Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Drug established name: fondaparinux sodium
Drug proposed trade name: Arixtra
Drug class: antithrombotic, synthetic pentasaccharide
Drug code name in this application: Org31540/SR90107A

The Sponsor's proposed indication is prevention of venous thromboembolic events in patients undergoing major orthopedic surgery of the lower limbs such as hip fracture, major knee or hip replacement surgeries.

The proposed dose regimen is 2.5 mg once daily administered post-operatively by subcutaneous injection.

Adult (18 years or older) population is proposed in the labeling and was used in the submitted clinical trials. Pediatric studies waiver has been granted to this product for the proposed indication prior to NDA submission.

B. State of Armamentarium for Indications

Current approved products for prophylaxis of DVT in patients undergoing total hip or knee replacement surgeries are listed in the table below by indication. There has no product approved in the U.S. for prophylaxis of DVT in patients undergoing hip fracture surgery.

Approved products for prophylaxis of DVT in patients undergoing total hip or knee replacement surgeries

Indications	Approved Products	Dosage And administration	Populations	Wording in Indications
Prophylaxis of DVT in patients undergoing hip replacement surgery	Lovenox® (enoxaparin sodium)	30 mg q12 hrs beginning post-operatively for 7-10 days, up to 14 days; 40 mg q.d. beginning pre-operatively for 7-10 days; may continue for 3 weeks; SC	Adults	"prevention of deep vein thrombosis, which may lead to pulmonary embolism: • in patients undergoing hip replacement surgery, during and following hospitalization;"
	Fragmin (dalteparin sodium)	5000 IU q.d.; may beginning pre-operatively for 5-10 days, up to 14 days; SC	Adults	"prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE): • in patients undergoing hip replacement surgery;"
	Orgaran® (danaparoid sodium)	750 Anti-Xa U b.i.d beginning pre-operatively for 7-10 days, up to 14 days; SC	Adults	"prophylaxis of post-operative deep venous thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing elective hip replacement surgery".
Prophylaxis of DVT in patients undergoing knee replacement surgery	Lovenox® (enoxaparin sodium)	30 mg q12 hrs beginning post-operatively for 7-10 days, up to 14 days; SC	Adults	"prevention of deep vein thrombosis, which may lead to pulmonary embolism: • in patients undergoing knee replacement surgery;"
	Normiflo[a] (ardeparin sodium)	50 Anti-Xa U /kg b.i.d. beginning pre-operatively for up to 14 days; SC	Adults	"prevention of deep vein thrombosis which may lead to pulmonary embolism following knee replacement surgery."
Prophylaxis of DVT (Non-specific patient population)	Heparin Sodium	5000 U t.i.d or b.i.d beginning pre-operatively for 7 days; SC	Adults	"Prevention (in a low-dose regimen) of postoperative deep venous thrombosis and pulmonary embolism in patients undergoing major abdominothoracic surgery or who, for other reasons, are at risk of developing thromboembolic disease."
	Coumadin (warfarin Sodium)	Individualized to INR of 2.0-3.0; Oral	Adults	"prophylaxis and/or treatment of venous thrombosis and its extension, and pulmonary embolism".

[a] no longer marketed
Reviewer's table

C. Important Milestones in Product Development

On March 27, 1998, an End-Of-Phase II meeting was held to discuss the sponsor's proposed Phase III clinical development plan and protocols. Agreements were made between Sponsor and Agency on the dose selection in Phase III trials that could be reasonably identified based on Phase II dose ranging studies. The Agency indicated "In order to support the indication of the prevention of DVT and/or PE, it would be necessary

to power/size the proposed studies to independently support both endpoints, DVT and PE". At this meeting, the Agency also indicated "the term 'lower limb major orthopedic surgeries' was unacceptable" regarding to proposed indication and "the terminology must be specific to the study populations: elective hip replacement surgery, knee replacement surgery, hip fracture surgery". The agency also indicated "a single study to support approval of an indication must meet the criteria guidance for a single study (dose-ranging studies may be considered supportive, but not pivotal)".

On August 5, 1998, a teleconference was held between the Sponsor and Agency regarding dose-range studies. The Agency indicated "The Phase II dose ranging studies for THR and TKR were prospectively designed as hypothesis generating studies" and "It is important to note that the proposed 2.5mg dose was not used in either of the dose ranging trials". In this teleconference, the Agency also indicated that two proposed THR phase III studies and 1 proposed TKR phase III studies appear adequately designed to support the indication(s) of the prevention of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients undergoing total hip replacement surgery, or total knee replacement surgery, and the study will be evaluated based on the "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products".

