

CENTER FOR DRUG EVALUATION AND RESEARCH

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA #20-287/S-008

SUBMISSION: Efficacy and Safety Supplement for New Indication

DRUG: FRAGMIN Injection (Dalteparin Sodium)

CLASS: Antithrombotic: Low Molecular Weight Heparin

INDICATIONS: Prophylaxis of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) in patients undergoing hip replacement surgery.

SPONSOR: Pharmacia & Upjohn Company, Kalamazoo, MI

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1.0 INTRODUCTION AND BACKGROUND

1.1 Thromboprophylaxis in Hip Replacement Surgery

Patients undergoing orthopedic surgery are at high risk of thromboembolic complications. Without thromboprophylaxis, the incidence of venous thromboembolic events (VTE) has been reported to be in excess of 50%. Non-fatal pulmonary embolism (PE) following orthopedic surgery occur in about 10% of patients; about 2% of PE have fatal outcome. The incidence of PE in the high risk orthopedic population is much higher than the 0.2% incidence of PE complicating major general surgery.

The connection between DVT in the lower extremities involving proximal veins and risk of pulmonary embolization is well established. Prior to the introduction of the Fibrinogen Uptake Test (FUT) as a diagnostic test for DVT in the early seventies, DVT was diagnosed by clinical criteria and confirmed by venography. The use of FUT has allowed to detect clinically asymptomatic DVT with an incidence rate of more ten times the rate of symptomatic DVT. More recent methods for the assessment of DVT include plethysmography, several types of ultrasound (Doppler flow, Duplex ultrasound). However, bilateral ascending phlebography remains the "reference standard" for diagnosis of DVT because of its objectivity even though considerable inter- and intra-variability in VG reading has been acknowledged. The majority of asymptomatic DVT are non-occlusive by VG assessment. However, asymptomatic DVT can also contribute to occurrence of PE. The VG diagnosis of DVT is based on "intraluminal filling defect" found on "at least two phlebogram".

The diagnosis of PE is based on clinical symptoms confirmed by ventilation/perfusion scintigraphy and/or pulmonary angiography (the "reference standard"). Historical data and data used in clinical trials to compare the PE incidence with the prophylactic effect of anticoagulant drugs are based on this diagnostic approach. The use of scintigraphy for screening of asymptomatic patients for PE has greatly increased the incidence of PE because of the detection of "moderate or high probability" PE involving small pulmonary vessels. The future clinical relevance of these asymptomatic PE is still unclear.

Following a better understanding of risk factors for DVT and PE, thromboprophylaxis has been widely used for prevention of asymptomatic DVT following orthopedic and/or other surgery with high risk for PE. Antithrombotic regimens have included heparin and warfarin. The NIH Consensus Conference on Prevention of Venous Thrombosis and Pulmonary Embolism in 1986 issued guidelines (*JAMA*. 1986; 286:745-9) which included the recommendation for the use of low-dose heparin (5000 IU, b.i.d. or t.i.d.).

In high risk surgical procedures, such as orthopedic surgery, thromboprophylaxis with fixed low-dose unfractionated heparin (UH) has been considered inadequate. However, sc administration of heparin at the dose of 5000 IU q8h has been shown to reduce the incidence of VTE in hip replacement surgery to approximately 20% compared to no treatment or to placebo. More effective thromboprophylaxis is achieved with the administration of sc heparin administered at doses adjusted according to APTT.

1.2 Low Molecular Weight Heparin (LMWH) for Perioperative Prophylaxis of DVT and PE

Antithrombotic compounds that have been extensively evaluated over the past decade for thromboprophylaxis in high risk patients are represented by the Low Molecular Weight Heparins (LMWH). LMWHs are fragments of unfractionated heparin (UH) produced by various processes of controlled chemical or enzymatic fractionation of heparin. Similar to UH, LMWHs exert their anticoagulant activity by activating AT-III, however they differ from UH in their relative inhibitory activity against factor Xa and IIa: whereas UH has equivalent anti-Xa and anti-IIa, LMWHs have greater anti-Xa than anti-IIa activity.

LMWHs differ in their manufacturing process, consequently, they differ chemically from each other and are not interchangeable. The MW distribution, mean MW, anti-Xa and anti-IIa activity and the anti-Xa/anti-IIa ratio differ for each LMWH.

