2. Secondary Efficacy Analysis

The following analyses were performed to support the primary efficacy data.

a. All-treated patient population Analysis - VG Data.

- Treatment failures included all patients with a positive venogram. The incidence of DVT was 10% (30/288) in the Fragmin group vs. 18% (53/292) in the warfarin group.
- Treatment failures included all patients with a positive VG or no evaluable VG (*worst case scenario*). The incidence of DVT was 39% for Fragmin vs. 49% for warfarin treated patients.
- Treatment failures included all patients with a positive venogram plus an estimated proportion of patients with no evaluable venogram (*censored scenario*). The incidence of DVT was 16% for Fragmin vs. 24% for warfarin treated patients.

All three analyses demonstrated that there was a statistically significant difference in favor of Fragmin.

b. Patients with symptomatic DVT.

The data are summarized in the following table.

PATIENTS WITH CLINICAL SYMPTOMS OF DVT

DVT diagnosis	Fragmin		Warfarin		p-value
	N=288	%	N=292	%	
Symptomatic DVT	23	7.9	13	4.4	<0.001; Fs W
Venography Performed:	23	100	13	100	
Positive	3	13.0	1	7.7	
Negative	13	56.5	9	69.2	
Not known	7	30.4	3	23.0	

From Table EF137-3.2 and 9.4.3 Patients with Clinical Symptoms/Signs of DVT (Vol.4, p. 8/1/76)

A discordance between clinical symptoms of DVT and VG confirmation was noted for 36 patients (F=23/W=13) with clinical signs or symptoms of VTE. DVT was not confirmed on ascending bilateral venography in 13 and 9 respectively. Three DVTs documented by VG were clinically symptomatic in the Fragmin group compared to one in the warfarin group.

c. Patients with symptomatic PE and scan confirmed PE.

The data are summarized in the following table.

PATIENTS WITH CLINICAL SYMPTOMS OF PE WITH AND W/O LUNG SCAN CONFIRMATION

PE diagnosis	Fragmin:288	%	Warfarin: 292	%	p-value
cPE (clinical symptoms)	13	4.5	6	2.1	<0.01 F≤ W
PE confirmed by lung scan	2	0.69	2	0.68	z=0.0145
PE rejected by lung scan	10		3		
Lung scan not available	1		1		

From Tables EF137-4.1 and 4.2 (Vol.4, pp. 8/1/160-1).

A discrepancy between clinical symptoms and lung scan diagnosis was noted, however, the distribution of patients with scan confirmed PE and patients with missing lung scan data was identical in both groups.

d. Subgroup Analyses. Incidence of DVT in All-treated

- Elderly (>65) vs. Young (65≤). More DVT occurred in the older population (17.5%). The incidence was lower with Fragmin that with warfarin (F=13%/W=22%).

- Males vs. Females. More DVT occurred in female patients and in the warfarin group. This difference was not significant.

- Patients stratified by weight category (<80 kg vs.>80 kg). Fragmin treated patients weighing more than 80 kg had higher incidence of DVT.

- Patients with ≥2 risk factors vs. patients with <2 risk factors. Patients with two and more risk factors had significantly higher incidence of DVT (F=14% vs.9%/W=23% vs.16%). Fragmin was superior to warfarin.

- Warfarin therapeutic level stratified by positive and negative VG. Less DVT occurred in patients with PT 1.2 - 1.4 (INR 2.0 - 3.0); more DVT occurred in patients with lower or higher therapeutic level of warfarin. The majority of patients with negative VG had higher PT (>1.4) or INR (>3.0).

4.5.3 Safety Evaluation

Patients who received at least one dose of study medication were assessed for safety. Patients were monitored for bleeding, adverse events and abnormal laboratory data during the treatment period from Day 0 (pre- and post-surgery) to Day 9 (venography and discharge). During a follow-up observational period of 5-7 weeks after hospital discharge, safety information for VTE and AE was collected.

1. Hemorrhagic Events (Primary safety endpoint)

Thirty (30) Fragmin patients and twelve (12) Warfarin patients experienced one or more hemorrhagic events; this difference was statistically significant (p=0.003, Fisher's Exact Test). Some patients had more than one bleeding episode. One Fragmin patient (#8035) was re-operated to stop the bleeding.