On October 2, 1998, a meeting was held between the Sponsor and the Agency to discuss the disagreement regarding to Phase II dose-ranging studies. After extensive discussion, an agreement was reached in both sides that "it is possible that the dose-ranging study in hip replacement might be satisfactory as a pivotal study. It needs to be evaluated for its scientific merit based on, but not limited to, the following: study size, study design, primary endpoints and objectives, statistical methods, and robust statistical significance based on adjustment for multiple comparisons, where applicable".

D. Other Relevant Information

Fondaparinux sodium has not been marketed in any other countries.

E. Important Issues with Pharmacologically Related Agents

Risk of spinal/epidural hematomas has been labeled in a "black box warning" for most antithrombotic class products. Hemorrhage and thrombocytopenia are major adverse reactions for the products in the antithrombotic class.

IV. Description of Clinical Data and Sources

A. Overall Data

The following material in the NDA submission was reviewed:

- NDA Volumes 1-301 (clinical), submitted February 15, 2001
- Amendment No. 2: Response to request for information-clinical, submitted March 21, 2001

- Amendment No. 4: Response to request for information-clinical, submitted May 1, 2001

These included four Phase III clinical trials and four Phase II clinical trials for proposed indications in addition to previous mentioned PK/PD studies. The sponsor has also submitted six completed or ongoing trials studied for other indications.

B. Tables Listing the Clinical Trials

The following table summarizes the submitted Phase II and Phase III clinical trials for the proposed indications (pharmacokinetic and pharmacodynamic studies have been discussed in Dr. Ann Farrell's review).

Summary of clinical trials for the proposed indications

Proposed Indication	Studies	Type of trials	# of patients enrolled	Dose regimen	Control group	Location of study
Prophylaxis of DVT in patients undergoing hip fracture surgery	EFC2698	Phase III trial	1711	2.5mg q.d. post-operatively, or pre-operatively if surgery 24-48 hrs after admission for 7±2 days; SC	enoxaparin 40mg q.d. pre-operatively for 7±2 days; SC	18 European countries, Australia, Argentina, and South Africa
Prophylaxis of DVT in patients undergoing hip replacement surgery	63118	Phase III	2309	2.5mg q.d. post-operatively for 7±2 days; SC	enoxaparin 40mg q.d. pre-operatively for 7±2 days; SC	16 European countries
	EFC2442	Phase III trial	2275	2.5mg q.d. post-operatively for 7±2 days; SC	enoxaparin 30mg q12 hrs post-operatively for 7±2 days; SC	US, Canada, and Australia
	DRI2643	Phase II dose-ranging study	950	0.75mg, 1.5mg, 3.0mg, 6.0mg, 8.0mg, q.d., post-operatively for 5 days; SC	enoxaparin 30mg q12 hrs post-operatively for 5 days; SC	US, Canada, and Australia
	ACT1840	Phase II	115	3 mg, bid starting pre-operatively with 2 mg dose and continued post-operatively for 8 days, SC	Nadroparin 100 anti-Xa ICU/kg for 5 days and 150 anti-Xa ICU/kg for 3 days; SC	The Netherlands, France, and Belgium
	ACT2545	Phase IIA	243	2.0 mg, 4.0 mg q.d daily post-operatively for 7 days, SC	40 mg once daily pre-operatively for 8 days, SC	The Netherlands, France, and Belgium
Prophylaxis of DVT in patients undergoing knee replacement surgery	95002	Phase III trial	1049	2.5mg q.d. post-operatively for 7±2 days, SC	enoxaparin 30mg q12 hrs post-operatively for 7±2 days; SC	US and Canada
	95001	Phase II dose-ranging study	318	0.75mg, 1.5mg, 3.0mg, 6.0mg, 8.0mg, q.d., post-operatively for 5-10 days; SC	None	US

Reviewer's table

The following table summarizes the clinical trials that have completed or are ongoing for other indications.

