Last day of active treatment [n(%)][a]	
< Day 5	137 (3.8%)
Day 5 to Day 9	3369 (93.7%)
> Day 9	89 (2.5%)

PGM: [redacted] OUT: output/OS713_A1 (10JAN01 - 10:24)
[a] Day 1 = day of surgery (or day of first study drug injection for non operated patients)
Ref.: Appendix 2.3.3

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Phase II/III Orthopedic Studies

Bleeding
The sponsor's table below shows the number of patients who had an adjudicated bleeding event.

Reviewer's Comment: For most categories, increasing fondaparinux dose was associated with increasing hemorrhage risk. There was no statistically significant difference for the bleeding categories between fondaparinux and enoxaparin. In general, fondaparinux 2.5 mg treatment was associated with a higher event rate than enoxaparin treatment.

Table (8.1.1.1) 1 - Number (%) of Patients Experiencing an Adjudicated Bleeding Event and/or With Bleeding-Related Criteria During the Treatment Period According to Study Type - All Treated Patients in Orthopedic Surgery Studies

		Org31540/SR90107A			Enoxaparin	Nadroparin[c]
Studies with pre-operative randomization[a]						
Patients With:		<2.5 mg (N = 77)	2.5 mg (N = 1971)	>2.5 mg (N = 141)	40 mg od (N = 2050)	(N = 45)
Bleeding event	Major bleeding 95% CI	1 (1.3%) [0.0;7.0]	65 (3.3%) [2.6;4.2]	4 (2.8%) [0.8;7.1]	54 (2.6%) [2.0;3.4]	0 (0.0%) [0.0;7.9]
	Minor bleeding 95% CI	17 (22.1%) [13.4;33.0]	78 (4.0%) [3.1;4.9]	28 (19.9%) [13.6;27.4]	66 (3.2%) [2.5;4.1]	4 (8.9%) [2.5;21.2]
	Any bleeding 95% CI	18 (23.4%) [14.5;34.4]	143 (7.3%) [6.1;8.5]	32 (22.7%) [16.1;30.5]	120 (5.9%) [4.9;7.0]	4 (8.9%) [2.5;21.2]
Bleeding-related criteria	Re-operation due to bleeding 95% CI	0 (0.0%) [0.0;4.7]	8 (0.4%) [0.2;0.8]	2 (1.4%) [0.2;5.0]	6 (0.3%) [0.1;0.6]	0 (0.0%) [0.0;7.9]
	Transfused patients 95% CI	61 (79.2%) [68.5;87.6]	1135 (57.6%) [55.4;59.8]	107 (75.9%) [68.0;82.7]	1168 (57.0%) [54.8;59.1]	32 (71.1%) [55.7;83.6]
Studies with post-operative randomization[b]						
Patients With:		<2.5 mg (N = 517)	2.5 mg (N = 1645)	>2.5 mg (N = 472)	30 mg bid (N = 1906)	NA
Bleeding event	Major bleeding 95% CI	3 (0.6%) [0.1;1.7]	31 (1.9%) [1.3;2.7]	41 (8.7%) [6.3;11.6]	21 (1.1%) [0.7;1.7]	NA NA
	Minor bleeding 95% CI	11 (2.1%) [1.1;3.8]	31 (1.9%) [1.3;2.7]	22 (4.7%) [2.9;7.0]	50 (2.6%) [2.0;3.4]	NA NA
	Any bleeding 95% CI	14 (2.7%) [1.5;4.5]	62 (3.8%) [2.9;4.8]	63 (13.3%) [10.4;16.8]	71 (3.7%) [2.9;4.7]	NA NA
Bleeding-related criteria	Re-operation due to bleeding 95% CI	0 (0.0%) [0.0;0.7]	4 (0.2%) [0.1;0.6]	8 (1.7%) [0.7;3.3]	5 (0.3%) [0.1;0.6]	NA NA
	Transfused patients 95% CI	214 (41.4%) [37.1;45.8]	815 (49.5%) [47.1;52.0]	246 (52.1%) [47.5;56.7]	869 (45.6%) [43.3;47.9]	NA NA

PGM: [redacted] OUT: output/OS81111_V2b (20DEC00 - 14:36)
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] Includes studies DRI2643, EFC2442, 095-001 and 095-002
Ref.: Appendix 2.4.1

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The sponsor's table below shows the number of patients experiencing a major bleed by adjudication criteria, site, and treatment group.