The incidence of patients with hemorrhage, and site of bleeding are summarized in the following table.

HEMORRHAGIC EVENTS		Fragmin	Warfarin	p=value
Number of patients treated		274	279	
Total patients with hemorrhagic events*		30 (10.9%)	12 (4.3%)	0.003 (Fisher's Exact)
Hemorrhagic events	Hematuria@	10	8	
	Wound Hematoma	7	2	
	GI Bleed (total)	6	3	
	Operative Site/Wound	3	0	
	Wound Drainage/Hemovac	2	1	
	Re-operation due to bleeding	1	0	

From Table: Reported Hemorrhagic Adverse Events (Vol.4, p.8/1/82), and Tables AE137-3.1-3.2. *Some patients may have more than one episode. @ Some patients had urinary catheter installed.

a. Blood Loss

The mean blood loss on the day of surgery was 1,381±908 mL for the Fragmin and 1,376±850 mL for the warfarin group. During 1-8 days post-op., mean blood loss for the Fragmin group (219±183 mL), and for the Warfarin group (225±161) were similar. The two treatment groups did not differ with respect to blood loss on day of surgery (p=0.57) or postoperatively (p=0.26).

b. Patients Receiving Blood Transfusion

The number of patients receiving blood transfusion on the day of surgery was comparable between the two treatment groups (F=187 or 69.0% versus W=182 or 65.2%). However, more patients in the Fragmin group received blood transfusion in the subsequent days (F=184 or 67.8% versus W=124 or 44.5%; $p<0.001$).

c. Bleeding in Subsets of Population

There was no difference between treatment groups in any evaluation. However, patients who had revision surgery experienced more blood loss and required more blood transfusions than those who had primary operation; patients with two and more risk factors had higher blood loss and required more blood transfusion, and more wound hematomas occurred in Fragmin treated patients with 2 and more risk factors. Body weight, Gender, and Age did not show any difference in bleeding events.

2. Non Hemorrhagic Adverse Events.

Non Hemorrhagic AEs by Body System and Preferred Term (WHO-ART Dictionary)

ADVERSE EVENTS		Fragmin		Warfarin	
		N=288	%	N=292	%
Dosed		274	100	279	100
Patients with at least 1 event		250	91.2	248	88.9
Skin & Appendages	Total	39	14	47	17
	Pruritus	21	8	26	9
	Rash	14	5	16	6
Musculo-Skeletal	Postop. pain	210	77	215	77
CNS+Peripheral nerv.system	Total	59	22	63	
	Dizziness	26	9	26	9
	Hypertonia	13	5	7	3
	Hyperesthesia	12	4	8	3
Vision	Total	4	1	4	1
Hearing/ Vestibular	Total	1	0	0	0.0
Psychiatric	Total	53	19	47	17
	Insomnia	38	14	37	13

GI System	Total	146	53	147	53
	Nausea	72	26	71	25
	Constipation	49	18	47	17
	Nausea/Vomiting	30	11	37	13
Liver & Biliary	Total	1	0	0	0.0
Metabolic & Nutrition	Total	37	14	31	11
	Hypokalemia	30	11	28	10
Endocrine	Total	1	0	0	0.0
CV General	Total	37	14	37	13
Myo Endo Valve	Total	4	1	2	1
Heart Rate/Rhythm	Total	19	7	21	8
	Tachy/Bradicardia	14	6	9	3
Vascular	Total	0	0.0	1	0
Respiratory	Total	39	14	29	10
	Pharyngitis	9	3	12	4
	Dyspnoea	9	3	3	1
Platelet, Bleeding, Clotting	Total	13	5	13	5
	Purpura	7	3	7	3
	Thrombocytopenia	3	1	0	0.0
	Thrombosis	1	0	3	1
Urinary System	Total	33	12	22	8
	UTI	20	7	11	4
Body as a Whole	Total	174	64	165	59
	Wound drainage	135	49	124	44
	Oedema legs	45	16	40	14
	Pain	15	9	32	12
Application Site	Total	6	2	3	1
	Skin necrosis	3	1	2	1
	Local reaction	0	0.0	1	0
Resistance Mechanism	Total	11	4	8	3
	Infection	5	2	5	2

