CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-345

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION — NDA

NDA #: 21-345

Drug Class: 1P

Applicant: Fonda BV

Name of Drug: Xantidar (fondaparinux sodium) Injection 2.5 mg

Indication: Prevention of Venous Thromboembolic Events in Hip Replacement
(Separate reviews for prevention of venous thromboembolic events in hip fracture surgery and prevention of venous thromboembolic events in major knee surgery)

Documents Reviewed: NDA Vol. 1-2, 117-208, 237, Dated February 15, 2001
Amendment No. 2: Response to Request for Information-Clinical Dated March 21, 2001
Amendment No. 4: Response to Request for Information – Clinical Dated May 1, 2001

User Fee Date: 8/16/01 (6 mos)

Medical Reviewer: This review has been discussed with medical officer, Min Lu, M.D.

Key Words: active controlled, VTE, missing observation

A. Background

In the current NDA, the applicant seeks approval of fondaparinux in three primary indications:

1). prevention of venous thromboembolic events in hip fracture surgery

2). prevention of venous thromboembolic events in major knee surgery

3). prevention of venous thromboembolic events in hip replacement

This review addresses only prevention of venous thromboembolic events in hip replacement. Separate reviews address the other two indications.

B. Prevention of Venous Thromboembolic Events in Hip Replacement

The applicant has submitted two clinical trials (63118 and EFC2442) in support of the proposed claim: prevention of venous thromboembolic events in hip replacement. Studies 63118 and EFC2442 utilized enoxaparin 40 mg o.d. starting pre-operatively and 30 mg

b.i.d. starting post-operatively, respectively as comparators. Study 63118 was performed in Europe and study EFC2442 in North America.

In the clinical trial, EFC2442, a subcutaneous once daily injection of fondaparinux 2.5mg starting post-operatively was compared to 30 mg b.i.d. subcutaneous injection of enoxaparin starting post-operatively, during 7±2 days, in patients undergoing hip replacement surgery.

In the clinical trial, 63118, a subcutaneous once daily injection of fondaparinux 2.5 mg starting post-operatively was compared to 40 mg once daily subcutaneous injection of enoxaparin starting pre-operatively.

Study treatment should be given for 7±2 days until the mandatory venogram was obtained whichever came first. Mandatory venography should be performed between Days 5-11 but not more than 2 calendar days after the day of last dose. Mandatory venography was not done before Day 5 or after Day 11. The follow-up period was from end of the treatment period up to Day 42±7.

The randomization was performed in balanced blocks of size 4.

The primary efficacy endpoint was any adjudicated VTE (venous thromboembolic event) up to Day 11 defined as symptomatic/asymptomatic (mandatory venogram) DVT and /or PE documented by suitable tests.

The primary endpoint (VTE) was blindly adjudicated by a single independent committee of experts [redacted]. The final DVT adjudication criteria used across two studies was the same.

The primary efficacy analyses were conducted on a modified intention to treat (ITT) population were defined as all randomized patients who satisfied the following criteria: a.) patient received at least one dose of study drug; b.) patient underwent the appropriate surgery; and c.) patient had a non-missing evaluation for the parameter analyzed.

For the primary efficacy endpoint, a patient who was considered to have non-missing evaluation if:

- an adjudicated and evaluable bilateral venogram performed between Day 5 and Day 11 was available, or
- a DVT had been adjudicated up to Day 11, or
- a non-fatal PE had been adjudicated up to Day 11, or
- a fatal PE (adjudicated results) had occurred up to Day 11

All endpoint both efficacy and safety were adjudicated by the [redacted]

The analysis of the primary efficacy endpoint consisted of the comparison of the two groups using a 2-sided Fisher's exact test. A 95% exact confidence interval on the difference between the two treatment groups was calculated.

For the secondary efficacy endpoints, point estimates and 95% CI per treatment group were presented. The analysis of adjudicated DVT, adjudicated proximal DVT, and adjudicated symptomatic VTE consisted of the comparison of the two groups using a 2-sided Fisher's exact test. A 95% exact confidence interval on the difference between the two treatment groups was calculated.

Studies 63118 and EFC2442 were designed with the same assumptions: Assuming a 9% VTE rate in the enoxaparin group and assuming 5% in the fondaparinux group (targeting a 44% risk reduction with fondaparinux), 800 evaluable patients per treatment group was sufficient to detect a significant superiority of fondaparinux over enoxaparin (two-sided, p=0.05) with a power greater than 85%. Assuming that approximately 30% of patients were expected to have a missing evaluation for the primary efficacy analysis, a total of 2,200 patients were to be randomized.

For testing the robustness of the primary result, three sensitivity analyses ('best' case, 'realistic' case, and 'worst' case) were performed for testing the impact of patients with missing efficacy evaluations. These three scenarios were defined as follows:

a.) Best case – every patient with a missing evaluation of the primary endpoint was considered as a treatment success (no VTE)

b.) Realistic case – the VTE rate for patients with a missing primary endpoint in either of the 2 groups was assumed to be the observed VTE rate in the worst group

c.) Worst case – every patient with a missing evaluation of the primary endpoint was considered as a treatment failure (positive for VTE)

I. Protocol EFC2442

1. Description of Study

This was a multicenter (139 centers), multinational (U.S., Canada, and Australia/New Zealand), randomized, double-blind study of fondaparinux 2.5 mg of o.d. as compared with 30 mg of enoxaparin b.i.d., both started post-operatively.

The objective of this study was to demonstrate superior efficacy of a once-daily, post-operative, subcutaneous injection of 2.5 mg fondaparinux for prevention of venous thromboembolic event (DVT or symptomatic PE), as compared with a twice daily post-operative subcutaneous injection of 30 mg of enoxaparin, in subjects undergoing primary elective total hip replacement (THR) surgery, or revision of component(s) of a THR,

2. Applicant's Analysis

A total of 2275 patients were randomized in this study; 1138 were assigned to receive fondaparinux or 1137 were assigned to receive enoxaparin.

There were 26 patients (1.1%) with treatment assigned out of order according to randomization list. As the number of patients involved was minimal, the number was balanced across treatment groups (13 in each); the involved patients experienced few events (fondaparinux: 1 VTE, 0 major bleeding; enoxaparin: 4 VTE, 0 major bleeding), and the rate of these events were completely consistent with the study results, these irregularities were considered by the applicant of no significance to the overall results of the study.

Note that the randomization code was broken for 7 patients (2 in fondaparinux group and 5 in enoxaparin group). With the exception of one fondaparinux patient (death, Patient 1600005), all other code breaks were for technical/administrative reasons.

2.1 All Treated Population

Of 2275 randomized patients, 18 (10 in fondaparinux group and 8 in enoxaparin group) did not receive any study drug. Data from these 18 patients were not included in any analyses.

A total of 2257 patients (1128 in the fondaparinux group and 1129 in the enoxaparin group) were randomized and treated. The number of randomized and treated patients by country is presented below.

Number of Randomized and Treated Patients by Country — Protocol EFC2442

Country (Number of Centers)	Fondaparinux 2.5 mg OD	Enoxaparin 30 mg BID	Total
United States (94)	655	644	1299
Canada (30)	310	318	628
Australia (15)	163	167	330
Total (139)	1128	1129	2257

Note: A patient was considered to be treated when he/she received at least 1 injection of study drug.
Copied from Table (6.1)2, page 63, Vol.163

A total of 127 of the 2257 randomized and treated patients prematurely stopped study drug (61 in fondaparinux group and 66 in enoxaparin group). The majority of premature discontinuations of study drug were due to non-serious/serious AEs. Most cases of premature treatment discontinuation occurred before Day 5 in each treatment group.

No patients were lost to follow-up during the treatment period. A total of 3 patients in fondaparinux group had no information on the final follow-up assessment form.

2.2 Population for the Primary Efficacy Analysis

Of 2257 randomized and treated patients, a total of 3 patients (2 in fondaparinux group and 1 in enoxaparin group) had no surgery/non-appropriate surgery. A total of 670 patients (339 in fondaparinux group and 331 in enoxaparin group) had non-evaluable/no VTE assessment up to Day 11.

A total of 1584 patients (787 in fondaparinux and 797 in enoxaparin) were included in primary efficacy analysis.

2.3 Treatment Group Comparability

The summary of results of comparability of treatment groups at baseline for all treated patients is given in Attached Table 1.

As seen from Attached Table 1, two treatment groups were similar for demographic, surgical characteristics especially those related to VTE risk (age, obesity, duration of surgery) and for specific medical and surgical history that might have influenced the VTE risk.

2.4 Applicant's Analysis of Primary Efficacy Variable

The primary efficacy endpoint in this study was the outcome event cluster of adjudicated symptomatic/asymptomatic DVT, and fatal or non-fatal PE recorded up to Day 11.

The summary of the number and percentage of patients with adjudicated VTE with a qualifying examination up to Day 11 is given below.

Number of Patients with Adjudicated VTE with a Qualifying Examination up to Day 11 — Protocol EFC2442

Primary Efficacy Population

Fondaparinux 2.5 mg o.d.	Enoxaparin 30 mg b.i.d.	Difference (fond – enox)	Exact 95% CI for Diff	Fisher's exact P-value
48/787 (6.1%)	66/797 (8.3%)	-2.2%	(-5.5%, 0.6%)	0.099

Copied from Tables (7.1.1) 1 and 2, page 80, Vol. 163.

As seen from table above, the VTE rate up to Day 11 was lower in the fondaparinux group than in the enoxaparin group. But, it failed to reach statistical significance.

2.4.1 Sensitivity Analysis

The results of the best case, realistic case and worst case scenario analyses are summarized below.

Sensitivity Analysis on the Primary Efficacy Endpoint
All Treated Patients Who Underwent the Appropriate Surgery —
Protocol EFC2442

Scenario	Fondaparinux 2.5 mg o.d. (N=1126)	Enoxaparin 30 mg b.i.d. (N=1128)	Difference (fond – nox) 95% CI	Fisher's exact P-value
Best Case	48 (4.3%)	66 (5.9%)	-1.6% (-4.04%, 0.41%)	0.102
Realistic	77 (6.8%)	93 (8.2%)	-1.4% (-4.21%, 0.96%)	0.231
Worst Case	387 (34.4%)	397 (35.2%)	-0.8% (-5.05%, 0.17%).	0.691

Copied from Table (7.2.2) 1, page 93, Vol.163
Fisher's exact p-values were obtained by this reviewer.

As seen from the table above, these results were consistent with those observed for the primary efficacy analysis.

2.5 Applicant's Analysis of Secondary Efficacy Variables

The summary of the number and percentage of patients with any adjudicated DVT, adjudicated proximal DVT, and adjudicated distal only DVT up to Day 11 are given below.

Number of Patients with Adjudicated Examination for Assessment of DVT up to Day 11 According to Location of DVT— Protocol EFC2442
Efficacy Evaluable Patients

Location of DVT	Fondaparinux 2.5 mg o.d.	Enoxaparin 30 mg b.i.d.	Diff (fond – enox) Exact 95 CI for Diff	Fisher's exact p-value
Any DVT	44/787 (5.6%)	65/796 (8.2%)	-2.6% (-5.9%, 0.2%)	0.047
Proximal DVT	14/816 (1.7%)	10/830 (1.2%)	0.5% (-1.0%, 2.6%)	0.42
Distal DVT	34/796 (4.3%)	54/800 (6.8%)	-2.5% (-5.6%, 0.0%)	0.037

Copied from Tables (7.1.2) 1 and 2, pages 81-82, Vol. 163.