Reviewer's Comment: The sponsor's table below shows the number of patients with a bleeding event during the treatment period (up to Day 11). For most categories, increasing fondaparinux dose was associated with increasing hemorrhage risk. There was no statistically significant difference for the bleeding categories between fondaparinux 2.5 mg and enoxaparin. In general, fondaparinux 2.5 mg treatment was associated with a higher bleeding rate than enoxaparin

treatment. Few bleeding events starting after Day 11 were reported. The inclusion of bleeding events reported after Day 11 does not change the conclusion that increasing fondaparinux dose was associated with increasing hemorrhage risk.

Table (8.1.1.2) 1 - Number (%) of Patients Experiencing a Major Bleeding Event During the Treatment Period by Adjudication Criteria, Site and Treatment Group According to the Study Type - All Treated Patients in Orthopedic Surgery Studies

	Org31540/SR90107A			Enoxaparin
Studies with pre-operative randomization[a]				
Patients With:	<2.5 mg (N=77)	2.5 mg (N=1971)	>2.5 mg (N=141)	40 mg od (N=2050)
Any major bleeding	1 (1.3%)	65 (3.3%)	4 (2.8%)	54 (2.6%)
Fatal bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Non-fatal critical bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other non-fatal major bleeding:	1 (1.3%)	65 (3.3%)	4 (2.8%)	53 (2.6%)
- at surgical site	1 (1.3%)	54 (2.7%)	2 (1.4%)	44 (2.1%)
- at non surgical site only	0 (0.0%)	11 (0.6%)	2 (1.4%)	9 (0.4%)
Studies with post-operative randomization[b]				
Patients With:	<2.5 mg (N=517)	2.5 mg (N=1645)	>2.5 mg (N=472)	30 mg bid (N=1906)
Any major bleeding	3 (0.6%)	31 (1.9%)	41 (8.7%)	21 (1.1%)
Fatal bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-fatal critical bleeding	1 (0.2%)	0 (0.0%)	1 (0.2%)	1 (0.1%)
- retroperitoneal	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)[c]
- spinal	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
Other non-fatal major bleeding:	2 (0.4%)	31 (1.9%)	40 (8.5%)	20 (1.0%)
- at surgical site	2 (0.4%)	23 (1.4%)	32 (6.8%)	15 (0.8%)[c]
- at non surgical site only	0 (0.0%)	8 (0.5%)	8 (1.7%)	5 (0.3%)

PGM: [redacted] OUT: output/OS81112_V2b (20DEC00 - 14:36)

NOTE: nadroparin column (study ACT1840) is not displayed because no major bleeding events were adjudicated in this treatment group

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

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

[c] One patient (EFC2442-0528-0021) was also re-operated but is not counted as a non-fatal major bleeding occurring at surgical site in this table

Ref.: Appendix 2.4.4

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Onset Day of Bleeding

The sponsor's table below shows the onset day for bleeding events.

Reviewer's Comment: Preoperative randomization and dosing studies showed the highest percentage of bleeding events occurred on Day 1 (day of dosing). Post-operative randomization and dosing studies showed the highest percentage of bleeding events occurred on Day 3 of dosing. Preoperative randomization and dosing studies showed the majority of bleeding events occurred by Day 4 of dosing. Post-operative randomization and dosing studies showed the majority of bleeding events occurred by Day 5 of dosing.