From Table AE137-4.2

a. Most frequent non-hemorrhagic Adverse Events

NON-HEMORRHAGIC EVENTS	Fragmin	Warfarin
Postoperative pain	210	215
Fever	135	124
Nausea	72	71
Constipation	49	47
Oedema legs	45	40
Insomnia	38	37
Nausea/Vomiting	30	37
Hypokalaemia	30	28
Dizziness	26	26
Pruritus	21	26

From Table AE137-4.3

b. Adverse Events Leading to Discontinuation

Eight patients were withdrawn (F=4 / W=4) due to AEs.
One Fragmin patient (F#1162) was withdrawn on study Day 6 because of GI bleeding, one because of MI, one for postop. ileus, and one for naso-gastric tube bleeding.
One Warfarin patient was withdrawn due to UA, one to chest pain, one to ileus, and one for revision surgery, Major bleedings lead to study discontinuation in two Fragmin patients.

c. Deaths

No deaths were reported during the study period.

3. Clinical Laboratory Evaluation

Laboratory Data: There was no difference between the two treatment groups with respect to the change from baseline in all three parameters of hemoglobin, hematocrit, and platelet count. However, in the Fragmin group hemoglobin was reduced by 25% (from 13 to 10 g/dL) while in the warfarin group the reduction was 15% (from 13 to 11 g/dL).

Thrombocytopenia: Eight Fragmin and 6 warfarin patients had at least one platelet count below 100,000/mm^3. No cases of HIT or HITTS were reported.

4. Summary of Safety Analyses

Patients treated with Fragmin for prophylaxis of DVT and PE following hip surgery, had three times more probability to experience any hemorrhage. The majority of these events were minor and did not require medical intervention.

4.6 CONCLUSIONS

Although open-label, study 91-137 was adequate and well controlled. The data support the efficacy of Fragmin for prophylaxis of DVT (detected by VG) in patients undergoing THR. The proposed regimen of Fragmin for DVT prophylaxis appeared to be safe.

5.0 REVIEW OF STUDY D-10 (NDA/S vol. 5)

Study Title: Comparison of Fragmin and Unfractionated Heparin in prophylaxis of deep vein thrombosis and pulmonary embolism in total hip replacement.

Principal Investigator: B. Eriksson, M.D., Ostra Hospital, Gothenburg, Sweeden

Study Period: The study was started in 1986 and completed in 1988. Date of the initial study report: 5-22-89; date of revised report: 3-18-96.

Study Drugs: Fragmin syringes 5, 000 IU = DxN 123, DxN 133
Heparin (KabiVitrum) syringes 5, 000 IU= DxN 120, DxN 131
Placebo syringes (NaCl 0.9%)= DxN 121, DxN 121-52, DxN 132.
Single dose syringes of 0.2 mL = 5,000 IU of Fragmin, Heparin 5.000 IU or placebo were used in the study.

5.1 OBJECTIVE OF THE STUDY

The objective of the study was to investigate the difference in prophylactic effect of low-dose heparin and Fragmin on postoperative VTE in elective hip replacement surgery. Safety was assessed for bleeding complication and transfusion requirements of each treatment group.

5.2 STUDY SYNOPSIS

This is a 1996 amended version of the D-10 study that was conducted in Sweden from 1986 to 1989. Study D-10 was initially reviewed at the time of the NDA 20-287 submission of 8-6-1992 and will be only summarized here. At the time of the NDA submission,

the study was considered to be marginally acceptable as pivotal study because of the selection of a suboptimal regimen (sc heparin) as comparator. The study was, however considered adequate to provide supportive evidence for the indication of Fragmin for thromboprophylaxis in hip replacement surgery.

The original study included 130 patients undergoing elective hip replacement surgery randomized to receive either fragmin 5000 IU sc qd starting the evening before surgery (N=65) or standard heparin 5000 IU sc tid (N=65) starting the morning before surgery.

DVTs were assessed by bilateral VG and PEs were diagnosed by perfusion/ventilation scintigraphy. Both procedures were performed about two weeks postoperatively.

Safety was assessed by measurement of blood loss, need of transfusion and recording adverse events.