As seen from table above, the DVT rate up to Day 11 was statistically significantly lower in the fondaparinux group than in the enoxaparin group. But, the proximal DVT rate up to Day 11 was higher in the fondaparinux group than in the enoxaparin group.

3. Safety

In the fondaparinux group, there was a slightly higher percentage of patients with major bleeding mainly at the surgical site (1.8% vs. 1.0%).

4. Reviewer's Evaluation

4.1 Reviewer's Comments on Applicant's Analysis of Primary Endpoint

The summary of adjudicated VTE by country is given below.

Summary of Adjudicated VTE by Country — Protocol EFC2442
Primary Efficacy Population

	Fondaparinux 2.5 mg o.d		Enoxaparin 30 mg b.i.d.				Between Treatment
	Total	Event	Total	Event	Diff	95% C.I.	p-value
Country:							
U.S.	422	21	436	35	-3.0%	(-7.8%, 0.8%)	0.074
Canada	238	21	241	18	1.4%	(-4.7%, 8.7%)	0.619
Australia	127	6	120	13	-6.1%	(-17.4%, 2.4%)	0.094
Overall (Unadjusted)	787	48	797	66	-2.2%		0.099

Compiled by this reviewer from Table (7.2.1) 1, page 88, Vol. 163.
95% CI was copied from Table 14.2.2.2.1, pages 6334-6335, Vol. 184.

As seen from the table above, there were inconsistent results among countries regarding the primary endpoint. The interaction between treatment and country was significant at 0.20 significance level (p=0.134, Breslow-Day method).

However, this reviewer performed an analysis using a logistic regression model adjusting for the interaction. The model included treatment, country and interaction. The resulting p-value for treatment was 0.0691, smaller than observed unadjusted p-value of 0.0921. It failed but was close to statistical significance.

4.2 **Reviewer's Comments on Applicant's Sensitivity Analyses**

Applicant's sensitivity analyses were performed on the all treated patients having undergone the appropriate surgery instead of all randomized patients as specified in protocol.

This reviewer performed the best case and worst case scenario analyses for all treated patients. The results are given below.

Sensitivity Analysis on the Primary Efficacy Endpoint — Protocol EFC2442
All Treated Patients

Scenario	Fondaparinux 2.5 mg o.d. (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)	Difference (fond – enox) 95% CI	Fisher's exact P-value
Best Case	48 (4.3%)	66 (5.8%)	-1.5% (-4.0%, 0.4%)	0.102
Worst Case	387 (34.3%)	397 (35.2%)	-0.9% (-5.1%,3.1%)	0.691

This table was complied by this reviewer.
Fisher's exact p-values were obtained by this reviewer.

Per medical officer's request, the applicant performed the best case, realistic case and worst case scenario analyses for randomized patients. The results are given below.

Sensitivity Analysis on the Primary Efficacy Endpoint — Protocol EFC2442 Randomized Patients

Scenario	Fondaparinux 2.5 mg o.d. (N=1138)	Enoxaparin 30 mg b.i.d. (N=1137)	Difference (fond – enox) 95% CI	Fisher's exact P-value
Best Case	48 (4.2%)	66 (5.8%)	-1.6% (-3.94%, 0.47%)	0.085
Realistic Case	78 (6.9%)	94 (8.3%)	-1.4% (-4.12%, 1.02%)	0.206
Worst Case	399 (35.1%)	405 (35.6%)	-0.6% (-4.70%, 3.51%)	0.793

Copied from Table (7.2.2) 1b, page 1, Attachment 2, Amendment dated 5/1/01.
Fisher's exact p-values were obtained by this reviewer

As seen from tables above, these results were consistent with those obtained by the applicant for the primary efficacy analysis.

4.3 **Subgroup Analysis**

Attached Table 2 summaries the number of patients with adjudicated VTE up to Day 11 by subgroup and treatment group.

Each covariate was analyzed in a logistic regression model separately for each treatment group using the covariate as explanatory variable, to test whether there was a significant covariate effect within treatment group. For covariate with n>2 categories, n-1 binary variables were created. Extremely small subgroups with ≤20 patients were combined with the adjacent subgroup. Each covariate by treatment interaction was tested on the binary covariate using the Breslow-Day test for homogeneity of the odds ratios.

As seen from Attached Table 2, significant heterogeneity of treatment effect was observed at the significance level of 0.2 for previous VTE and creatinine before surgery. In both the fondaparinux and enoxaparin groups, patients without previous VTEs experienced less adjudicated VTEs than those patients with previous VTE. For patients with creatinine before surgery < median, enoxaparin group had statistically significantly more patients with adjudicated VTEs than fondaparinux group.

The applicant also performed an exploratory analysis of adjudicated VTE up to Day 11 adjusting for baseline covariates using forward logistic regression for selection of covariates. In addition to treatment, four baseline covariates: previous VTE, age < 65, creatinine before surgery ≥ median and general anesthesia were entered into the model. The resulting p-value for treatment was 0.1424.

II. Protocol 63118 (EPHESUS)

1. Description of Study

This study, European Pentasccharide Hip Elective Surgery Study (EPHESUS), was a multiceter (74 centers in 16 countries), randomized, double-blind study.

The object of this study was to demonstrate superior efficacy of once-daily subcutaneous injection of 2.5 mg fondaparinux as compared with once-daily injection of 40 mg

enoxaparin, for the prevention of venous thromboembolic events (VTE), i.e. deep vein thrombosis (DVT) or symptomatic pulmonary embolism (PE), in subjects undergoing primary elective total hip replacement (THR) surgery, or revision of component(s) of a THR.

The design of this study was similar to that of Study EFC2442.

The administration of fondaparinux started post-operative (at 6± 2 hours after surgery closure) and that of enoxaparin pre-operatively (at 12± 2 hours before surgery start).

2. Applicant's Analysis

During the blind review of data before database lock, 15 patients were identified to be excluded from all analyses. Among them, 3 patients were "randomized" to study medication already assigned to previously randomized but not treated patients. These patients received pseudo subject numbers not used in the randomization scheme and were considered not randomized. Furthermore, all 12 patients of center 0454 were excluded from all analyses due to lost CRFs and limited credibility of the remaining data.

Of the remaining 2309 patients randomized, 1155 were assigned to receive fondaparinux and 1154 were assigned to receive enoxaparin group.

2.1 **All Treated Population**

Of 2309 randomized patients, 36 (15 in fondaparinux group and 21 in enoxaparin group) did not receive any study drug. Data from these 36 patients were not included in any analyses.

A total of 2273 patients (1140 in the fondaparinux group and 1133 in the enoxaparin group) were randomized and treated. The number of randomized and treated patients by country is presented below.

Number of Randomized and Treated Patients by Country — Protocol 63118

Country (Number of Centers)	Fondaparinux 2.5 mg OD	Enoxaparin 40 mg OD	Total
Denmark (15)	279	278	557
Finland (6)	118	119	237
Germany (4)	107	106	213
Austria (3)	88	88	176
Sweden (6)	89	87	176
The Netherlands (5)	90	83	173
Norway (5)	86	84	170
Czech Republic (5)	69	69	138
Belgium (4)	59	60	119
United Kingdom (3)	56	58	114
France (7)	40	40	80
Hungary (3)	18	18	36
Poland (2)	17	18	35
Spain (3)	10	12	22
Greece (1)	8	7	15
Italy (1)	6	6	12
Total (73)	1140	1133	2273

Note: A patient was considered to be treated when he/she received at least 1 injection of study drug
Copied from Table (6.1) 2, page 64, Vol.117.

Noted that two patients were randomized twice in this trial. One patient was randomized the first time as patient #04510171 to enoxaparin without being operated and treated due to technical problems, and a second time as patient #04510430 to fondaparinux who completed the study. One patient was randomized the first time as patient #03510099 to enoxaparin, had a surgery on the left side and completed the study. This patient was randomized a second time as patient #03510873 to fondaparinux had a surgery on the right side and completed the study again. No adjudicated VTE or major/minor bleed was reported for these patients. The 2 cases were considered as 2 different patients in the statistical analysis.

A total of 70 (6.1%) patients who received fondaparinux and 58 (5.1%) who received enoxaparin permanently discontinued study drug prematurely.

2.2 **Population for the Primary Efficacy Analysis**

A total of 21 patients (11 in fondaparinux group and 10 in enoxaparin group) had no surgery/non-appropriate surgery.

A total of 425 patients (221 in fondaparinux group and 204 in enoxaparin group) had non-evaluable/no VTE assessment up to Day 11.

A total of 1827 patients (908 in fondaparinux group and 919 in enoxaparin group) were included in primary efficacy analysis.

2.3 Treatment Group Comparability

The summary of results of comparability of treatment groups at baseline for all treated patients is given in Attached Table 3.

As seen from Attached Table 3, two treatment groups were similar for demographic, surgical characteristics especially those related to VTE risk (age, obesity, duration of surgery) and for specific medical and surgical history that might have influenced the VTE risk, with the exception of history of cancer. There were fewer patients with a history of cancer in the fondaparinux group than in the enoxaparin group (4.8% vs. 7.3%).

2.4 Applicant's Analysis of Primary Efficacy Variable

The summary of the number and percentage of patients with adjudicated VTE with a qualifying examination up to Day 11 is given below.

Number of Patients with Adjudicated VTE with a Qualifying Examination up to Day 11 — Protocol 63118

Primary Efficacy Population

Fondaparinux 2.5 mg o.d.	Enoxaparin 40 mg o.d.	Difference (fond – enox)	Exact 95% CI for Diff	Fisher's exact P-value
37/908 (4.1%)	85/919 (9.2%)	-5.2%	(-8.1%, -2.7%)	<0.0001

Copied from Tables (7.1.1) 1 and 2, page 85, Vol. 117.

As seen from the table above, fondaparinux 2.5 o.d. was highly superior to enoxaparin 40 mg o.d. for prophylaxis of VTE.

2.4.1 Sensitivity Analysis

The results of the best case, realistic case and worst case scenario analyses are summarized below.

Sensitivity Analysis on the Primary Efficacy Endpoint — Protocol 63118
All Treated Patients Who Underwent the Appropriate Surgery

Scenario	Fondaparinux 2.5 mg o.d. (N=1129)	Enoxaparin 40 mg o.d. (N=1123)	Difference (fond – enox) 95% CI	Fisher's exact P-value
Best Case	37 (3.3%)	85 (7.6%)	-4.3% (-6.7%, .-2.2%)	<0.0001
Realistic	58 (5.1%)	103 (9.2%)	-4.0% (-6.7%, -1.7%)	0.0002
Worst Case	258 (22.9%)	289 (25.7%)	-2.9% (-6.8%, 0.8%).	0.116

Copied from Table (7.2.2) 1, page 95, Vol.117
Fisher's exact p-values were obtained by this reviewer.

As seen from the table above, these results were consistent with those observed for the primary efficacy analysis.

2.5 Applicant's Analysis of Secondary Efficacy Variables

The summary of the number and percentage of patients with any adjudicated DVT, adjudicated proximal DVT, and adjudicated distal only DVT up to Day 11 are given below.