Table (8.1.1.3) 1 - Number (%) of Patients Experiencing a Major Bleeding Event During Treatment Period by Day of Onset and According to the Study Type- All Treated patients in Orthopedic Surgery Studies

	Org31540/SR90107A			Enoxaparin
Studies with pre-operative randomization[a]				
Onset day of major bleeding	**<2.5 mg (N = 77)**	**2.5 mg (N = 1971)**	**>2.5 mg (N = 141)**	**40 mg od (N = 2050)**
Day 1	0 (0.0%)	29 (1.5%)	0 (0.0%)	24 (1.2%)
Day 2	0 (0.0%)	7 (0.4%)	0 (0.0%)	8 (0.4%)
Day 3	1 (1.3%)	8 (0.4%)	0 (0.0%)	7 (0.3%)
Day 4	0 (0.0%)	7 (0.4%)	3 (2.1%)	6 (0.3%)
Day 5	0 (0.0%)	5 (0.3%)	0 (0.0%)	2 (0.1%)
Day 6	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Day 7	0 (0.0%)	3 (0.2%)	0 (0.0%)	3 (0.1%)
Day 8	0 (0.0%)	2 (0.1%)	0 (0.0%)	1 (0.0%)
Day 9	0 (0.0%)	2 (0.1%)	1 (0.7%)	2 (0.1%)
Day 10	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Day 11	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Total	1 (1.3%)	65 (3.3%)	4 (2.8%)	54 (2.6%)
Studies with post-operative randomization[b]				
Onset day of major bleeding	**<2.5 mg (N = 517)**	**2.5 mg (N = 1645)**	**>2.5 mg (N = 472)**	**30 mg bid (N = 1906)**
Day 1	0 (0.0%)	2 (0.1%)	3 (0.6%)	3 (0.2%)
Day 2	0 (0.0%)	7 (0.4%)	10 (2.1%)	3 (0.2%)
Day 3	1 (0.2%)	10 (0.6%)	14 (3.0%)	7 (0.4%)
Day 4	0 (0.0%)	6 (0.4%)	6 (1.3%)	3 (0.2%)
Day 5	2 (0.4%)	1 (0.1%)	4 (0.8%)	1 (0.1%)
Day 6	0 (0.0%)	2 (0.1%)	2 (0.4%)	1 (0.1%)
Day 7	0 (0.0%)	0 (0.0%)	1 (0.2%)	2 (0.1%)
Day 8	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Day 9	0 (0.0%)	2 (0.1%)	1 (0.2%)	0 (0.0%)
Day 10	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 11	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	3 (0.6%)	31 (1.9%)	41 (8.7%)	21 (1.1%)

PGM: [redacted] OUT: output/OS81121_V2c (20DEC00 - 14:36)

NOTE: Day 1 = day of surgery; nadroparin column (study ACT1840) is not displayed because no major bleeding events were adjudicated in this treatment group

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

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

Ref.: Appendices 2.4.12 and 2.4.13

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Drug-demographic and drug-baseline characteristic interactions

The sponsor's table below shows the number of patients with major bleeding events by baseline covariate.

Reviewer's Comment: Major bleeding rates were increased with decreased kidney function (creatinine clearance < 30 ml/min), lower body weight (< 50 kg), and older age (65-75 and > 75). The timing of the first post-operative injection is an important variable for bleeding. The table

below shows decreased bleeding rate with increased time elapsed between end of operation and time of first post-operative injection.

Table (8.1.2.4) 1 - Number (%) of Patients Experiencing Major Bleeding Events From First Active Org31540/SR90107A Injection up to Day 11 by Baseline Covariates - All Org31540/SR90107A 2.5 mg Treated Patients in Orthopedic Surgery Studies