There was no significant difference between the two treatment groups regarding the overall incidence of DVT (F=30.6% / H=40.3%; numerical difference not statistically significant). The frequency of proximal thrombosis was significantly lower in the fragmin group (F=5 / H=11). The frequency of PE was also significantly reduced in the fragmin group (total PE: F=12.7% / H=31.7%; p=0.011)). The overall reduction of VTE in the Fragmin group was significant (p=0.033) due to the reduction of PE.

The revised D-10 study enrolled 140 patients (randomized to fragmin 70, and heparin 70). The overall incidence of DVT was not significantly different between treatment groups (29.9% in the Fragmin group and 39.1% in the heparin group), however, the incidence rates of proximal DVT and femoral DVT were significantly lower in the fragmin group (9.0% versus 26.1% for proximal DVT and 7.5% versus 18.8% for femoral vein DVT; p=0.006). There was a significant difference of incidence of clinically silent PE detected by scan (13.4% in the Fragmin group versus 27.5% in the heparin group; p=0.032).

Total blood loss and transfusion requirements were not significantly different in the two groups. A total of 20 patients reported hemorrhage (F=4, all mild / H=16, 1 severe, 15 mild). There was no significant difference of the incidence of other adverse events between treatment groups. Thrombocytopenia was not reported in either group.

5.3 SUMMARY OF THE INVESTIGATIONAL PLAN

a. Study Design

This was a single center, randomized, double-blind, two parallel groups, active treatment controlled clinical trial. A total of 136 patients undergoing hip replacement received Fragmin (N=67) or low-dose heparin (N=69) in randoimized blocks of ten patients.

Fragmin and heparin were given subcutaneously for 10 days.

Efficacy was evaluated by bilateral ascending VG and pulmonary scans about two weeks after surgery. In case of death, thromboembolic events (VTE) were diagnosed by autopsy if performed.

The safety monitoring included blood loss and transfusion requirements after surgery and the decrease from baseline of hemoglobin levels at day 7 postoperatively. Platelet count was also recorded. Other complications such as wound infections, allergic reactions, pain and hematoma at the injection site were specifically looked for. The patients had a follow-up period of six weeks postoperatively.

b. Control Group

Low-dose heparin was the comparator regimen chosen in the study. The regimen of low-dose heparin administered sc is not approved for thromboprophylaxis in orthopedic surgery, but it has been widely used in the past for this indication. Furthermore, study D-10 was designed to show superiority of Fragmin vs. sc Heparin.

c. Study Population

Patients undergoing elective hip replacement surgery at one center were enrolled in the study.
Eligibility criteria included hip surgery and age above 40.
Exclusion criteria were history of bleeding or recent serious bleeding events, renal insufficiency, hypersensitivity to heparin, recent treatment with other anticoagulants.
The patients were randomized to each treatment groups using block size of 10.

d. Effectiveness Variables

- Incidence of venous thromboembolic event (VTE) was defined as occurrence of DVT, PE or death by thromboembolism.

- VTE was confirmed by one of the following:
  - DVT diagnosed by venography (VG) 2 weeks after surgery.
  - Clinical signs of DVT, verified by VG at any time during drug prophylaxis.
  - PE diagnosed by lung scintigraphy about 2 weeks after surgery.
  - Clinical signs of PE documented by lung scintigraphy at any time during the study period.
  - Clinical signs of VTE and/or PE verified at any time between the 2 weeks VG/lung scan examinations and the six weeks follow-up visit.
  - Autopsy verified DVT of PE.

VGs were analyzed twice by two experienced radiologists. Proximal DVT included thromboses of the femoral and iliac veins. Thromboses of the muscular veins, tibial and fibular veins and popliteal veins were defined as distal DVT.

Perfusion lung scans were performed immediately before the VG; ventilation scans and chest radiography were performed on the following day in every patient, except for patients with normal perfusion scans. Only high probability scans was classified as PE. The scans were evaluated blindly by an expert reader.

e. Safety Variables:

- Hemorrhage: The following were recorded in all patients:
  - Blood loss during operation estimated by the anesthetist (mL).
  - Post-operative blood loss measured daily from suction drain bottles.(mL)
  - Transfusion requirements in blood units.(changed to mL)
  - Hemoglobin level at baseline and one week postoperatively.
- Platelet count was measured postoperatively and one week after surgery.
- Adverse Events
  - Hemorrhagic: Excessive bleeding, wound hematoma, hematoma at site of injection, reoperation due to bleeding.
  - Non-Hemorrhagic: Deep and superficial wound infections. Pain at the injection site; Allergic reactions.
- Anti-Xa, t-PA and PAI-1 activity and antigen were analyzed.