Number of Patients with Adjudicated Examination for Assessment of DVT up to Day 11 According to Location of DVT — Protocol 63118

Efficacy Evaluable Patients

Location of DVT	Fondaparinux 2.5 mg o.d.	Enoxaparin 40 mg o.d.	Diff (fond – enox) Exact 95 CI for Diff	Fisher's exact p-value
Any DVT	36/908 (4.0%)	83/918 (9.0%)	-5.1% (-8.0%, -2.6%)	<0.001
Proximal DVT	6/922 (0.7%)	23/927 (2.5%)	-1.8% (-3.7%, -0.5%)	0.0021
Distal DVT	30/909 (3.3%)	67/917 (7.3%)	-4.0% (-6.8%, -1.7%)	0.0001

Copied from Tables (7.1.2) 1 and 2, pages 86-87, Vol. 117.

As seen table above, fondaparinux 2.5 mg o.d. was highly superior to enoxaparin 40 mg o.d. for prophylaxis of DVT, as shown by the DVT rate up to Day 11 which was statistically significantly lower in the fondaparinux group than in the enoxaparin group. Similar results were observed for proximal DVTs and distal DVTs.

3. Safety

In the fondaparinux group, there was a somewhat higher percentage of patients with major bleeding mainly at the surgical site (4.1% vs. 2.8%), as well as more patients experiencing a decrease in hemoglobin (16.5% vs. 11.0%).

4. Reviewer's Evaluation

4.1 Reviewer's Comments on Applicant's Analysis of Primary Endpoint

The summary of adjudicated DVT event by country is given below.

Summary of Adjudicated DVT Event by Country — Protocol 63118
Primary Efficacy Population

	Fondaparinux 2.5 mg o.d		Enoxaparin 40 mg o.d.				
	Total	Event	Total	Event	Diff	95% C.I.	p-value
Country:							
Denmark	217	1	211	5	-1.9%	(-7.5%, 1.8%)	0.118
Finland	97	4	110	2	2.3%	(-5.0%, 13.6%)	0.422
Germany	90	4	86	7	-3.7%	(-17.8%, 6.5%)	0.363
Austria	78	8	79	4	5.2%	(-6.6%, 20.0%)	0.246
Norway	75	4	78	13	-11.3%	(-26.9%, 0.8%)	0.038
Sweden	70	2	67	6	-6.1%	(-22.3%, 5.6%)	0.159
Netherlands	60	1	56	8	-12.6%	(-30.9%, 0.8%)	0.014
Czech Rep	54	6	59	15	-14.3%	(-33.9%, 2.8%)	0.057
United Kingdom	43	0	49	4	-8.2%	(-28.3%, 5.8%)	0.120
Belgium	40	3	43	7	-8.8%	(-31.9%, 9.8%)	0.316
France	34	2	33	3	-3.2%	(-29.1%, 17.4%)	0.673
Poland	16	0	16	6	-37.5%	(-68.0%, -0.7%)	0.018
Hungary	15	1	15	2	-6.7%	(-43.6%, 29.8%)	1.000
Spain	10	1	9	1	-1.1%	(-51.7%, 42.9%)	1.000
Greece	8	0	7	2	-28.6%	(-76.8%, 24.1%)	0.200
Italy	1	0	1	0	0.0%	(-97.6%, 97.6%).	
Total	908	37	919	85	-5.2%		<0.0001

Copied from Table (7.2.1) 1, page 91, Vol. 117.
95% CI was copied from Table 14.2.2.2.1, Vol. 138.
P-values were obtained by this reviewer using Fisher's exact test.

As seen from the table above, all countries except Finland and Austria showed a trend in favor of fondaparinux. There were four countries (Norway, Netherlands, Czech Rep, and Poland) where the difference between treatment groups achieved statistical significance in favor of fondaparinux.

There was heterogeneity of odds ratios among countries. The interaction between treatment and country was statistically significant at 0.20 significance level (p=0.063, Breslow-Day method).

Furthermore, this reviewer performed an analysis using a generalized linear model by using SAS GENMOD procedure for adjusting for country and interaction between treatment and country. The resulting p-value for treatment was 0.0001. It reconfirmed the applicant's finding.

4.2 Reviewer's Comments on Applicant's Sensitivity Analyses

Applicant's sensitivity analyses were performed on the all treated patients having undergone the appropriate surgery instead of the all randomized patients as specified in protocol.

This reviewer performed the best case and worst case scenario analyses for all treated patients. The results are given below.

Sensitivity Analysis on the Primary Efficacy Endpoint — Protocol 63118
All Treated Patients

Scenario	Fondaparinux 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)	Difference (fond – enox) 95% CI	Fisher's exact P-value
Best Case	37 (3.2%)	85 (7.5%)	-4.3% (-6.6%, -2.2%)	<0.0001
Worst Case	269 (23.6%)	299 (26.4%)	-2.8% (-6.7%, 0.9%).	0.133

Compiled by this reviewer.
Fisher's exact p-values were obtained by this reviewer.

Per medical officer's request, the applicant performed the best case, realistic case and worst case scenario analyses for randomized patients. The results are given below.

Sensitivity Analysis on the Primary Efficacy Endpoint — Protocol 63118
Randomized Patients

Scenario	Fondaparinux 2.5 mg o.d. (N=1155)	Enoxaparin 40 mg o.d. (N=1154)	Difference (fond – enox) 95% CI	Fisher's exact P-value
Best Case	37 (3.2%)	85 (7.4%)	-4.2% (-6.48%, -2.11%)	<0.0001
Realistic Case	60 (5.2%)	106 (9.2%)	-4.0% (-6.59%, -1.65%)	0.0002
Worst Case	284 (24.6%)	319 (27.6%)	-3.1% (-6.95%, 0.71 %).	0.097

Copied from Table (7.2.2) 1b, page 1, Attachment 2, Amendment dated 5/1/01.
Fisher's exact p-values were obtained by this reviewer.

As seen from tables above, these results were consistent with those obtained by the applicant for the primary efficacy analysis.

4.3 **Subgroup Analysis**

Attached Table 4 summaries the number of patients with adjudicated VTE up to Day 11 by subgroup and treatment group.

As seen from Attached Table 4, significant heterogeneity of treatment effect was observed at the significance level of 0.2 for gender, obesity, type of anesthesia, and creatinine before surgery.

There were consistent results in favor of fondaparinux against enoxaparin for gender, use of cement, and duration of surgery subgroups. There were significantly fewer adjudicated VTE in the fondaparinux group compared with the enoxaparin group for subgroups of patients with age ≥ 65, BMI $< 30 kg/m^2$, regional anesthesia, primary surgery, no previous VTE, creatinine before surgery $\geq$ median, and no previous antithrombotic treatment.

The applicant also performed an exploratory analysis of adjudicated VTE up to Day 11 adjusting for baseline covariates using forward logistic regression for selection of covariates. In addition to treatment, covariates: countries: Czech Republic, Denmark, Finland, Poland, Belgium, Norway, Greece, previous VTE, age < 65, type of surgery: revision, and age ≥ 75 were entered into the model. The resulting p-value for treatment was 0.0001.

C. Overall Summary and Recommendation

Study EFC2442 showed that the VTE rate up to Day 11 was lower in the fondaparinux 2.5 mg o.d. group than in the enoxaparin 30 mg b.i.d. group. But, it failed to reach statistical significance. However, the DVT rate up to Day 11 was statistically significantly lower in the fondaparinux group than in the enoxaparin group. But, the proximal DVT rate up to Day 11 was higher in the fondaparinux group than in the enoxaparin group.

Study 63118 showed that the fondaparinux 2.5 o.d. was highly superior to enoxaparin 40 mg o.d. for prophylaxis of VTE. Furthermore, the fondaparinux 2.5 mg o.d. was highly superior to enoxaparin 40 mg o.d. for prophylaxis of DVT, as shown by the DVT rate up to Day 11 which was statistically significantly lower in the fondaparinux group than in the enoxaparin group. Similar results were observed for proximal DVTs and distal DVTs.

Milton C. Fan, Ph.D.
Mathematical Statistician

This review consists of 15 pages of text and 6 pages of tables.

concur: Dr. Permutt
Dr. Nevius

cc:
Archival NDA 21-345
HFD-180
HFD-180/Dr. Talarico
HFD-180/Dr. Robie-Suh
HFD-180/Dr. Lu
HFD-180/Ms. Oliver
HFD-700/Dr. Anello
HFD-715/Dr. Nevius
HFD-715/Dr. Permutt
HFD-715/Dr. Rashid
HFD-715/Dr. Fan

Table 1 Summary of Demographic and Baseline Characteristics --- Protocol EFC2442

Characteristics	Fondaparinux 25 mg o.d. (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)	Between Treatment p-value
Sex			0.146
Male	556 (49.3%)	522 (46.2%)	
Female	572 (50.7%)	607 (53.8%)	
Race			0.573
White	1059 (93.9%)	1057 (93.6%)	
Black	50 (4.4%)	46 (4.1%)	
Asian/Oriental	4 (0.4%)	3 (0.3%)	
Other	15 (1.3%)	23 (2.0%)	
Age (yr)			0.93
Mean (SD)	64.6 (12.7)	64.6 (12.6)	
Age			0.037
<65	490 (43.3%)	478 (42.3%)	
[65, 75)	353 (31.3%)	405 (35.9%)	
≥ 75	285 (25.3%)	246 (21.8%)	
Height (cm)			0.082
N	1122	1125	
Mean (SD)	169.2 (10.5)	168.4 (10.5)	
Weight (kg)			0.092
N	1128	1127	
Mean (SD)	82.3 (18.8)	81.0 (19.3)	
BMI (kg/m^2)			0.846
<30	749 (66.8%)	746 (66.4%)	
≥30	373 (33.3%)	378 (33.6%)	
Missing	6	5	
Type of Surgery			0.083
Primary	948 (84.0%)	978 (86.6%)	
Revision	180 (16.0%)	151 (13.4%)	
Use of Cement			0.376
Yes	577 (51.2%)	598 (53.0%)	
No	551 (48.8%)	530 (47.0%)	
Missing	0	1	
Type of Anaesthesia			0.460
General only	792 (70.2%)	815 (72.2%)	
Regional only	288 (25.5%)	263 (23.3%)	
Combination	48 (4.3%)	51 (4.5%)	
Duration of Surgery			0.49
N	1125	1128	
Mean (hh:mm)	2:29	2:27	

P-values for categorical data were obtained by this reviewer using Chi-square test.

Table 1 Summary of Demographic and Baseline Characteristics --- Protocol EFC2442 (Continued)

Characteristics	Fondaparinux 25 mg o.d. (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)	Between Treatment p-value
Specific medical history			
VTE	52 (4.6%)	63 (5.6%)	0.295
Stroke	25 (2.2%)	34 (3.0%)	0.236
Myocardial infraction	65 (5.8%)	60 (5.3%)	0.642
Cancer	151 (13.4%)	145 (12.8%)	0.702
Orthopedic surgery within the previous 12 months			
Any surgery	134 (11.9%)	124 (11.0%)	0.503
Hip replacement	78 (6.9%)	70 (6.2%)	0.493
Knee replacement	18 (1.6%)	13 (1.2%)	0.365
Other surgery	51 (4.5%)	46 (4.1%)	0.601

P-values for categorical data were obtained by this reviewer using Chi-square test.