LMWHs exhibit pharmacologic characteristics that make them more suitable for thromboprophylaxis than unfractionated heparin, among which, nearly 100% absorption from sc administration and longer duration of activity. LMWHs have better bioavailability and produce a more predictable anticoagulant response than UH. At thromboprophylactic doses, LMWH do not prolong global tests of coagulation such as PT, APTT and ACT, and consequently do not require laboratory monitoring of anticoagulant effect.

There are two major safety concerns regarding the use of LMWH for thromboprophylaxis in surgery: hemorrhagic complications and heparin-induced thrombocytopenia/thrombosis. Major bleeding events, defined on the basis of location (intracranial, neuraxial, retroperitoneal), size (ecchymosis/hematoma ≥ 5 cm diameter), amount of hemoglobin decrease (≥ 2 g/dL), and number of blood transfusions (≥ 2 units), are uncommon with the administration of LMWHs at doses used for thromboprophylaxis.

Heparin-induced thrombocytopenia (HIT) is an immune-mediated adverse event occurring in about 3% of patients receiving heparin for longer than 5-10 days. The *de novo* incidence of HIT is significantly lower in patients receiving LMWH, however, preformed anti-heparin antibodies cross-react with LMWHs in nearly 100% of cases.

Other adverse events reported in patients receiving Fragmin or other LMWH are classified according to COSTART BODY SYSTEM Dictionary.

Three LMWH, including Lovenox (enoxaparin sodium), Normiflo (ardeparin sodium), Fragmin (dalteparin sodium), and one heparinoid compound, Orgaran (danaparoid sodium) are approved in US for thromboprophylaxis in hip or knee replacement surgery or in high risk abdominal surgery.

1.3 Fragmin for Thromboprophylaxis in Hip Replacement Surgery

Fragmin (Dalteparin sodium) is a LMWH composed of acidic sulfated polysaccharide chains produced through controlled nitrous acid depolymerization and chromatographic purification of sodium heparin obtained from porcine intestinal mucosa. Fragmin is a mixture of heparin fragments; approximately 3-15% of the fragments have a MW of less than 3000, 65-78% of the fragments have a MW of 3000-8000, and 14-26% have a MW greater than 8000. The average MW of dalteparin is 5000 D.

At present, Fragmin has been authorized for use in 44 countries all over the world. Approved indications include: thromboprophylaxis, hemodialysis, and treatment of DVT. The first approval was granted in Germany, 1985. Since the first marketing in 1985 to May 1996, it is estimated that approximately 22 million patients worldwide have been treated with Fragmin.

The drug product is approved as single dose syringe (2,500 IU, and 5,000 IU), ampule (2,500 IU, 5,000 IU, 10,000 IU), and vials (4 and 10 mL; multidose).

On 8-6-1992, an NDA (#20-27) was submitted for the US approval of Fragmin for prophylaxis against DVT and PE in high risk patients undergoing general abdominal surgery or hip replacement surgery. In December 1994, Fragmin, at the dose of 2500 anti-Xa U sc qd, was approved for prophylaxis of DVT in patients undergoing abdominal surgery who are at risk of TE complications. Approval for Fragmin for thromboprophylaxis in hip replacement was not granted because one of the two pivotal studies (D-4) was unacceptable and the second study (D-10) was found to be inadequate as single pivotal study.

Fragmin, at the dose of 5000 anti-Xa U once daily sc, was subsequently approved also for thromboprophylaxis in patients undergoing abdominal surgery at high risk of TE complications.

An efficacy supplement (S-008) to NDA 20-287 has been submitted for the approval of Fragmin for the indication "for prophylaxis against DVT which may lead to pulmonary embolism (PE), in patients undergoing hip replacement surgery." The new indication

is supported by two pivotal studies conducted with patients undergoing hip replacement surgery: Study 91-137, a multi-center, warfarin-controlled clinical trial of 580 patients conducted in the U.S. and Study D-10, the single center, heparin-controlled trial of 140 patients conducted in Sweden and submitted in the initial NDA on 8-6-1992.

In addition to the two pivotal trials, other controlled clinical trials submitted in the original NDA (20-287) have been submitted as supportive studies, as well as a meta-analysis of Heparin-controlled Fragmin studies in hip arthroplasty.