Covariate*	Org31540/SR90107A 2.5 mg (N = 3595)
Type of surgery	
Total Hip Replacement	51/2249 (2.3%)
Hip Fracture	18/829 (2.2%)
Total Knee Replacement	11/517 (2.1%)
Gender	
Male	34/1429 (2.4%)
Female	46/2166 (2.1%)
Race	
Missing	0/1 (0.0%)
Caucasian	74/3458 (2.1%)
Black	3/91 (3.3%)
Asian	2/11 (18.2%)
Others	1/34 (2.9%)
Age (years)	
Missing	0/4 (0.0%)
<65	23/1253 (1.8%)
[65-75[	24/1111 (2.2%)
≥75	33/1227 (2.7%)
Weight (kg) [n (%)]	
Missing	1/37 (2.7%)
<50	7/130 (5.4%)
[50,100[	63/3030 (2.1%)
≥100	9/398 (2.3%)
Creatinine clearance (mL/min) [n (%)]	
Missing	1/155 (0.6%)
<30	4/83 (4.8%)
[30,50[	19/504 (3.8%)
[50,80[	31/1288 (2.4%)
≥80	25/1565 (1.6%)
Timing of first post-operative active injection (hours)	
Missing	2/28 (7.1%)
<4	5/106 (4.7%)
[4, 5[	14/489 (2.9%)
[5, 6[	16/742 (2.2%)
[6, 7[	28/1403 (2.0%)
[7, 8]	13/609 (2.1%)
]8, 9]	0/107 (0.0%)
]9,10]	0/23 (0.0%)
>10	2/88 (2.3%)

PGM: [redacted], OUT: output/OS81141_A1 (21DEC00 - 9:39)

NOTE: includes studies EFC2442, 63118, EFC2698 and 095-002

* Per covariate, only non missing observations were taken into account

Ref.: Appendix 2.4.74

Drug-drug interaction studies showed that concomitant medications might increase the bleeding risk.

Reviewer's Comment: Although the event rate is higher with concomitant oral anticoagulant use, the difference is not statistically significant.

Hemorrhage rates for fondaparinux treated patients with and without concomitant medication

Concomitant medication	Rate of hemorrhage
Heparin	
With	2.6%
Without	2.2%
Aspirin	
With	2.7%
Without	2.2%
NSAID	
With	1.9%
Without	2.3%
Oral Anticoagulants	
With	7.7%
Without	2.6%

Reviewer's Table

Adverse Events
The sponsor's table below shows the numbers and percentages of patients experiencing at least one adverse event for all orthopedic trials.