Table 2 The Number of Patients with Adjudicated VTE up to Day 11 by Subgroup --- Protocol EFC2442

Subgroup	Fondaparinux 25 mg o.d.	Enoxaparin 30 mg b.i.d.	Difference	95% C.I.	Breslow-Day p-value
Age					0.869
<65	17/335 (5.1%)	21/319 (6.6%)	-1.5%	(-7.1%, 2.9%)	
≥65	31/452 (6.9%)	45/478 (9.4%)	-2.6%	(-7.4%, 1.5%)	
Sex					0.399
Male	25/386 (6.5%)	28/375 (7.5%)	-1.0%	(-6.4%, 3.3%)	
Female	23/401 (5.7%)	38/422 (9.0%)	-3.3%	(-8.3%, 0.9%)	
Race					0.335
White	46/748 (6.1%)	64/753 (8.5%)	-2.4%	(-5.9%, 0.6%)	
Black	1/22 (4.5%)	2/22 (9.1%)	-4.6%	(-35.3%, 22.9%)	
Asian	0/4 (0.0%)	0/3 (0.0%)	0.0%	(-81.3%, 64.8%)	
Other	1/13 (7.7%)	0/19 (0.0%)	7.7%	(-20.3%, 48.4%)	
Obesity					0.323
BMI<30 kg/m^2	34/542 (6.3%)	41/541 (7.6%)	-1.3%	(-5.4%, 2.3%)	
BMI≥30 kg/m^2	14/240 (5.8%)	25/252 (9.9%)	-4.1%	(-11.3%, 1.6%)	
Type of Anesthesia					0.914
Regional only	17/220 (7.7%)	20/183 (10.9%)	-3.2%	(-11.8%, 3.6%)	
Other	31/567 (5.5%)	46/614 (7.5%)	-2.0%	(-5.9%, 1.2%)	
Type of Surgery					0.398
Primary	41/668 (6.1%)	54/691 (7.8%)	-1.7%	(-5.4%, 1.4%)	
Revision	7/119 (5.9%)	12/106 (11.3%)	-5.4%	(-17.7%, 3.8%)	
Use of Cement					0.500
Yes	27/411 (6.6%)	43/441 (9.8%)	-3.2%	(-8.3%, 1.1%)	
No	21/376 (5.6%)	23/355 (6.5%)	-0.9%	(-6.2%, 3.2%)	
Duration of Surgery					0.375
< median	25/364 (6.9%)	30/381 (7.9%)	-1.0%	(-6.5%, 3.4%)	
≥ median	23/422 (5.5%)	36/416 (8.7%)	-3.2%	(-8.1%, 0.9%)	
Previous VTE					0.177
Yes	7/40 (17.5%)	6/50 (12.0%)	5.5%	(-13.1%, 28.2%)	
No	41/747 (5.5%)	60/747 (8.0%)	-2.5%	(-5.9%, 0.4%)	
Creatinine before Surgery					0.048
< median	18/302 (6.0%)	37/324 (11.4%)	-5.5%	(-11.7%, -0.3%)	
≥ median	30/448 (6.7%)	27/438 (6.2%)	0.5%	(-3.2%, 5.2%)	

Copied from Table 14.2.2.2.1, pages 6334-6335, Vol. 184
Breslow-Day p-values were obtained by this reviewer.

Table 3 Summary of Demographic and Baseline Characteristics --- Protocol 63118

Characteristics	Fondaparinux 25 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)	Between Treatment p-value
Sex			0.470
Male	493 (43.2%)	473 (41.7%)	
Female	647 (56.8%)	660 (58.3%)	
Race			0.345
White	1128 (99.0%)	1125 (99.4%)	
Black	6 (0.5%)	6 (0.5%)	
Asian/Oriental	2 (0.2%)	1 (0.1%)	
Other	3 (0.3%)	0 (0.0%)	
Age (yr)			0.40
Mean (SD)	65.1 (11.3)	65.5 (11.1)	
Age			0.245
<65	493 (43.2%)	465 (41.0%)	
[65, 75)	402 (35.3%)	438 (38.7%)	
≥ 75	245 (21.5%)	230 (20.3%)	
Height (cm)			0.067
N	1117	1098	
Mean (SD)	168.4 (9.0)	167.7 (9.0)	
Weight (kg)			0.88
N	1136	1126	
Mean (SD)	76.2 (14.6)	76.3 (14.7)	
BMI (kg/m^2)			0.21
<30	899 (80.5%)	838 (76.5%)	
≥30	218 (19.5%)	258 (23.5%)	
Missing	23	37	
Type of Surgery			0.206
Primary	1002 (88.8%)	978 (87.0%)	
Revision	127 (11.2%)	146 (13.0%)	
Missing	2	0	
Use of Cement			0.911
Yes	674 (59.8%)	673 (60.0%)	
No	453 (40.2%)	448 (40.0%)	
Missing	4	3	
Type of Anaesthesia			0.240
General only	394 (34.8%)	430 (38.3%)	
Regional only	685 (60.6%)	646 (57.5%)	
Combination	52 (4.6%)	48 (4.3%)	
Duration of Surgery			0.060
N	1123	1120	
Mean (hh:mm)	2:20	2:24	

P-values for categorical data were obtained by this reviewer using Chi-square test.

Table 3 Summary of Demographic and Baseline Characteristics --- Protocol 63118 (Continued)

Characteristics	Fondaparinux 25 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)	Between Treatment p-value
Specific medical history			
VTE	45 (3.9%)	56 (4.9%)	0.250
Stroke	16 (1.4%)	26 (2.3%)	0.115
Myocardial infraction	40 (3.5%)	44 (3.9%)	0.636
Cancer	56 (4.9%)	81 (7.1%)	0.025
Orthopedic surgery within the previous 12 months			
Any surgery	113 (9.9%)	105 (9.3%)	0.602
Hip replacement	62 (5.4%)	60 (5.3%)	0.880
Knee replacement	7 (0.6%)	4 (0.4%)	0.370
Hip fracture	20 (1.8%)	10 (0.9%)	0.069
Other surgery	31 (2.7%)	33 (2.9%)	0.781

P-values for categorical data were obtained by this reviewer using Chi-square test.

Table 4 The Number of Patients with Adjudicated VTE up to Day 11 by Subgroup --- Protocol 63118

Subgroup	Fondaparinux 25 mg o.d.	Enoxaparin 40 mg o.d.	Difference	95% C.I.	Breslow-Day p-value
Age					0.790
<65	12/385 (3.1%)	25/377 (6.6%)	-3.5%	(-8.2%, 0.2%)	
≥65	25/523 (4.8%)	60/542 (11.1%)	-6.3%	(-10.6%, -2.7%)	
Sex					0.043
Male	9/396 (2.3%)	37/402 (9.2%)	-6.9%	(-11.6%, -3.3%)	
Female	28/512 (5.5%)	48/517 (9.3%)	-3.8%	(-8.2%, -0.2%)	
Obesity					0.185
BMI<30 kg/m^2	28/721 (3.9%)	70/702 (10.0%)	-6.1%	(-9.6%, -3.1%)	
BMI≥30 kg/m^2	9/173 (5.2%)	14/193 (7.3%)	-2.1%	(-10.5%, 4.4%)	
Type of Anesthesia					0.091
Regional only	19/555 (3.4%)	54/529 (10.2%)	-6.8%	(-10.8%, -3.4%)	
Other	18/353 (5.1%)	31/390 (7.9%)	-2.8%	(-8.1%, 1.4%)	
Type of Surgery					0.870
Primary	35/802 (4.4%)	79/800 (9.9%)	-5.5%	(-8.7%, -2.7%)	
Revision	2/106 (1.9%)	6/119 (5.0%)	-3.1%	(-13.8%, 4.3%)	
Use of Cement					0.362
Yes	25/542 (4.6%)	51/558 (9.1%)	-4.5%	(-8.6%, -1.2%)	
No	12/365 (3.3%)	34/360 (9.4%)	-6.1%	(-11.3%, -1.9%)	
Duration of Surgery					0.800
< median	17/448 (3.8%)	40/441 (9.1%)	-5.3%	(-9.8%, -1.5%)	
≥ median	20/457 (4.4%)	45/476 (9.5%)	-5.1%	(-9.6%, -1.4%)	
Previous VTE					0.560
Yes	4/35 (11.4%)	7/40 (17.5)	-6.1%	(-30.5%, 15.2%)	
No	33/873 (3.8%)	78/879 (8.9%)	-5.1%	(-8.1%, -2.6%)	
Creatinine before Surgery					0.105
< median	20/436 (4.6%)	35/442 (7.9%)	-3.3%	(-8.0%, 0.3%)	
≥ median	15/452 (3.3%)	50/465 (10.8%)	-7.5%	(-11.9%, -3.8%)	
Previous Antithrom Treatment					
Yes	0/6 (0.0%)	0/1 (0.0%)	0.0%	(-69.5%, 99.6%)	
No	37/902 (4.1%)	85/918 (9.3%)	-5.2%	(-8.1%, -2.7%)	

Copied from Table 14.2.2.2.1, Vol. 138.
Breslow-Day p-values were obtained by this reviewer.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Milton Fan
7/10/01 10:30:26 AM
BIOMETRICS

added nda review and clinical studies in Key Words

Thomas Permutt
7/10/01 03:42:25 PM
BIOMETRICS
See my secondary review.

S. Edward Nevius
7/12/01 02:50:07 PM
BIOMETRICS
Concur with review.

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA #: 21-345

Drug Class: 1P

Drug: Xantidar (fondaparinux sodium)

Indication: Prevention of venous thromboembolic events (VTE) in patients undergoing major orthopedic surgery of the lower limb such as hip fracture, major knee or hip replacement surgeries

Sponsor: Fonda BV

Clinical Reviewers: Min Lu, M.D. and Ann Farrell, M.D.

Statistical Reviewer: Mushfiqur Rashid, Ph.D.

Documents Reviewed: Volumes 1 - 301, Dated February 15, 2001

User Fee Due Date: February 14, 2001

Key words: VTE, hip replacement, knee replacement, hip fracture

1. INTRODUCTION

This submission addresses the efficacy and safety of fondaparinux compared with enoxaparin for the prevention of venous thromboembolic events (VTE) in patients undergoing major orthopedic surgery of the lower limb such as hip fracture, major knee or hip replacement surgeries. Enoxaparin is an approved drug for the prevention of VTE in patients undergoing primary elective hip and knee replacement.

This submission contains four studies:

1) EFC2698 ——— which compared fondaparinux 2.5 mg subcutaneous once daily (o.d.) with enoxaparin 40 mg once daily in the prevention of deep vein thrombosis and symptomatic pulmonary embolism in hip fracture surgery;

2) 095-002 ——— which compared fondaparinux 2.5 mg subcutaneous once daily with enoxaparin 30 mg subcutaneous injection twice daily (b.i.d) in the prevention of VTE after elective major knee surgery or revisions of component(s);

3) 63118 (Ephesus) which compared fondaparinux 2.5 mg subcutaneous once daily with enoxaparin 40 mg once daily in the prevention of deep vein thrombosis in subjects with elective total hip replacement;

4) EFC2442 ——— which compared fondaparinux 2.5 mg subcutaneous once daily with enoxaparin 30 mg b.i.d. in the prevention of deep vein thrombosis in the subjects undergoing elective total hip replacement.