Other Studies that support the indication of high risk surgery include "abdominal surgery for patients at risk for thrombosis such as cancer, or history of previous DVT or PE."

The Fragmin dosage regimen for patients undergoing hip replacement surgery is 2500 anti-Xa IU, SC, within 2h prior to surgery and again in the evening of the day of surgery (at least 6h after the first dose). If surgery is performed in the evening, the second dose on the day of surgery is omitted. Starting on the first postoperative day, Fragmin is administered at the dose of 5000 IU SC once daily. Alternatively, the initial dose of 5000 IU once daily can be started in the evening of the day of surgery. In both regimens, treatment is continued throughout the period of postoperative care until the risk of DVT has diminished. Up to 14 days of treatment was well tolerated in clinical trials, where the usual duration of treatment was 5-10 days postoperatively.

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2.0 NDA 20-287/S-008 TABLE of CONTENT

SUPPLEMENT 20-287/S-008 CLINICAL DATA

CONTENT	
Vol.1	Index, Application Summary (Annotated Package Insert, Foreign Marketing History)
Vol.2	Chemistry, Manufacturing and Controls. Part IV. Environmental Assessment.
Vol.3	Samples, Methods Validation and Labeling. Samples. Labeling.
Vol.4	Study 91-137: Clinical Data. Electronic Files (Diskettes in Item 10, Review Copy). A. List of investigators. B. Background/Overview of Clinical Investigations. D. Controlled Clinical Studies. Publication.
Vol.5	Study D-10: Revised Research Report . (p.1-256) Investigational Plan, Statistical Methods Planned, Disposition of Patients Entered, Efficacy Results, Safety Results, Summary and Conclusions, References. Appendix (p.257-575) Protocol and Amendments, Publications, List of Investigators, Statistical Methods and Randomization Codes, Patient Data Listings, Individual Patient data Listing.
Vol.6	Synopses of Other Controlled Hip Replacement Surgery Studies submitted with the same NDA. Study E-4, E-5, E-7 and E-8. E. Uncontrolled Clinical Studies. F. Other Studies and Information. G. Integrated Summary of Effectiveness Data (pivotal, supportive, meta-analysis of LMWH in hip surgery, Study 91-137). Integrated Summary of Safety Data (List of studies. Patient exposure. Hemorrhagic events. Non-hemorrhagic adverse events. Deaths and premature withdrawals. Laboratory data. Study 91-137. I. Drug Abuse & Overdose Information. J. Integrated Summary of Benefits and Risks of the Drug.
Vol.7-9	Statistical Section

Electronic data were submitted only in SAS format. They were available for statistical analysis. No data in electronic form were available in WP or Word formats.

3.0 MATERIAL REVIEWED IN NDA 20-287/S-008

a. Clinical Data

The NDA Supplement was submitted in 32 volumes. The clinical and statistical data from the two pivotal studies and from supportive studies are presented in volumes 1 through 9.

The data from the pivotal study 91-137 were submitted in volume 4 and the data from study D-10 were submitted in volume 5.

The study protocol with amendments were included in Vol.22-24. Case Report Tabulations, Patient Profiles, and Case Report Forms for Patients who Discontinued were submitted in electronic format.

This NDA supplement was reviewed by the Dr. Markovic who submitted a draft review on March 13, 1998. Material from Dr. Markovic's draft review and revised tables of data have been included in the present review.

b. 4-Month Safety Update (Amendment to Supplement S-008).

This update includes new safety data that have become available between 07/01/95 and 02/28/97.

The safety data from this amendment are also included in the Integrated Assessment of Safety.

REVIEW OF THE CLINICAL DATA: PIVOTAL STUDIES

4.0 REVIEW OF STUDY 91-137 (NDA/S Vol.4)

Title: An open, randomized study evaluation the thromboprophylactic efficacy of low molecular weight heparin (Fragmin®) vs. warfarin in total hip replacement.

Indication: Prophylaxis of DVT in patient undergoing total hip replacement.

Study Drugs: Test Drug: Fragmin 2500 IU (Batch Nos.DXN 1 85,94046A01) 2h before surgery followed by 2500 after 12 hours and 5000 IU (Batch Nos.DXN 186, DXN 241, 94032A02) q.d. afterwards.
Control drug: Warfarin, dose adjusted for INR 2.0-3.0. The treatment was continued for up to 9 days following surgery.