f. Disposition of Patients

The following information was collected at baseline or during the study:

- Demographics.
- Risk Factors for thromboembolism following hip replacement, including:
  - Time between the first dose and surgery
  - Factors related to the surgical procedure: anesthesia, prosthesis, dextran-70 during surgery.
- Concomitant Medication, particularly ASA and NSAIDs within seven days prior to operation.
- Dropouts, Protocol Violations, Study Discontinuation.
- Deaths.

5.4 Statistical Methods

a. Statistical Analyses of Efficacy and Safety

The proportions of DVT, PE and both in each of the treatment groups were compared using the two-tailed Fisher's exact test. Two-sided 95% CI were calculated for the difference of proportions.

Statistical analyses were applied to the safety variables blood loss and transfusion volumes. The change of hemoglobin level from Day -1 to Day- 7 was also analyzed. The Wilcoxon rank sum (non-parametric test) was chosen for the comparison of treatments.

b. Sample Size

The original sample size of 120 patients was based on the expected rate of VTE of 45% for heparin and 20% for Fragmin (two-sided α =0.05 and power 80%). An interim analysis was performed when 2/3 of patients had been included because the observed high frequency of VTE in the fragmin group. The level of significance was decreased from 5% to 4.7%, and the sample size was increased by 20 patients per group because of the interim analysis.

5.5 STUDY RESULTS

5.5.1 Patient Disposition

The number of patients for each study populations were as follows:

- Randomized (ITT): 140 F=70 H=70
- All-treated patient population: 136 F=67 H=69
- Per-protocol population: 129 F=65 H=64
- Evaluable patient population: 125 F=63 H=62

The All-treated patient population was defined as the operated patients who had received at least one dose of study medication.

One hundred twenty-nine (129) patients completed the study as scheduled. Eight patients discontinued the study because of patient wish (2 heparin patients); poor compliance (1 Fragmin, 2 heparin); therapy failure (1Fragmin); adverse event (2 Heparin). The Per-Protocol (P-P) population included 129 patients (92.8% of ITT population). The evaluable patient population included a total of 125 patients (F=63/H=62).

There was no significant difference between treatment groups with regard to baseline demographics and risk factors.

5.5.2 Efficacy Assessment

Efficacy analyses were performed on the all-treated patient and in the Per-Protocol patient populations.

a. Primary Efficacy Results

1) Incidence of VTE

The primary efficacy variable was incidence of VTE (DVT, PE or death by TE). Only one patient died during the treatment period (pt#1051) and autopsy revealed no thrombosis.

The efficacy data for the All-treated population are summarized in the following table.

INCIDENCE OF VTE. ALL-TREATED PATIENT POPULATION

Event	Fragmin		Heparin	
	N=67	%=100	N=69	%=100
Missing	4	6.0	7	10.1
DVT or sPE	20	29.9	27	39.1
DVT only (VG)	11	16.4	8	11.6
sPE only (lung scan)	1	1.5	2	2.9
DVT and sPE	8	11.9	17	24.6

From Table Thromboembolism 9C1.1 and 9C1.2 (Vol.5, pp.8/2/120-21).

The overall incidence rate of VTE (DVT/PE) in both treatment groups was 34.6%. This rate was higher than expected due mostly to the high incidence of PE diagnosed by lung scans. In this study, popliteal DVT were considered distal DVT.

The incidence of DVT in the P-P population and the DVT sites are summarized in the following table.

INCIDENCE OF DVT PER LOCATION. PER-PROTOCOL PATIENT POPULATION

DVT		Fragmin		Heparin		p-value
		N=67	%	N=69	%	
DVT total		19	28.4	25	36.2	
Proximal	Total	6	9.5	18	26.1	0.010*
	Femoral	5	7.5	13	18.8	0.006*
Distal	Total	13	20.6	7	11.2	z=0.838
	Popliteal	1	1.5	2	2.9	N.S.

From Table: 9C1.6 (Vol.5, pp.8/2/129-30).

These data show that fragmin was superior to low-dose heparin for the incidence of proximal (femoral) DVT.