Reviewer's Comment: The table below suggests that the adverse event rates for 2.5 mg fondaparinux and enoxaparin were similar. There were no statistically significant differences for AE categories between fondaparinux 2.5 mg and enoxaparin. The SAE rate was slightly higher for fondaparinux in both preoperative and post-operative studies. The SAE rate increased with increasing fondaparinux dose in the preoperative and post-operative randomization studies.

Table (9.1.1.1) 1 - Overview of Patients [Number (%)] With at Least One Adverse Event During Treatment Period According to the Study Type - All Treated Patients in Orthopedic Surgery Studies

	Org31540/SR90107A			Enoxaparin	Nadroparin[a]
Studies with pre-operative randomization[b]					
	<2.5mg (N = 77)	2.5mg (N = 1971)	>2.5mg (N = 141)	40mg od (N = 2050)	(N = 45)
Patients with any AEs[c]	44 (57.1%)	1081 (54.8%)	77 (54.6%)	1122 (54.7%)	21 (46.7%)
Patients with any AEs of severe intensity[d]	1 (1.3%)	96 (4.9%)	6 (4.3%)	92 (4.5%)	1 (2.2%)
Patients with SAEs[e]	3 (3.9%)	104 (5.3%)	8 (5.7%)	93 (4.5%)	0 (0.0%)
Deaths	0 (0.0%)	11 (0.6%)	0 (0.0%)	18 (0.9%)	0 (0.0%)
Patients permanently discontinued study drug for any AE	1 (1.3%)	44 (2.2%)	2 (1.4%)	47 (2.3%)	0 (0.0%)
Patients with platelet, bleeding and clotting disorders	19 (24.7%)	227 (11.5%)	17 (12.1%)	214 (10.4%)	0 (0.0%)
Patients stopped due to platelet, bleeding and clotting disorders	1 (1.3%)	18 (0.9%)	0 (0.0%)	8 (0.4%)	0 (0.0%)
Studies with post-operative randomization[f]					
	<2.5mg (N = 517)	2.5mg (N = 1645)	>2.5mg (N = 472)	30mg bid (N = 1906)	NA
Patients with any AEs[c]	497 (96.1%)	1278 (77.7%)	457 (96.8%)	1526 (80.1%)	NA
Patients with any AEs of severe intensity[d]	47 (9.1%)	70 (4.3%)	61 (12.9%)	82 (4.3%)	NA
Patients with SAEs[e]	20 (3.9%)	92 (5.6%)	41 (8.7%)	86 (4.5%)	NA
Deaths	0 (0.0%)	4 (0.2%)	0 (0.0%)	3 (0.2%)	NA
Patients permanently discontinued study drug for any AE	18 (3.5%)	53 (3.2%)	38 (8.1%)	63 (3.3%)	NA
Patients with platelet, bleeding and clotting disorders	95 (18.4%)	223 (13.6%)	129 (27.3%)	242 (12.7%)	NA
Patients stopped due to platelet, bleeding and clotting disorders	6 (1.2%)	18 (1.1%)	25 (5.3%)	22 (1.2%)	NA