Study Dates: 05/19/92 to 03/30/95. Date of Report: 03/31/96

Investigators: Multicenter (n=8, all in the U.S.).

Adjudicator: Blinded radiologist who evaluated the venograms from all study sites (S.Totterman, M.D., Radiologists. Univ. of Rochester Med. Cnt.).

4.1 STUDY OBJECTIVES

- A. The primary objective was to compare the incidence of verified postoperative DVT after unilateral total hip replacement [THR] in patients receiving fragmin vs. warfarin.
- B. Secondary objectives of the study were to:
1. Compare the incidence of postoperative verified proximal DVT within approximately one week after surgery.
 2. Compare the incidence of postoperative verified pulmonary embolism (PE) in patients with suggestive clinical findings within approximately one week after surgery.
 3. Compare the incidence of clinical thromboembolic events (verified DVT and/or PE) within about one week post-operatively.
 4. Compare the incidence of clinical thromboembolic events within the follow-up period (5-7 weeks post-op).
 5. Evaluate the safety parameters such as bleeding during and after surgery, re-operation due to bleeding, surgically or spontaneously evacuated wound hematoma, other bleeding complications, blood transfusion requirements, and hemoglobin, hematocrit, and platelet count.

4.2 SYNOPSIS OF STUDY 91-137

Study 91-137 was designed and completed in the U.S. to serve as a pivotal trial for the approval of fragmin for prophylaxis of DVT/PE in patients undergoing hip replacement surgery.

The objective of the study was to demonstrate that fragmin is safe and superior to warfarin for thromboprophylaxis in hip replacement surgery.

The study enrolled 580 patients at eight centers in the U.S. The patients were randomly assigned to either Fragmin (2500 IU prior to operation, followed by 2500 IU after operation, and 5000 IU daily for 5-9 days) or Warfarin (first dose night before surgery, followed by the same dose the day of surgery, and then dosed to maintain INR approximately about 2.5). Per protocol population included 192 Fragmin patients and 190 warfarin patients.

At the end of the study (day 5-9) all patients were examined by a bilateral ascending venography. Venograms (VG) were evaluated for thrombosis by radiologists and by an adjudication committee blinded for study drug allocation. The primary efficacy endpoint, DVT was found in 28/192 (15%) patients on Fragmin, and 49/190 (26%) patients on Warfarin treatment. This difference was significant ($p=0.006$).

Patients in the Fragmin group had more hemorrhagic episodes than those in the Warfarin group (F=30/274 or 10.9%; W=12/279 or 4.3%). At least two patients in the Fragmin group had major hemorrhage and discontinued the study. Non-hemorrhagic adverse events were comparable in the two treatment groups. Eight Fragmin and six Warfarin patients had at least one platelet count value below 100,000/mm³. No case of HIT was reported. No deaths were reported.

The study 91-137 demonstrated that Fragmin reduced the risk of postoperative DVT compared to warfarin, however, this benefit carried a moderate risk of perioperative hemorrhage.

4.3 SUMMARY OF THE INVESTIGATIONAL PLAN

a. Study Design

The study was multicenter (n=8), randomized, open-label, assessor blinded, parallel group, active treatment controlled clinical trial. Five hundred-eighty (580) enrolled patients were randomly assigned by a central coordinating center to receive either Fragmin (288 patients) or Warfarin (292 patients).

Patients treated with Fragmin received 2500 IU sc within two hours prior to surgery. This dose was repeated in the evening the day of the surgery. Fragmin was continued with 5000 IU sc every morning thereafter for 7±2 days of study.

Patients treated with Warfarin received the first dose in the evening before surgery followed by the second equal dose (5 or 7.5 mg) the evening after surgery. Thereafter, daily doses of Warfarin were adjusted to maintain a prothrombin time index (PTI) of 1.4-1.5 or INR approximately 2.5. Warfarin was given for the same time as Fragmin (7±2 days).

Bilateral ascending phlebography was performed 7±2 days after surgery. Efficacy assessment included incidence of DVT and PE. Venograms were assessed by an independent radiologist who had no knowledge of the treatment groups. Patients who presented clinical signs or symptoms suggestive of acute PE, were subject to perfusion/ventilation scintigraphy and/or pulmonary angiography for confirmation of diagnosis.