In addition, there are two dose finding studies (DRI2643: ——— and 095-001 ———, which compared different doses (0.75, 1.5, 3, 6, and 8 mg o.d.) of Fondaparinux with enoxaparin. ——— included patients undergoing total hip replacement surgery whereas ——— included patients undergoing total knee replacement surgery. The sponsor indicated that fondaparinux 2.5 mg dose was chosen for the four studies on the basis of ——— and ——— studies.

The study EFC2698 ———) showed that fondaparinux 2.5 mg was significantly more effective (p-value <0.0001) in the prevention of VTE than enoxaparin in patients undergoing hip fracture surgery. The study 095-002 ——— showed that Fondaparinux 2.5 mg was significantly more effective (p-value < 0.0001) in the prevention of VTE than enoxaparin in patients undergoing total knee replacement surgery. The Ephesus and ——— trials for hip replacement surgery have been reviewed by Dr. Milton Fan (HFD-715).

This review is organized as follows: Section 1 describes study EFC2698 ———, Section 2 describes study 095-002 ——— and Section 3 summarizes the conclusions.

1. Study EFC2698 ———

Study EFC2698 was a multinational, multicenter, randomized, double blind, parallel group enoxaparin-controlled trial evaluating the efficacy of fondaparinux (2.5 mg o.d.) in patients undergoing a hip fracture surgery.

Primary Objective:

The objective of this study was to compare the efficacy (i.e., determine superiority) and safety of a 2.5 mg once daily(o.d.) subcutaneous (SC) injection of fondaparinux to once daily SC injection of enoxaparin 40 mg for prevention of deep vein thrombosis (DVT) and symptomatic pulmonary embolism (PE), in patients undergoing hip fracture surgery.

Design

This study was a multi-center, double blind, parallel design, enoxaparin-controlled trial.

The administration of fondaparinux started post-operatively (at 6 ± 2 hours after surgery closure) and that of enoxaparin pre-operatively (at 12± 2 before surgery start) when surgery was planned within 24 hours after hospital admission. If surgery was delayed to 24-48 hours after admission, both study drugs were administered 12 ± 2 hours before surgery. Study treatment was given up to day 7 ± 2 (day 1 of the start of the surgery) or until the mandatory venogram was obtained, whichever came first. A mandatory venogram had to be performed between day 5 and day 11, but not more than 2 calendar days after the last study treatment administration.

Sample Size:
The sponsor indicated that there were no pilot clinical trials conducted for hip fracture surgery with fondaparinux. The incidence of VTEs under enoxaparin group had been cited as 22% in a small hip fracture study (less than 150 patients per group). Therefore, the VTE rate was set at 22% in the sample size calculation and a risk reduction of about 30% with Fondaparinux treatment was targeted. With 600 evaluable (non-missing efficacy assessment) patients per group, the power to detect a significant difference (with a 2-sided alpha of 0.05) between the enoxaparin group (22%) and fondaparinux group (155) was greater than 85%. Thus approximately 1700 patients were to be randomized with 30% of patients expected to have a missing evaluation for the primary efficacy analysis.

Interim analyses:
The sponsor mentioned that the uncertainty in the estimates of the VTE rates as well as the risk reduction between the two products for sizing this phase III study justified the need for reassessment of study size during the trial. As planned in the protocol, an interim analysis was carried out when half of the number of patients (i.e., 850 patients) were randomized and when adjudication of the primary efficacy criterion was available and validated for those patients. No statistical type I error rate adjustment for the final analysis was required according to simulations performed during the protocol development in order to measure the impact of sample size reassessment. Following the interim analysis, which became available on July 6, 1999, the DMC recommended to continue the study as planned without increasing the sample size.

Patient Disposition:
There were 1711 patients randomized to two treatment groups: 849 to fondaparinux 2.5 mg and 862 to enoxaparin 40 mg. The following table gives the composition of different patient populations by treatment group.

Table 1.1 (sponsor's): Disposition of Patients Enrolled: Number of Patients (extracted from Volume 81 of Submission, page 2)

Population	fondaparinux 2.5 mg	Enoxaparin 40 mg	Total
Total Randomized	849	862	1711

Randomized and Treated (ITT)	831	842	1673
Evaluable population for primary efficacy analysis (primary efficacy population)	626	624	1250

Baseline Demographics

The sponsor summarized demographic characteristics (age, sex, race, weight, height, etc.) by treatment groups. There was no relevant difference between the treatment groups regarding demographic characteristics. Summary statistics for age, sex, and race by treatment group are given in the following table.

Table 1.2 (sponsor's): Disposition of Patients Enrolled By Demograhic Characterstics: Number (%) of Patients (extracted from Table 6.4.1, Volume 81 of submission)

Subgroup	fondaparinux 2.5 mg N=831	enoxaparin 40 mg N=842	Total N=1673
Age n	827	839	1666
Mean age	76.8	77.3	77.0
<65 years	111 (13.4%)	104 (12.4%)	215 (12.9%)
≥ 65 years	716 (86.2%)	735 (84.29%)	1451 (87.09%)
Missing	4 (0.05%)	3 (0.04%)	7 (0.04%)
Sex			
Male	187 (22.5%)	224 (26.6%)	411 (24.6%)
Female	644 (77.5%)	618 (73.4%)	1262 (75.4%)
Race			
Caucasian	826 (99.4%)	833 (98.9%)	1659 (99.2%)
Black	2 (0.2%)	1 (0.1%)	3 (0.2%)
Asian/Oriental	3 (0.4%)	5 (0.6%)	8 (0.5%)
Other race	0 (0.0%)	3 (0.4%)	3 (0.2%)

Diagnosis and Criteria for Inclusion:

- Patients undergoing standard surgery for fracture of upper third of the femur, including femoral head and neck, not more than 48 hours after admission

- ≥ 18 years of age

- Men or women of non-child bearing potential or those having a negative pregnancy test within 48 hours prior to surgery or first study drug administration, whichever came first

- Written informed consent

Treatment Allocation:

The sponsor indicated that patients were randomly assigned to treatment using balanced randomization blocks consisting of equal numbers of fondaparinux and enoxaparin treatments (blocks of 4). Allocation was made within the sites. At inclusion, each patient was assigned by the investigator to a treatment number within each block; the investigators had to complete a block before starting the following one. In all cases, the randomization was performed as close to treatment as possible and within 24 hours after admission and before surgery. A patient was considered as randomized if a date and a treatment number were recorded in the 'treatment assignment' form of the CRF. Randomized patients who did not complete treatment were not replaced.

Test Product, Dose and Mode of Administration

Fondaparinux

Dose: 2.5 mg o.d.

Mode of Administration:Subcutaneous

Enoxaparin:

Dose: 40 mg o.d.

Mode of Administration: Subcutaneous

Duration of Treatment: up to day 7±2

Duration of Observation: Treatment period and follow-up period (from end of treatment up to day 42±7)

Criteria of Evaluation:

The primary endpoint was the cluster of the following VTE outcome results recorded up to day 11:

- Adjudicated venogram positive for DVT or adjudicated symptomatic/asymptomatic DVT

- Adjudicated PE

All venograms, scheduled or unscheduled, and other available diagnostic tests (ultrasonography, ventillation/perfusion lung scan, pulmonary angiography, spiral computed tomography scan, autopsy report, etc) were adjudicated blindly by independent experts of the Central Independent Adjudication Committee (CIAC).

Secondary efficacy endpoints included:

- All DVTs, all proximal DVTs, distal DVTs only, PEs, up to day 11

- Adjudicated symptomatic VTEs up to day 49.

Institution of curative treatment by the investigator after local VTE assessment was also reported.

Safety:

The main safety endpoint was the incidence of major bleeding (determined as any investigator-reported bleeding adjudicated as major or minor bleeding by the CIAC) recorded between the first injection of study drug (active drug or placebo) and day 11.

Major bleeding was defined as:

- Fatal bleeding

- Clinically overt bleeding including retroperitoneal or intracranial bleeding,or bleeding into a critical organ (eye, adrenal gland, pericardium, spine)

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

Other safety variables were: minor bleeding, transfusion requirements, adverse events (AEs), serious AEs (SAEs), deaths, and changes in laboratory parameters

Statistical Methods:

The VTE, DVT, proximal DVT, symptomatic VTE rates up to day 11, as well as the symptomatic VTE rate up to day 49 and the incidence of major bleeding, and minor only bleeding up to day 11 and up to day 49, were compared between the two treatment groups using two-sided Fisher's exact test. Statistical comparisons of safety data (other than major bleeding) were made using chi-square test for categorical data, and Wilcoxon rank sum test for continuous data.

1.1 Efficacy

The "primary efficacy" population (included in the primary efficacy analysis) was a subset of the all treated patients population including patients who underwent the appropriate surgery (i.e., hip fracture surgery of the upper third of the femur), with a non-missing VTE assessment up to day 11 included. All efficacy parameters were analyzed according to the intent to treat principle.

The sponsor's efficacy evaluation was based on the number of VTEs. Table 1.3 summarizes the efficacy evaluation for the primary efficacy patient population.

Table 1.3 (sponsor's): Proportion (%) of Patients with Confirmed Thromboembolic Events During Prophylaxis Period (%) for Primary Efficacy Patient Population (Extracted from Sponsor's Volume 81, Page 5)

Adjudicated Endpoint	Treatment		
	fondaparinux 2.5 mg	Enoxaparin 40 mg	p-value
VTE (Primary efficacy analysis)	52/626 (8.3 %)	119/624 (19.1%)	<0.0001
DVT	49/624 (7.9%)	117/623 (18.8%)	<0.0001
PE	3/626 (0.5%)	3 /624 (0.5%)	1.00
Distal DVT	42/627 (6.7%)	94/626 (15.0%)	<0.0001
Proximal DVT	6/650 (0.9%)	28/646 (4.3%)	0.0001

It is seen from the above table that fondaparinux is significantly more effective in preventing VTE in comparison with enoxaparin for the primary efficacy patient population. Similar conclusions were reached for all the components of VTE except PE.

Sensitivity Analysis:

The sponsor considered two scenarios for the primary efficacy endpoint (in addition to the best scenario already planned in the protocol), which considered all patients with missing evaluations as having no VTEs:

- Realistic case scenario: The VTE rate for patients with missing primary efficacy endpoint any of the two groups was assumed to be the observed VTE rate in the worst group
- Worst case scenario (patient based): all missing evaluations were classified as a VTE.

The following table presents the results of the best case, realistic case and worst case scenario analyses.

Table 1.4 (sponsor's/reviewer's): Sensitivity Analysis of the Primary Efficacy Endpoint- All Treated Patients Who Underwent the Appropriate Surgery Extracted from Sponsor's **Volume 81, Table 7.2.2)**

Scenario	fondaparinux 2.5 mg (N=831) n (%)	enoxaparin 40 mg (N=840) n(%)	Difference and exact 95% CI	p-value (Fisher's exact)
Best Case Scenario	52 (6.3%)	119 (14.2%)	--7.9(-11.46, -4.82)	<0.0001
Realistic Case Scenario	92 (11.1%)	160 (19.0%)	-8.0 (-11.99, -4.36)	<0.0001
"Sponsor's Worst Case Scenario"	257 (30.9%)	335 (39.9%)	-9.0 (-13.80, -4.8)	0.0002

The results were consistent with those observed for the primary efficacy analysis. Note that the "Sponsor's Worst Case Scenario" is for the patient because a missing evaluation is classified as VTE. Note that in the standard worse case analysis a missing observation in the fondaparinux group would be replaced by VTE and a missing observation in the enoxaparin group outcome would be replaced by no VTE.