PGM: [redacted] OUT: output/OS91111_V2b (24JAN01 - 20:09)

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] Including SAE

[d] Including missing intensity

[e] Including SAE leading to death

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

Ref.: Appendices 2.5.1.1 and 2.5.1.2

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The sponsor's next two tables show the adverse event rates for patients in the preoperative and post-operative randomization studies.

Reviewer's Comment: In the preoperative randomization studies, there was a greater incidence of anemia and post-operative hemorrhage for fondaparinux 2.5 mg compared with enoxaparin. There were no statistically significant differences for AE categories between fondaparinux 2.5 mg and enoxaparin.

Table (9.1.1.1) 2 - 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 Pre-Operative Randomization

WHO Organ Class	Org31540/SR90107A			Enoxaparin	Nadroparin*
Adverse Events (WHO Preferred Term)	<2.5 mg (N = 77)	2.5 mg (N = 1971)	>2.5 mg (N = 141)	40 mg od (N = 2050)	(N = 45)
Any event	44 (57.1%)	1081 (54.8%)	77 (54.6%)	1122 (54.7%)	21 (46.7%)
Gastro-intestinal system disorders					
Total	20 (26.0%)	384 (19.5%)	17 (12.1%)	405 (19.8%)	7 (15.6%)
Nausea	8 (10.4%)	166 (8.4%)	8 (5.7%)	169 (8.2%)	2 (4.4%)
Constipation	2 (2.6%)	129 (6.5%)	1 (0.7%)	169 (8.2%)	1 (2.2%)
Vomiting	9 (11.7%)	102 (5.2%)	4 (2.8%)	95 (4.6%)	2 (4.4%)
Diarrhoea	2 (2.6%)	48 (2.4%)	4 (2.8%)	47 (2.3%)	2 (4.4%)
Abdominal pain	1 (1.3%)	21 (1.1%)	1 (0.7%)	30 (1.5%)	3 (6.7%)
Dyspepsia	0 (0.0%)	22 (1.1%)	1 (0.7%)	19 (0.9%)	1 (2.2%)
Body as a whole - General disorders					
Total	9 (11.7%)	301 (15.3%)	18 (12.8%)	291 (14.2%)	2 (4.4%)
Fever	2 (2.6%)	129 (6.5%)	4 (2.8%)	126 (6.1%)	2 (4.4%)
Wound drainage increased	3 (3.9%)	92 (4.7%)	1 (0.7%)	81 (4.0%)	0 (0.0%)
Oedema peripheral	0 (0.0%)	43 (2.2%)	0 (0.0%)	37 (1.8%)	0 (0.0%)
Pain	1 (1.3%)	14 (0.7%)	4 (2.8%)	19 (0.9%)	1 (2.2%)
Chest pain	1 (1.3%)	11 (0.6%)	3 (2.1%)	14 (0.7%)	0 (0.0%)
Allergic reaction	2 (2.6%)	4 (0.2%)	0 (0.0%)	5 (0.2%)	0 (0.0%)
Red blood cell disorders					
Total	12 (15.6%)	302 (15.3%)	19 (13.5%)	275 (13.4%)	2 (4.4%)
Anaemia	12 (15.6%)	300 (15.2%)	18 (12.8%)	273 (13.3%)	2 (4.4%)
Platelet, bleeding and clotting disorders					
Total	19 (24.7%)	227 (11.5%)	17 (12.1%)	214 (10.4%)	0 (0.0%)
Haematoma	15 (19.5%)	73 (3.7%)	15 (10.6%)	74 (3.6%)	0 (0.0%)
Haemorrhage NOS	1 (1.3%)	53 (2.7%)	0 (0.0%)	61 (3.0%)	0 (0.0%)
Post-operative haemorrhage	2 (2.6%)	53 (2.7%)	2 (1.4%)	36 (1.8%)	0 (0.0%)
Central and peripheral nervous system disorders					
Total	3 (3.9%)	185 (9.4%)	11 (7.8%)	183 (8.9%)	1 (2.2%)
Dizziness	1 (1.3%)	47 (2.4%)	4 (2.8%)	52 (2.5%)	0 (0.0%)
Confusion	1 (1.3%)	46 (2.3%)	0 (0.0%)	46 (2.2%)	0 (0.0%)
Headache	2 (2.6%)	27 (1.4%)	1 (0.7%)	28 (1.4%)	1 (2.2%)
Urinary retention	1 (1.3%)	21 (1.1%)	3 (2.1%)	26 (1.3%)	0 (0.0%)
Psychiatric disorders					
Total	1 (1.3%)	156 (7.9%)	6 (4.3%)	176 (8.6%)	0 (0.0%)
Insomnia	0 (0.0%)	125 (6.3%)	5 (3.5%)	133 (6.5%)	0 (0.0%)
Urinary system disorders					
Total	1 (1.3%)	135 (6.8%)	5 (3.5%)	136 (6.6%)	0 (0.0%)
Urinary tract infection	0 (0.0%)	83 (4.2%)	4 (2.8%)	82 (4.0%)	0 (0.0%)
Cardiovascular disorders, general					
Total	5 (6.5%)	108 (5.5%)	7 (5.0%)	124 (6.0%)	1 (2.2%)
Hypotension	4 (5.2%)	73 (3.7%)	3 (2.1%)	77 (3.8%)	1 (2.2%)

(continued)

Table (9.1.1.1) 2 - 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 Pre-Operative Randomization (continued)