Patients were evaluated for safety starting preoperatively and through the 5-7 week follow-up period. Patients were monitored for bleeding, clinically observed and reported adverse events, and events which would result in premature withdrawal from the trial.

b. Choice of Control Group

The active control drug, Warfarin, is approved for prophylaxis of DVT and PE in general, but not specifically for the indication of this trial. However previous clinical experience has established the efficacy of warfarin compared to no treatment, therefore, study 91-137 was accepted as pivotal study. Furthermore, the study was designed to show superiority of Fragmin over Warfarin.

c. Study Population

Patients scheduled for hip replacement were screened for eligibility in order to allow enrollment of 580 patients to enter the study.

d. Randomization

Patients were randomly assigned to one of two treatment regimens by central randomization. Random numbers were provided to each center.

Within two weeks prior to surgery, the investigator called the Randomization Center either at the Strong Memorial Hospital, Rochester, NY, or the [REDACTED]

[REDACTED] Patients were allocated a consecutive patients number and treatment (Fragmin or Warfarin) in the order of entering the study.

e. Study Medication

Test Drug: Dalteparin was provided in single dose syringes for sc injection, containing either 2,500 IU/0.2 mL, or 5,000 IU/0.2 mL. For morning operations, dalteparin (2,500 IU) was administered 2h prior to surgery and in the evening of the same day (2,500 IU), but at least six hours after the preoperative injection. For evening surgery (4.00 pm and later), the evening dose was not given. All patients received 5,000 IU the first postoperative day, and 5-9 following days.

ELIGIBILITY CRITERIA

Inclusion Criteria

1. Male and female patients 18 years or older.
2. Scheduled for unilateral total hip replacement surgery within two weeks after randomization.
3. Written informed consent.

Exclusion Criteria

1. Previously undergone surgery in this study.
2. Simultaneous participation in another study involving investigational drug.
4. Renal insufficiency (serum creatinine ≥ 1.7 mg/dL).
5. Liver insufficiency (abnormal prothrombin time).
6. Documented bleeding, e.g., gastrointestinal, within three months prior to surgery.
7. Defect hemostasis, e.g., thrombocytopenia or ongoing anticoagulant treatment.
8. Cerebral hemorrhage within three months prior to surgery.
9. Eye, ear or CNS surgery within one month prior to surgery.
10. Known hypersensitivity to heparin, LMWH or contrast media.
11. Severe hypertension (diastolic pressure ≥ 120 mm Hg).
12. Septic endocarditis.
13. Weight less than 90 pounds.
14. Known pregnancy or breast feeding.
15. Positive pregnancy test in woman of reproductive potential.
16. Patients who are expected to be unable to follow instructions given in connection to the study.

Control Drug: The first warfarin dose was weight adjusted. Patients ≤ 125 lb (57 kg) received 5 mg. Those >125 lb (57 kg) received 7.5 mg. The initial fixed, weight adjusted dose was given on the evening before surgery and the evening after surgery. Thereafter, daily dose was adjusted according to individual response to maintain an INR of approximately 2.5. Duration of therapy 7 \pm 2 Days after surgery.

Venography was mandatory for all patients on Day 8 or earlier if clinical symptoms of an outcome were present. Patients with positive venography were treated at the discretion of the physician. For patients with negative venography, anticoagulant therapy was discontinued.

Concomitant use of ASA, NSAID, dextran or compression stockings was not allowed.

f. Efficacy and Safety Variables

● Efficacy

- 1) The primary efficacy variable was the incidence of a venous thromboembolic event (VTE), defined as objectively confirmed DVT, PE, death by thromboembolism, or any combination, in the Per-Protocol patient population (P-P), within one week following surgery.
- 2) The secondary efficacy variables were:
 - the incidence of VTE in the All-Treated patient population (all randomized patients who were operated on and received any study medication) within one week following surgery, and
 - the incidence of clinically symptomatic VTE within the follow-up period of 5-7 weeks after surgery.

● Criteria for efficacy endpoints

DVT: DVT was diagnosed if a constant filling defect was present in more than one VG projection. DVT was classified as distal (calf veins) or proximal (popliteal and more proximal veins).

PE: Two criteria were used for confirmation of PE:

- a positive pulmonary angiogram, and
- high clinical probability together with high probability lung scan.