Subgroup Analyses:

This reviewer performed subgroup analyses with respect to gender, age-group and country for the primary efficacy patient population. The subgroup analyses are summarized below.

Gender

This reviewer conducted treatment by the gender interaction test using the logistic regression model with country, treatment group, gender and gender x treatment -group as fixed effects. It was seen that there was no interaction (p-value 0.6274) between gender and the treatment-group. The following table summarizes the event rates in the two treatment groups by gender for the primary efficacy patient population.

Table 1.5 (reviewer's):Proportion (%) of Patients with Confirmed Thromboembolic Events During Prophylaxis Period for the Primary Efficacy Patient Population by Gender

Gender	fondaparinux 2.5 mg	enoxaparin 40 mg	p-value: Fisher's exact
Male	6/144 (4.2%)	22/174 (12.6%)	0.0091
Female	46/482 (9.5%)	97/450 (21.6%)	<0.0001

It is seen that the fondaparinux treated group has significantly lower event rates in comparison to the enoxaparin treated group for either sex.

Age Group

This reviewer conducted treatment by the age-group interaction test using the logistic regression model with country, treatment group, age-group (<65 and ≥ 65) and age-group x treatment-group as fixed effects. The test failed to detect interaction (p-value 0.1775) between age and the treatment-group. The following table summarizes the event rates in the two treatment groups by gender for the primary efficacy patient population.

Table 1.6 (reviewer's):Proportion (%) of Patients with Confirmed VTE During Prophylaxis Period for Primary Efficacy Patient Population by Age-Group

Age-group	fondaparinux 2.5 mg	enoxaparin 40 mg	p-value:Fisher's exact
<65	3/90 (3.3%)	13/80 (16.3%)	0.0068
≥ 65	49/532 (9.21%)	106/542 (19.56%)	<0.0001

It is seen from the above table that the fondaparinux treated group has significantly lower event rates than the enoxaparin treated group in both age-group.

Country:

This reviewer conducted homogeneity of odds ratios using Breslow-Day test. The test failed to detect interaction (p-value 0.141) between country and the treatment-group. The following table summarizes the event rates in the two treatment groups by country.

Table 1.7 (reviewer's): Proportion (%) of Patients with Confirmed VTE During Prophylaxis Period for Primary Efficacy Patient Population by Country

Gender	fondaparinux 2.5 mg	enoxaparin 40 mg	p-value : Fisher's exact
Czechk Republic	6/78 (7.7%)	28/75 (37.3%)	<0.0001
Australia	6/76 (7.9%)	18/76 (23.7%)	0.013
Denmark	2/52 (3.8%)	2/56 (3.6%)	1.0

Sweden	0/43 (0.0%)	2/45 (4.4%)	0.495
France	2/38 (5.3%)	4/38 (10.5%)	0.674
The Netherlands	0/35 (0.0%)	7/29 (24.1%)	0.0025
Belgium	3/32 (9.4%)	2/27 (7.4%)	1.0
Greece	6/31 (19.4%)	6/27 (22.2%)	1.0
Hungary	3/29 (10.3%)	5/27 (18.5%)	0.462
Spain	2/26 (7.7%)	5/27 (18.5%)	0.420
Italy	9/26 (34.6%)	9/25 (36.0%)	1.0
Switzerland	2/26 (7.7%)	6/23 (26.1%)	0.125
Portugal	1/20 (5.0%)	3/28 (10.7%)	0.631
Poland	0/19 (0.0%)	6/23 (26.1%)	0.024
Germany	0/20 (0.0%)	4/20 (20.0%)	0.106
Norway	1/15 ((6.7%)	1/24 (4.2%)	1.0
United Kingdom	3/21 (14.3%)	3/16 (18.8%)	1.0
Argentina	2/15 (13.3%)	4/15 (26.7%)	0.651
Finland	1/12 (8.3%)	1/10 (10.0%)	1.0
South Africa	3/10 (3.0%)	2/11 (18.2%)	0.635
Austria	0/2 (0.0%	½ (50.0%)	1.0

Although it was expected that the treatment effect would be consistent among all the centers, analyses of treatment effectiveness by each center separately showed mixed results. It is seen that the fondaparinux group in Czechk Republic, Australia, The Netherlands, and Poland have significantly lower VTE rates than the enoxaparin treated group. In rest of the countries, there are no significant differences between the two treatment groups. In Norway and Denmark, the enoxaparin treated group has a slight numerical advantage over the fondaparinux treated group. In the rest of the countries, fondaparinux group has numerical advantage over the enoxaparin treated group. These numerical differences are meaningless and not necessary to explain because the test failed to detect interaction (between treatment and center). A non-significant test result, however, is often accepted as reasonable evidence that the treatment differences are sufficiently consistent to justify pooling the results across the countries. It is worth noting that there is a variation of sample sizes among countries. In addition, the trial was not sized for testing

treatment differences in each country separately and there is a problem of testing multiple hypotheses because of many subgroup analyses.

Race:

This reviewer conducted a test for homogeneity of odds ratios using the Breslow- Day test. It was seen that the test failed to detect interaction (p-value 0.180) between race and the treatment-group. The following table summarizes the event rates in the two treatment groups by race.

Table 1.8 (reviewer's): Proportion (%) of Patients with Confirmed VTE During Prophylaxis Period for Primary Efficacy Patient Population by Race

Race	fondaparinux 2.5 mg	enoxaparin 40 mg	p-value: Fisher's exact
Caucasian	51/ 622 (8.2%)	118/ 619 (19.1%)	<0.0001
Black	0/1 (0.0%)	0/1 (0.0%)	1.0
Asian	1/ 3 (33.3%)	0/2 (0.0%)	1.0
Other Races	0/0	½ (50%)	-

Although it was expected that treatment effectiveness would be consistent among all centers, analyses of treatment effectiveness by center showed mixed results. In the Caucasian (largest group), fondaparinux is significantly more effective than enoxaparin in preventing VTE. However, in non-Caucasian groups, fondaparinux has a slight numerical advantage over the enoxaparin. These numerical advantages are meaningless and therefore, it is not appropriate to conclude that fondaparinux is more effective in Caucasians than in non-Caucasians. It is worth noting that the trial was not sized for testing treatment differences in each race separately.

1.2 Safety:

The 'all treated patients' population (included in the safety analyses) was defined as all randomized patients who received at least one dose of study drug (placebo or active drug). The bleeding events for the two treatment groups are summarized below.

Table 1.9(sponsor's/reviewer's): Number (%) of Patients with any Adverse Experiences During the Treatment Period for Randomized Patients (Extracted from Sponsor's Table 9.1-1, Volume 79)

Bleeding events	fondaparinux 2.5 mg (N=831)	enoxaparin 40 mg	p-value :Fisher's exact

Adjudicated bleeding			
Major bleeding (main safety analysis)	18 (2.2%)	19 (2.3%)	1.00
Any bleeding	52 (6.3%)	37 (4.4%)	0.102
Fatal bleeding	0 (0.0%)	1 (0.1%)	1.00
Minor bleeding only	34 (4.1%)	18 (2.1%)	0.024
Related bleeding criteria			
Transfusion	421 (50.7%)	422 (50.1%)	0.845
Hemoglobin			
Values < 8 g/dL	113/816 (13.8%)	100/820 (12.2%)	0.092
Decrease ≥ 2 g/dL	245/817 (30.0%)	202/826 (24.5%)	0.013

The percentage of patients experiencing an adjudicated major bleeding were similar between the two treatment groups. Any bleeding and fatal bleeding events in both groups are not significantly different. However, the number of any bleeding is higher in fondaparinux group than enoxaparin group. A greater percentage of patients experienced adjudicated minor bleeding only (p=0.024) in the fondaparinux group which was also reflected in a trend toward an increased percentage of patients with hemoglobin decrease greater than or equal to 2 g/dL. The sponsor claimed that these observations were of little clinical consequence as there was no difference between treatment groups in the percentages of patients transfused, and only 3 patients in the fondaparinux treatment group were permanently discontinued of the study drug prematurely due to minor bleeding.

The safety profiles for both drugs were also similar with respect to AES/SAEs.

Table 1.10 (sponsor's/reviewer's): Propotion (%) of Patients with Adverse Experiences by Bleeding Category During the Treatment Period for Randomized Patients (Extracted from Sponsor's Table 9.1.2-1, Volume 79)

Parameter	fondaparinux 2.5 mg	enoxaparin 40 mg	p-value
Any AE	415 (49.9%)	420 (49.9%)	1.00
Any AE of severe intensity	48 (5.8%)	57 (6.8%)	0.365
Any SAE	58 (7.0%)	52 (6.2%)	0.556
Death	11 (1.3%)	16 (1.9%)	0.438

Permanent premature discontinuation of study drug due to any AE	29 (3.5%)	32 (3.8%)	0.794

1.3 **Conclusions**

Efficacy:

The efficacy data in this study showed that Fondaparinux 2.5 mg once daily(o.d.) subcutaneous (SC) injection of Fondaparinux to once daily SC injection of enoxaparin 40 mg in patients undergoing hip fracture surgery provided a significantly more effective prophylaxis of thromboembolic complications in comparison to enoxaparin.

Safety:

The safety data in this study showed that the safety profiles of fondaparinux 2.5 mg and enoxaparin 40 mg were mostly comparable. Although there were significantly more minor bleedings in fondaparinux treated group in comparison to the enoxaparin treated group, the two treatment groups were comparable with respect to major bleeding and any bleedings.

2. Study 095-002 [redacted]

Study 095-002 was a multinational, multi-center, randomized, double blind, parallel group enoxaparin 30 mg controlled trial evaluating the efficacy of fondaparinux (2.5 mg o.d.) in patients undergoing elective major knee surgery or a revision of components.

Primary Objective:

The objective of this study was to compare the efficacy (i.e., determine superiority) and safety of a 2.5 mg once daily (o.d.) subcutaneous (SC) injection of fondaparinux to once daily SC injection of enoxaparin 30 mg for prevention of deep vein thrombosis (DVT) and symptomatic pulmonary embolism (PE), in patients undergoing elective major knee surgery or a revision of components.

Design

This study was a multi-center, multinational, double blind study of fondaparinux 2.5 mg (o.d.) as compared to enoxaparin 30 mg (b.i.d.). Both started postoperatively.

The administration of fondaparinux started post-operatively at 6 ± 2 hours after surgery closure on day 1 and that of enoxaparin at least 12 hours but less than 24 hours after surgical closure. Study treatment was given up to day 7 ± 2 (day 1 of the start of the surgery) or until the mandatory venogram was obtained, whichever came first. A mandatory venogram had to be performed between day 5 and day 11, but not more than 2 calendar days after the last study treatment administration.

Patient Population:

The general patient population undergoing orthopedic surgery was considered to be at high risk of developing thromboembolic events, among which DVT occurs most frequently.
The trial population consisted of cooperative patients aged 18 years or older, weighing 50 kg or more, who underwent an unilateral primary elective total knee replacement (no revision) with a cemented or non-cemented prosthesis.

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Sample Size:

Based on publications and a phase II knee replacement study, it was assumed that the DVT rate for enoxaparin group is between 25% and 34%. Sample size was calculated for various scenarios of estimated event rates. A sample size of 319 evaluable subjects per group would allow detection of a difference of 23% and 345 between fondaparinux and enoxaparin (based on two sided chi-square test with continuity correction, and using a type I error of 5% and 85% power). Thus, about 912 patients were to be randomized, assuming an approximate 30% non-evalauble case.