2) Incidence of sPE

The incidence rates of PE detcted by lung scans are summarized in the following table.

INCIDENCE OF SCAN PE (sPE). ALL-TREATED PATIENT POPULATION

Pulmonary Embolism	Fragmin		Heparin		p-value
	N=67	%	N=69	%	
Missing Data	2	3.0	7	10.1	N.A.
sPE	9	13.4	19	27.5	0.032

The high incidence of PE in this study is due to the detection by routine lung scans. A statistically significant difference was noted between sPE in Fragmin and Heparin groups.

3) Primary efficacy variable statistical analysis

The results are summarized in the following Table.

SUMMARY OF TEST RESULTS: PRIMARY ANALYSIS OF EFFICACY. EVALUABLE PATIENT POPULATION

Event	Fragmin		Heparin		Fisher's Exact 2-tailed test
	N = 65	%	N = 62	%	
Total VTE	20	31.7%	27	43.5%	0.199
DVT	19	30.1%	25	41.6%	0.194
sPE	9	13.8%*	19	30.6%*	0.032*
Proximal DVT (femoral)	6	9.5%*	18	30.0%*	0.006*

95% Confidence intervals (95% CI)

Event	Fragmin	Heparin	Difference
VTE	0.21, 0.45	0.31, 0.57	-0.05, 0.29
DVT	0.19, 0.43	0.29, 0.55	-0.05, 0.28
sPE	0.07, 0.25	0.20, 0.44	0.03, 0.31*
Proximal DVT (femoral)	0.04, 0.20	0.19, 0.43	0.07, 0.34*

* = Significant difference. PE diagnosed by lung scans.

Both statistical methods, the Fisher's Exact test and the CI demonstrated a statistically significant difference between treatment groups for sPE and proximal DVT.

5.5.3 Safety Assessment

Safety was evaluated as:

- Extent of Exposure
- Adverse Events (hemorrhage, infection, other)
- Study Discontinuation and Deaths.
- Change of Clinical Laboratory values.

Statistical analyses were applied to the safety variables blood loss and transfusion requirements.

1. Extent of Exposure

On the average, 98.6% patients were exposed for 96% of days of therapy with 95% total active dose or placebo and with 94.8% of planned injections. There was no statistically significant difference between study treatments with regard to study drug exposure. The mean duration of therapy was 10.6 $\pm$ 1.9 days for the Fragmin group and 9.6 $\pm$ 1.7 days for the heparin group.

The number of patients exposed to the first injection of study medication close to the time of operation (fragmin <6 h preop. or heparin <1.5 h preop.) was similar in the two groups.

2. Hemorrhage

Hemorrhage was analyzed as BLOOD LOSS and TRANSFUSION VOLUMES used. The data are summarized in the following table.

BLOOD LOSS AND TRANSFUSION REQUIREMENTS. ALL-TREATED POPULATION

Parameter		Fragmin, N=67	Heparin, N=69	p-value
Blood Loss (mL)	median (range)	1280 (410 - 3190)	1400 (870 - 8950)*	0.0076
Transfusion (mL/U)	median (range)	900 (450 - 4500)	1350 (450 - 9450)	0.0002

From Table: Analysis of Adverse Events, Vol.5, p.8/2/179. * = mostly because of loss during operation

Compared to the heparin group, there was significantly less total blood loss in the fragmin group, as well as a significantly less need for transfusion. It is of note, however, that the difference in transfusion requirement is enhanced by the method of assessment, i.e., mL of blood transfused rather than units of blood or packed RBC transfused, or proportion of patients transfused.

No difference was noted between the two treatment groups for risk factors for bleeding (i.e., use of ASA or other NSAIDs). However, five patients received heparin close to the surgical operation.

3. Adverse Events

Adverse events other than bleeding were rare. Total hemorrhagic events occurred in 4 patients in the Fragmin group (all mild) and in 15 patients in the heparin group (1 event was severe).

In the heparin group, four heparin patients experienced wound infection, one patients experienced cerebral infarction and three had hip luxation.

The statistical analysis of the overall incidence of adverse events showed significant difference in favor of patients receiving fragmin (p=0.007).

Serious AE, AE leading to discontinuation, and Clinical Laboratory Results did not show treatment differences.

Only one patient died in the fragmin group.