● *Safety*

Hemorrhage (bleeding) was considered the primary safety variable. The following variables were assessed and recorded on CRF for statistical analysis of safety:

- 1) Bleeding evaluated as a composite endpoint including:
 1. Perioperative blood loss (mean in mL) - estimation by anaesthetist.
 2. Postoperative blood loss (mean in mL) - measurement of blood loss in drains.
 3. Blood transfusion requirements (number of patients requiring transfusion) - information from the Blood Bank.
 4. Plasma substitute - type and amount.
 5. Reoperation due to bleeding.
 6. Surgically or spontaneously evacuated wound hematoma.
 7. Other bleeding complications.
- 2) Allergic Reactions.
- 3) Adverse Events including the two primary efficacy variables (DVT and PE), the primary safety variable (bleeding), and Non-Hemorrhagic Adverse Events.
 1. Bleeding was assessed as a composite variable including the following WHO-ART terms: Hemorrhage, Wound Hematoma, GI Bleeding, Bleeding, Ecchymosis at Wound and Injection Site.
 2. Non-hemorrhagic adverse events were summarized by WHO-ART Body System and by WHO-ART Preferred Term within body system.
- 4) Analyses of Subsets of Patient Population/Sub-Group:
 - . Elderly vs. Young
 - . Males vs. Females
 - . Patients with Body Weight <80 kg vs. ≥80 kg.
 - . Patients with Risk Factors ≥2 vs. <2.
 - . Primary Operation vs. Revision Surgery.
- 5) Withdrawals/Dropouts. The following reasons were considered for withdrawal: allergic reaction, serious intercurrent illness, verified DVT/PE, patient request, and canceled operation.

All events were presented by their frequency and distribution parameters in tables. In some instances different statistical methods were used. Conclusions were based on statistical significance ($\alpha=0.05$; power 95%).

● **Laboratory Tests**

Laboratory Analysis.

- Change from baseline for: Hemoglobin, Hematocrit, Platelets
- Baseline: Hemoglobin, hematocrit, platelets, PT, creatinine.
- Daily: PT for patients on warfarin
- Ad hock: Anti-Xa, PT, APTT, hemoglobin, platelet count.
- End of study: Platelet count, hemoglobin.

g. Disposition of Study Patients

Information was obtained for the following parameters:

- Demographics: Gender, age (<65), race, body weight.
- Risk Factors: type of operation, duration of anesthesia and operation, previous VTE, cancer, trauma, varicose veins and postphlebotic syndrome, CV disease.
- Exposure to Study Medication, Concomitant Medication
- Dropouts, Protocol Violations
- Study Discontinuation
- Deaths

4.4 STATISTICAL METHODS

a. Statistical Analyses of Efficacy and Safety

The statistical analyses are outlined in the following table.

OUTCOME		ENDPOINT	POPULATION	STATISTICAL METHOD
Efficacy	Primary	VTE: DVT, PE or death due to TE events	Per-Protocol	two-sided t-test, $\alpha=0.05$
	Secondary	VTE: DVT, PE or death due to TEc event	All-Treated	
		Symptomatic VTE (5-7 weeks)	All-treated	
Safety		Hemorrhage and Adverse Events	All-treated	

From Protocol Plan: Statistics and Medical Data (Vol.4, 8/1/238)

The statistical plan was changed and Cochran-Mantel-Haenzel Test was used by the sponsor.

b. Sample Size

The sample size was calculated based on 25% failure rate (incidence of VTE) for warfarin, and 15% failure rate for Fragmin. A sample size of at least 250 patients per treatment group was required for a 10% treatment difference with a power of 80% using a two-tailed test at the 5% level of significance. Considering a drop-out rate of about 15%, a total of 580 patients was included to provide at least 500 evaluable patients.

4.5 STUDY RESULTS

4.5.1 Data Sets Analyzed

a. Patients Disposition

All-treated population consisted of patients operated and who received at least one dose of study medication. Per protocol population consisted of patients who were operated, dosed, and had an evaluable venogram. Only the All-Treated and Per-Protocol (P-P) populations were used in the statistical analysis. P-P population was used for primary efficacy analysis. All-treated population was used for safety analyses.

A total of 580 patients were randomized in the study in order to have 500 evaluable patients. Approximately 5% of randomized patients did not enter the study because they either were not operated or not dosed. Approximately one third of the All-Treated patients (30.5%) did not have evaluable VG and were excluded from the P-P population. Consequently, the primary efficacy analysis was performed without the prestated power of 80% due to the reduction of the P-P population. The disposition of the study patients is summarized in the following table.