Interim Analyses:

The sponsor indicated that the uncertainty in the estimates of the VTE rates as well as the risk reduction between the two products for sizing this phase III study justified the need for

reassessment of study size during the trial. As planned in the protocol, an interim analysis was carried out when half of the planned number of patients (i.e., 500 patients) were randomized and when adjudication of the primary efficacy criterion was available and validated for those patients. No statistical type-I error adjustment for the final analysis was required according to simulations performed during protocol development in order to measure the impact of sample size re-assessment.

Patient Disposition:

There were 1049 patients randomized to two treatment groups: 526 to fondaparinux 2.5 mg and 523 to enoxaparin 40 mg. The following table gives the composition of different patient populations by treatment groups.

Table 2.1 (sponsor's): Disposition of Patients Enrolled: Number of Patients (Extracted from Volume 209 of Submission, page 2)

Population	fondaparinux 2.5 mg	enoxaparin 30 mg	Total
Total Randomized	526	523	1049
Randomized and Treated (all treated patients population, evaluable for safety)	517	517	1034
Evaluable for primary efficacy analysis (primary efficacy population)	361	363	724

Baseline Demographics

The sponsor summarized demographic characteristics (age, sex, race, weight, height, etc.) by treatment group. There was no relevant difference between the treatment groups regarding demographic characteristics. Summary statistics for age, sex, and race by treatment groups are given in the following table.

Table 2.2 (sponsor's): Disposition of Patients Enrolled By Demograhic Characterstics: Number (%) of Patients (Extracted from Table 6.4.1, Volume 209 of submission)

Subgroup	fondaparinux 2.5 mg N=517	enoxaparin 30 mg N=517	Total N=1034
Age n			
Mean	67.5	67.5	67.5
<65 years	168 (32.5%)	175 (33.8%)	343 (33.2%)
≥ 65 years	349 (67.5%)	342 (66.15%)	1451 (66.8%)

Sex			
Male	204 (39.5%)	223 (43.1%)	427 (41.3%)
Female	313 (60.5%)	294 (56.9%)	607 (58.7%)
Race			
Caucasian	465 (89.9%)	449 (86.8%)	914 (88.4%)
Black	34 6.6%)	47 (9.1%)	81(7.8%)
Asian	2 (0.4%)	2 (0.4%)	4 (0.4%)
Other race	16(3.1%)	19(3.7%)	35 (3.4%)

The baseline demographic characteristics are comparable between the two treatment groups.

Diagnosis and Criteria for Inclusion:

- Patients undergoing either an elective major knee surgery or a revision of at least 1 component (Elective major knee surgery knee surgery was defined as surgery requiring resection of the distal end of the femur or proximal end of the tibia. Enrollment of patients with surgery limited to an osteotomy was not permitted.)

- ≥ 18 years of age

- Men or women of non-child bearing potential (i.e., post menopausal or with hysterectomy of bilateral tubal ligation) or women of childbearing potential using highly effective birth control and having a negative pregnancy test within 48 hours prior to randomization

- Signed written informed consent

- Hemostasis established on the calendar day of surgery no later than 8 hours after closure of the incision

Treatment Allocation:

Balanced randomization treatment blocks were predefined per site. Post-operatively, the investigator or designated staff called an automated telephone randomization system to obtain a

patient number within the site in accordance with the pre-specified site randomization sequence. To confirm, investigators were required to reenter the information received.

Test Product, Dose and Mode of Administration

Fondaparinux

Dose: 2.5 mg (expressed as a salified compound) and placebo o.d. administered as a SC injection

Mode of Administration:Subcutaneous

Enoxaparin:

Dose: 30 mg b.i.d.

Mode of Administration: Subcutaneous

Duration of Treatment: Minimum of 5 days to a maximum of 9 days

Duration of Observation: From 35 to 49 days, including an operative (pre- and post-) period, a subsequent treatment and a telephone follow-up period.

Criteria of Evaluation:

The primary endpoint was the cluster of the following venous thromboembolic event (VTE) outcome results recorded up to day 11:

- Adjudicated venogram positive for DVT or adjudicated symptomatic/asymptomatic DVT
- Adjudicated non-fatal and fatal PE

All venograms, scheduled or unscheduled were adjudicated blindly by independent experts of the Central Independent Adjudication Committee (CIAC).

Secondary efficacy endpoints included:

- All DVTs, all proximal DVTs, distal DVTs only, PEs, up to day 11
- Adjudicated symptomatic VTEs up to day 49.

Institution of curative treatment by the investigator after local VTE assessment was also reported.

Safety:

The main safety endpoint was the incidence of major bleeding (any investigator-reported unusual bleeding adjudicated as major or minor bleeding by the CIAC) recorded between the first injection of study drug (active drug or placebo) and day 11.

Major bleeding was defined as:

- Fatal bleeding

- Clinically overt bleeding including retroperitoneal or intracranial bleeding,or bleeding into a critical organ (eye, adrenal gland, pericardium, spine)

- Reoperation due to bleeding /hematoma at the operative site

- Clinically overt bleeding leading to a fall in hemoglobin ≥ 2 g/dL (1.6 mmol/L) and /or a transfusion ≥ 2 units of packed red blood cells or whole blood and for which the combined calculated index was ≥ 2

Other safety variables were: minor bleeding, transfusion requirements, adverse events (AEs), serious AEs (SAEs), deaths, and changes in laboratory parameters

Statistical Methods:

Efficacy Analysis

The "all treated patients" population (included in the safety analyses) was defined as all randomized patients who received at least one dose of the study drug (placebo or active drug).

The "primary efficacy" population (included in the primary efficacy analysis) was a subset of the all treated patient population including patients who underwent the appropriate surgery (i.e., elective major knee surgery) and who had a VTE assessment up to day 11. All efficacy parameters were analyzed according to the intent to treat principle.

Statistical Tests:

The VTE , DVT, proximal DVT, and symptomatic VTE rates up to day 11, as well as the symptomatic VTE rate up to day 49 and the incidence of major bleeding and minor only bleeding

up to day 11 and up to day 49, were compared between the two treatment groups using two-sided Fisher's exact test.

2.1 Efficacy

The sponsor's efficacy evaluation was based on the number thromboembolic events (DVT + PE). Table 2.3 summarizes the efficacy evaluation for the primary efficacy patient population.

Table 2.3 (sponsor's): Proportion (%) of Patients with Confirmed VTE During Prophylaxis Period (%) for Primary Efficacy Population (Extracted from Sponsor's Volume 209, Page 5)

Adjudicated Endpoint	Treatment		
	fondaparinux 2.5 mg	enoxaparin 30 mg	p-value : Fisher's exact
VTE (Primary efficacy analysis)	45/361 (12.5%)	101/363 (27.8%)	<0.0001
DVT	45/361 (2.5%)	98/361 (27.1%)	<0.0001
PE	1/361 (0.3%)	4/363 (1.1%)	0.373
Distal DVT	35/372 (9.4%)	78/366 (21.3%)	<0.0001
Proximal DVT	9/368 (2.4%)	20/372 (5.4%)	0.057

It is seen from the above table that fondaparinux is significantly more effective in preventing VTE in comparison to enoxaparin for the primary efficacy population. Similar conclusions were reached for all the components of VTE except PE.

Sensitivity Analysis:

The sponsor considered two scenarios for the primary efficacy endpoint (in addition to the best scenario already planned in the protocol), which considered all patients with missing evaluation as having no VTEs:

- Realistic scenario: The VTE rate for patients with missing primary efficacy endpoint in any of the two groups was assumed to be the observed VTE rate in the worst group
- Worst scenario: all missing evaluations were classified as a VTE.

The following table presents the results of the best case, realistic case and worst case scenario analyses.

Table 2.4: Sensitivity Analysis of the Primary Efficacy Endpoint- All Treated Patients Who

Underwent the Appropriate Surgery (Extracted From Sponsors Table 7.2.2, Volume 209)

Scenario	fondaparinux 2.5 mg (N=517) n (%)	enoxaparin 30 mg (N=517) n(%)	Difference and exact 95% CI	p-value: Fisher's exact
Best Case Scenario	45 (8.7%)	101 (19.5%)	-10.8 (-15.9, -6.2)	<0.0001
Realistic Case Scenario	89 (17.2%)	143 (27.7%)	-10.4 (-16.2, -5.0)	0.0001
Sponsor's Worst Case Scenario	201 (38.9%)	255 (49.3%)	-10.4 (-16.6, -4.2)	0.0001

The results were consistent with those observed for the primary efficacy analysis. Note that the "Sponsor's Worst Case Scenario" is for the patient because a missing evaluation is classified as VTE. Note that in the standard worse case analysis a missing observation in the fondaparinux group would be replaced by VTE and a missing observation in the enoxaparin group outcome would be replaced by no VTE.

Subgroup Analyses:

This reviewer performed subgroup analyses with respect to gender, age-group, country and race for the primary efficacy patient population. The subgroup analyses are summarized below.

Gender

This reviewer conducted treatment by gender interaction test using the logistic regression model with treatment group, gender and gender x treatment-group as fixed effects.
It was seen that there was no interaction (p-value 0.3390) between gender and the treatment groups. The following table summarizes the event rates in the two treatment groups by gender for the primary efficacy patient population.

Table 2.5 (reviewer's):Proportion (%) of Patients with Confirmed Thromboembolic Events During Prophylaxis Period for the Primary Efficacy Patient Population by Gender

Gender	fondaparinux 2.5 mg	enoxaparin 30 mg	p-value (Fisher's exact)
Male	19/144 (13.19%)	38/154 (24.68%)	0.0085
Female	26/217 (11.98%)	63/209 (30.14%)	<0.0001

It is seen that the fondaparinux treated group has significantly lower event rates in comparison to the enoxaparin treated group for either sex.

Age Group

This reviewer conducted treatment by age-group interaction test using the logistic regression model with country, treatment group, age-group (<65 and ≥ 65) and age-group x treatment-group as fixed effects. The test failed to detect interaction (p-value 0.1115) between gender and the treatment-group. The following table summarizes the event rates in the two treatment groups by gender for the primary efficacy patient population.

Table 2.6 (reviewer's): Proportion (%) of Patients with Confirmed Thromboembolic Events) During Prophylaxis Period for Primary Efficacy Patient Population by Age-Group

Age-group	fondaparinux 2.5 mg	enoxaparin 30 mg	p-value (Fisher's exact)
<65	19/111 (17.12%)	29/109 (26.61%)	0.103
≥ 65	26/250 (10.4%)	72/254 (28.4%)	<0.0001

Analyses of the primary endpoint by the age group separately showed mixed results. It is seen from the above table that the fondaparinux treated group has significantly lower event rates than the enoxaparin treated group in the age-group ≥ 65. However, fondaparinux treated group has numerical advantage (non-significant) over the enoxaparin treated group for the age-group <65.This non-significant result does not imply that fondaparinux is not an effective drug for the patients who are younger than 65. Note that there were more patients in the age group ≥ 65. The trial was not sized for testing treatment differences in either age-group.

Country:

This reviewer conducted a test for treatment by country interaction using the logistic regression model with country, treatment group, and treatment-group x country as fixed effects. It was seen that there was interaction (p-value 0.0285) between country and the treatment-group. Therefore, the treatment effect was not consistent between the two countries. The following table summarizes the event rates in the two treatment groups by country.