WHO Organ Class	Org31540/SR90107A			Enoxaparin	Nadroparin[a]
Adverse Events (WHO Preferred Term)	<2.5 mg (N = 77)	2.5 mg (N = 1971)	>2.5 mg (N = 141)	40 mg od (N = 2050)	(N = 45)
Skin and appendages disorders					
Total	7 (9.1%)	111 (5.6%)	7 (5.0%)	92 (4.5%)	2 (4.4%)
Bullous eruption[b]	3 (3.9%)	22 (1.1%)	4 (2.8%)	16 (0.8%)	0 (0.0%)
Rash	1 (1.3%)	17 (0.9%)	0 (0.0%)	13 (0.6%)	1 (2.2%)
Angioedema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Respiratory system disorders					
Total	2 (2.6%)	103 (5.2%)	1 (0.7%)	97 (4.7%)	2 (4.4%)
Bronchospasm	0 (0.0%)	5 (0.3%)	0 (0.0%)	3 (0.1%)	1 (2.2%)
Pulmonary oedema	0 (0.0%)	4 (0.2%)	0 (0.0%)	2 (0.1%)	1 (2.2%)
Metabolic and nutritional disorders					
Total	1 (1.3%)	96 (4.9%)	0 (0.0%)	70 (3.4%)	2 (4.4%)
Hypokalaemia	0 (0.0%)	63 (3.2%)	0 (0.0%)	46 (2.2%)	2 (4.4%)
Liver and biliary system disorders					
Total	2 (2.6%)	55 (2.8%)	13 (9.2%)	74 (3.6%)	5 (11.1%)
Hepatic enzymes increased	1 (1.3%)	10 (0.5%)	5 (3.5%)	22 (1.1%)	3 (6.7%)
Gamma-GT increased	0 (0.0%)	3 (0.2%)	4 (2.8%)	1 (0.0%)	1 (2.2%)
Hepatocellular damage	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Secondary terms					
Total	2 (2.6%)	49 (2.5%)	2 (1.4%)	54 (2.6%)	0 (0.0%)
Heart rate and rhythm disorders					
Total	0 (0.0%)	51 (2.6%)	1 (0.7%)	54 (2.6%)	0 (0.0%)
Musculo-skeletal system disorders					
Total	0 (0.0%)	46 (2.3%)	2 (1.4%)	54 (2.6%)	2 (4.4%)
Back pain	0 (0.0%)	16 (0.8%)	0 (0.0%)	21 (1.0%)	1 (2.2%)
Arthrosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	1 (2.2%)
Resistance mechanism disorders					
Total	2 (2.6%)	37 (1.9%)	1 (0.7%)	34 (1.7%)	0 (0.0%)
Myo-, endo-, pericardial and valve disorders					
Total	0 (0.0%)	24 (1.2%)	0 (0.0%)	25 (1.2%)	0 (0.0%)
Autonomic nervous system disorders					
Total	1 (1.3%)	22 (1.1%)	1 (0.7%)	13 (0.6%)	1 (2.2%)
Syncope	0 (0.0%)	18 (0.9%)	0 (0.0%)	9 (0.4%)	1 (2.2%)
Vascular (extracardiac) disorders					
Total	0 (0.0%)	10 (0.5%)	0 (0.0%)	10 (0.5%)	0 (0.0%)
Vision disorders					
Total	0 (0.0%)	9 (0.5%)	0 (0.0%)	9 (0.4%)	0 (0.0%)
Reproductive disorders, female					
Total	0 (0.0%)	6 (0.3%)	0 (0.0%)	7 (0.3%)	0 (0.0%)

(continued)

Table (9.1.1.1) 2 - 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 Pre-Operative Randomization (continued)

WHO Organ Class	Org31540/SR90107A			Enoxaparin	Nadroparin[a]
Adverse Events (WHO Preferred Term)	<2.5 mg (N = 77)	2.5 mg (N = 1971)	>2.5 mg (N = 141)	40 mg od (N = 2050)	(N = 45)
Reproductive disorders, male					
Total	0 (0.0%)	3 (0.2%)	0 (0.0%)	6 (0.3%)	0 (0.0%)
Collagen disorders					
Total	0 (0.0%)	4 (0.2%)	0 (0.0%)	3 (0.1%)	0 (0.0%)
Application site disorders					
Total	0 (0.0%)	2 (0.1%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
Hearing and vestibular disorders					
Total	0 (0.0%)	4 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neoplasm					
Total	0 (0.0%)	2 (0.1%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
Endocrine disorders					
Total	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Foetal disorders					
Total	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
White cell and reticulo-endothelial system disorders					
Total	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

PGM: OUT: output/OS91121_T2a (24JAN01 - 20:19)

NOTE: includes studies ACT1840, ACT2545, 63118 and EFC2698

NOS = not otherwise specified ; GT = glutamyl transferase

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

[b] Localized blister coded as bullous eruption

Ref.: Appendix 2.5.1.11

Sponsor's table volume 3.238 pp.105-107

Reviewer's Comment: In the post-operative randomization studies, there was a greater incidence of anemia for fondaparinux 2.5 mg compared with enoxaparin. There were no statistically significant differences for AE categories between fondaparinux 2.5 mg and enoxaparin.