Patient Disposition		Number of Patients	
		Fragmin	Warfarin
Randomized		288	292
ITT	Included in ITT analysis (all-treated);	271	279
	Excluded: Total	17	13
	No VG Never dosed, No operation,	14	13
	VG Dosed but Surgery canceled, No	3	0
P-P	Included in P-P analysis;	192 (66.6%)	190 (65.1%)
	Excluded: Total	96 (33.4%)	102 (34.9%)
	Never dosed, No operation, No VG	14	13
	VG Dosed but Surgery canceled, No	3	0
	Dosed but No VG	53	70
	Dosed but VG misplaced or missing	7	8
	Dosed but VG not evaluable	19	11

From Tables :Vol 4, p8-1-62, and p.8-1-63

Approximately 10% of patients were withdrawn from the study. The reasons for withdrawal are summarized in the following table.

PATIENTS WHO COMPLETED THE STUDY. REASON FOR WITHDRAWAL.

		Fragmin (n=288)	Warfarin (n=292)
Randomized/Completed		288/262	292/270
Withdrawn	Total	26	22
	Adverse Event	3	3
	Intercurrent Illness	1	1
	DVT/PE	1	1
	Patient Request	7	4
	Operation Canceled	10	7
	Other	4	6

From Table Patient Disposition (Vol.4, p8-1-77)

b. Compliance (Protocol Violations)

Five patients were excluded because of protocol violation: renal insufficiency at baseline [E=2/W=1], hypersensitivity to heparin [F=1], body weight <90 lbs [F=1]).

Another protocol violation was represented by the practice of local investigators to use lower dose of warfarin than specified in the protocol.

A total of 163 patients (85%) of P-P population treated with Fragmin met dosing compliance. One hundred-eighty-two (182) patients (96%) treated with warfarin met compliance criteria. Therefore, the population of patients who were operated on, received dose medication as planned, and had evaluable VGs was even smaller than the P-P population as defined by the sponsor. In either case, neither treatment groups reached the calculated sample size needed for the pre-determined sample power.

c. Demographics

There were no imbalances between the two treatment groups for demographics, patients characteristics, underlying conditions, surgical and anesthesia characteristics, and risk factors for VTEs.

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d. Duration of Treatment

The majority of patients received treatment as specified in the protocol pre-operatively, on the day of surgery and post-operatively for five days (Day 1-5). The number of patients receiving the study drugs decreased from Day 6 and by Day 10 only a few patient were receiving the study drugs. No significant difference was found between treatment groups.

4.5.2 Efficacy Assessment

1. Primary Efficacy Analysis

The primary efficacy endpoint was the incidence of DVT in the P-P population as assessed on VG by an independent blinded radiologist. The results are summarized below:

PRIMARY EFFICACY ENDPOINT: RATES OF VERIFIED DVT AND SUPERFICIAL VEINS THROMBOSIS IN P-P POPULATION*.

DVT Location	Fragmin		Warfarin		P-value
	N=192	%	N=190	%	
Any Deep Vein Thrombosis (total DVT)	28	14.6	49	25.8	0.006*
Risk Ratio-Odds Ratio@	28/164=0.17		49/141=0.35		OR:0.48
Any Superficial Vein Thrombosis**	23	11.9	43	22.6	0.005*
Superficial and deep venous thrombosis	51	26.5	92	48.4	<0.001*
Distal DVT (Calf): Total	21	10.9	43	22.6	0.005*
Proximal DVT (Leg): Total	10	5.2	16	8.4	0.185
Popliteal	2	1	7	4	
Superf. Thigh.	4	2	9	5	
DVT Thigh	4	2	1	1	

From Table: Vol.4, p.8/1/71-72. * Significant difference.

** Superficial vein category (not in the protocol) was analyzed aside of categories any vein, proximal and distal. Some DVT may have been counted in more than one location.

Significant difference was found in the incidence of primary efficacy variable: the 'any DVT' category due to the difference found in 'distal DVT'. A slight numerical difference in favor of Fragmin was found for the proximal DVT which was not statistically significant.

The net reduction in DVT rates in the Fragmin group was 11.2%.