Table 2.7 (reviewer's): Proportion (%) of Patients with Confirmed Thromboembolic Events During Prophylaxis Period for Primary Efficacy Patient Population by Country

Gender	fondaparinux 2.5 mg	enoxaparin 30 mg	p-value : Fisher's exact (reviewer's)
USA	32/289 (11.07%)	85/286 (29.72%)	<0.0001
Canada	13/72 (18.1%)	16/77 (20.8%)	0.686

In order to examine which country was responsible for interaction, this reviewer analyzed each

country separately. It is seen that fondaparinux group in the USA has significantly lower VTE rate than enoxaparin treated group. However, fondaparinux group in Canada has a slight numerical advantage over the enoxaparin treated group. It is worth noting that the trial was not sized for testing treatment differences in each country separately. Also there were more patients in the USA than in Canada. However, even if we drop Canada from the efficacy analysis, the efficacy data from the USA will show significant superiority of fondaparinux over enoxaparin. It is worth mentioning that the presence of a statistically significant interaction does not mean that the overall estimate of the treatment effect is inappropriate.

Race:

This reviewer conducted a test for treatment by race interaction using the logistic regression model with treatment group, race and treatment-group x race as fixed effects. The test failed to detect interaction (p-value 0.0850) between race and the treatment-group. The following table summarizes the event rates in the two treatment groups by race.

Table 2.8 (reviewer's): Proportion (%) of Patients with Confirmed Thromboembolic Events During Prophylaxis Period for Primary Efficacy Patient Population by Race

Race	fondaparinux 2.5 mg	enoxaparin 30 mg	p-value: Fisher's exact (reviewer's)
Caucasian	36/327 (11.01%)	93/326 (28.53%)	<0.0001
Black	5/20 (5.0%)	6/25 (24.0%)	1.00
Asian	½ (50%)	0/1 (0.0%)	1.00
Other Races	3/12 (25.0%)	2/11 (18.2%)	1.00

Although the test failed to detect inconsistency of the treatment effectiveness among the different ethnic groups, analyses by each race separately showed mixed results. It is seen that the fondaparinux group in the Caucasian (largest group) has significantly lower VTE rate than enoxaparin treated group. For non-Caucasians, the fondaparinux group has a slight numerical advantage over the enoxaparin treated group. These numerical advantages are meaningless and not necessary to explain. Note the trial was not sized for testing the efficacy of fondaparinux for each race separately. It is not appropriate to conclude that fondaparinux is more effective in Caucasians than in non-Caucasisans

2.2 Safety:

The bleeding events for the two treatment groups are summarized below.

Table 2.9 (sponsor's/reviewer's): Number (%) of Patients with any Adverse Experiences During the Treatment Period for Randomized Patients (Extracted from Sponsor's Volume 209, page 5/183)

Bleeding events	fondaparinux 2.5 mg (N=517)	enoxaparin 30 mg (N=517)	p-value :Fisher's exact (reviewer's)
Adjudicated bleeding			
Major bleeding (main safety analysis)	11/517 (2.13%)	1/517 (0.19%)	0.0061
Any bleeding	25/517 (4.84%)	20/517 (3.87%)	0.543
Fatal bleeding	0 (0.0%)	(0.0%)	1.00
Minor bleeding only	14/517 (42.9%)	19/517(38.1%)	0.48
Related bleeding criteria up to day 11			
Transfusion	222/517 (42.9%)	197/517 (38.1%)	.128
Hemoglobin			
Values < 8 g/dL	76/517 (14.7%)	72/517 (13.9%)	.790

Decrease ≥ 2 g/dL	357/516 (69.2%)	338/517 (65.4%)	.208

The incidence of major bleeding up to day 11 and up to day 49 were significantly higher in Fondaparinux group than in the enoxaparin group (p-value =0.006 for between treatment comparison up to day 11. In both treatment groups, most episodes of major bleeding occurred up to day 11. The sponsor reported that the higher percentage of patients with major bleeding events in the fondaparinux group was recorded mainly at the surgical site: these bleeding events led to surgical intervention in 2 patients treated with Fondaparinux and one patient treated with enoxaparin. No fatal bleeding and no bleeding into a critical organ occurred in either treatment group.

The sponsor reported that percentage of patients who permanently discontinued study drug due to adverse events were similar in the two treatment groups. A total of 5 patients (2 in fondaparinux group and 2 in enoxaparin group) died between the first injection and day 49; 3 of these deaths (1 in the fondaparinux group and 2.in the enoxaparin group) occurred between the first injection and day 11.

There were no significant differences between the two treatment groups with respect to any bleeding, fatal bleeding and minor bleeding only events. In addition, there were no significant differences between the two treatment groups with respect to blood transfusion and hemoglobin.

The following table shows that the safety profiles for both drugs were similar based on AE/SAEs.

Table 2.10 (sponsor's/reviewer's): Proportion (%) of Patients with Adverse Experiences by Bleeding Category During the Treatment Period for Randomized Patients (Extracted from Sponsor's Volume 209, Page 6/183)

Parameter	fondaparinux 2.5 mg	enoxaparin 30 mg	p-value:Fisher's exact (reviewer's)
Any AE	424/517 (82.0%)	419/517 (81.0%)	0.749
Any AE of severe intensity	17 (3.3%)	17 (3.3%)	1.00
Any SAE	38 (7.4%)	28 (5.4%)	0.252
Death	1(0.2%)	2 (0.4%)	1.00
Permanent premature discontinuation of study drug due to any AE	20 (3.9%)	12 (2.3%)	0.208

2.3 Conclusions

Efficacy:

The efficacy data in this study showed that fondaparinux 2.5 mg started postoperatively and administered s.c. once daily in patients undergoing primary elective total hip replacement provided a significantly more effective prophylaxis of thromboembolic complications in comparison to enoxaparin.

Safety:

The safety data in this study showed that the safety profiles of Fondaparinux 2.5 mg and enoxaparin 40 mg were mostly comparable. There were significantly more bleedings in fondaparinux treated group in comparison to the enoxaparin treated group.

3. Conclusions

Efficacy:

There are two studies in this review: one is a hip fracture surgery study (EFC2698: ——— and the other is a knee replacement surgery study (095-002 ——— . Thus, there is a single study for each indication.

The hip fracture surgery study showed that once daily (o.d.) subcutaneous (SC) injection of fondaparinux in patients undergoing hip fracture surgery provided a significantly more effective (VTE rates 8.3% vs. 19.1% : p-value < 0.0001)) prophylaxis of thromboembolic complications in comparison to once daily SC injection of enoxaparin 40 mg . The knee replacement surgery study showed that once daily (o.d.) subcutaneous (SC) injection fondaparinux 2.5 mg in patients undergoing primary elective total hip replacement provided a significantly more effective prophylaxis of thromboembolic complications in comparison to enoxaparin 30 mg (b.i.d.) (VTE rates 12.5% (Fondaparinux) vs. 27.8% (enoxaparn): p-value < 0.0001)

Safety:

The safety data in the hip fracture surgery showed that the safety profiles of Fondaparinux 2.5 mg and enoxaparin 40 mg were mostly comparable. The safety data in the knee replacement surgery showed that the safety profiles of fondaparinux 2.5 mg and enoxaparin 30 mg were mostly comparable.

However, in hip fracture study there were significantly more minor bleedings in fondaparinux treated group in comparison to the enoxaparin treated group. The two treatment groups were

comparable with respect to major and any bleedings. There were significantly more major bleedings in fondaparinux treated group in comparison to the enoxaparin treated group in the knee replacement surgery study. However, the two groups are comparable with respect to minor and any bleedings.

M. Mushfiqur Rashid, Ph.D.
Mathematical Statistician

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/s/

Mushfiqur Rashid
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Thomas Permutt
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S. Edward Nevius
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Concur with review.

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Statistical Review and Evaluation

CLINICAL STUDIES

(SECONDARY REVIEW)

NDA 21-345
Name of drug: Arixtra (was Xantidar; fondaparinux)
Applicant: Fonda
Indication: Prevention of venous thrombo-embolic events (VTE) in patients undergoing major orthopedic surgery of the lower limb such as hip fracture, major knee or hip replacement surgeries
Documents reviewed: primary reviews by Mushfiqur Rashid, Ph.D. and Milton Fan, Ph.D.
Project manager: Karen Oliver
Medical officers: Min Lu, M.D. and Ann Farrell, M.D.
Classification: 1P
Dates: received 14 February 2001; user fee goal (6 months) 14 August 2001
Reviewer: Thomas Permutt

Fondaparinux is a synthetic anticoagulant of a new class. The application concerns prophylactic use to prevent venous thrombo-embolic events in patients undergoing knee or hip replacement or who have suffered fractures of the hip. The indication for hip fracture is unique, so that the application has been assigned a priority review. Because of the short review time, the primary review was divided between Drs. Rashid and Fan.

Dr. Rashid reviewed one study in hip fracture and one study in knee replacement, while Dr. Fan reviewed two studies in hip replacement. In all four studies fondaparinux was compared to enoxaparin, which is an approved anticoagulant but whose indications do not presently include hip fracture.

In three of the four studies, fondaparinux was superior to enoxaparin with respect to the primary endpoint. The rates of venous thrombo-embolic events were roughly half as big in the fondaparinux group as in the enoxaparin group. The results were statistically significant with very small p-values.

The exceptional fourth study was ———— or EFC2442, one of the hip-replacement trials reviewed by Dr. Fan. As he notes, the difference between fondaparinux and enoxaparin in this study was not statistically significant, and the estimated effect was more modest: 6 percent of fondaparinux patients and 8 percent of enoxaparin patients had venous thrombo-embolic events.

Considering the trials together, there is substantial evidence that fondaparinux was effective in preventing venous thrombo-embolic events. Although the three successful trials

were in different conditions that may be considered separate indications, the trials corroborate one another's findings that the drug is effective. Different balances of risks and benefits may apply to the different indications, however.

The fourth trial was a failure in a sense. The results, being statistically nonsignificant, do not appreciably strengthen the findings from the other studies. They should not be seen as weakening them, either, though. Even in this fourth study fondaparinux appeared to be superior to enoxaparin, although not at the usual level of confidence. Furthermore, while the difference between the treatments in this study was not significantly different from zero, neither was it significantly different from that in the other study in hip replacement. That is, both studies are consistent with a true effect intermediate between the estimates from each separate study. Conversely, taken together, the two studies are strongly inconsistent with a true difference of zero or a difference in the other direction.

As usual, many aspects of the safety of fondaparinux are more appropriately dealt with case by case than statistically, and these aspects are addressed in the medical officers' reviews. One kind of adverse event, however, was predictable enough to be specified in the protocols as a primary outcome, namely bleeding. While the incidence of minor bleeding was somewhat higher with fondaparinux in some studies, there did not appear to be substantial differences with respect to major bleeding.

Labeling will be addressed in a separate review. I note here, however, that the standard of comparison for a claim of superiority may be higher than that for a finding of efficacy. If fondaparinux is better than enoxaparin in any regimen that can confidently be assumed to be not worse than nothing, then fondaparinux is an effective drug. To say that it is superior to enoxaparin, however, would require it to be superior under the optimal or at least the usual conditions of use of enoxaparin.

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Thomas Permutt
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S. Edward Nevius
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Concur with review.

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