Summary of clinical trials (completed or ongoing) for the other indications

Indication	Studies	Type of trials	# of patients treated	Dose regimen	Control group	Location of study
Treatment of [redacted]	DRI2440	Phase II	453	5 mg, 7.5 mg, 10 mg q.d, SC for 5-10 days	Dalteparin 100 IU/kg bid for 5-10 days	Canada, The Netherlands, France, Italy, Australia, Belgium, Switzerland and New Zealand
	EFC2441, ongoing	Phase III	30 randomized as cut-off date	5mg, 7.5mg, 10mg q.d, SC for ≥ 5 days	enoxaparin 1mg/kg, SC, for ≥ 5 days	Five countries as of cut-off date
Treatment of [redacted]	ACT2445	Phase IIA	71	12 mg IV bolus injection over 5 minutes before [redacted]	Not applicable	France
Treatment of [redacted]	DRI3196	Phase II	326	4 mg, 8 mg, 12mg, IV bolus on day 1 then SC for 3-5 days	Heparin 5000 IU iv bolus then 1000 IU/hr IV infusion for 48-72 hours	Belgium, France, Germany, Netherlands, Switzerland, and United Kingdom
Treatment of [redacted]	63119, ongoing	Phase II	341	2.5mg, 4mg, 8mg 12 mg, IV bolus injection on day1 then SC for 6 days	Placebo; enoxaparin 1mg/kg bid SC	Belgium, France, Germany, Netherlands, and Poland
Prevention of [redacted]	63113	Phase II	13	4mg, 6mg, 8mg, 10mg IV bolus injection	Dalteparin Individualized IV bolus injection	Netherlands

Reviewer's table

C. Postmarketing Experience

Fondaparinux sodium has not been marketed in any countries.

D. Literature Review

PubMed search identified 6 publications of Phase I or Phase II clinical trials sponsored by the applicant. These reports were included in submitted PK/PD and dose-ranging studies.

V. Clinical Review Methods

A. Describe How Review was conducted

All four pivotal Phase III trials submitted and two Phase II dose-ranging trials were reviewed for the efficacy evaluation for the proposed indications. All of these trials were reviewed separately in the same depth. These trials and other submitted trials were used in the integrated safety summary.

B. Overview of Materials Consulted in Review

The whole NDA was submitted electronically. The datasets the four pivotal studies were examined for the efficacy evaluation.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Three largest centers in three different pivotal trials (EFC2698, 63118 and 95002) were requested to be inspected by the FDA Division of Scientific Investigation. The report is pending at the time of review.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The four pivotal trials were conducted in accordance with accepted ethical standards. Informed consents were required from patients in all four pivotal trials. Sample written consent forms in this submission provided adequate information including risk/discomfort, alternative treatment, and confidentiality to patients. Independent ethics committees/institutional review boards at all participating centers were required to give permission for these studies.

E. Evaluation of Financial Disclosure

The sponsor certified that Sanofi-Synthelabo, Inc. and Organon, Inc. (sponsors of these trials) had not entered into any financial arrangement with any clinical investigators, who conducted the four pivotal clinical studies and two dose-ranging studies (Form FDA 3454).

VI. Integrated Review of Efficacy

A. *Briefly* Present Conclusions and Any Critical Differences from Sponsor's Proposed Label Claims.

The Sponsor's efficacy results from four pivotal trials demonstrated that fondaparinux sodium 2.5mg SC once daily was superior to enoxaparin sodium 40mg SC once daily for

the prophylaxis of DVT in patients undergoing hip fracture surgery and hip replacement surgery, and was also superior to enoxaparin 30mg SC every 12 hours for the prophylaxis of DVT in patients undergoing knee replacement surgery.

The Sponsor's proposed indication was for the prevention of venous thromboembolic events in patients undergoing major orthopedic surgery of the lower limbs such as hip fracture, major knee or hip replacement surgeries.

Critical differences between the study results and the Sponsor's proposed labeling are identified as follows:

Indicated population:

Study results: Patients undergoing hip fracture surgery, total elective hip replacement, or knee replacement surgery were studied in separate clinical trials.

Proposed indication: "Patients undergoing major orthopedic surgery of the lower limbs such as hip fracture, major knee or hip replacement surgeries" is stated as the indication in the proposed labeling.

The proposed "major orthopedic surgery of lower limbs" includes a broad range of surgeries: surgeries for fractures for any part of lower limbs and any ankle/foot surgeries besides the three specific surgeries that have been studied in the submitted clinical trials. Patients undergoing other types of surgeries have never been studied for this drug and they may well have different benefit/risk from the treatment.

In the End-Of-Phase II meeting (March 27, 1998), the Agency indicated clearly that "the term 'lower limb major orthopedic surgeries' was unacceptable" with regard to proposed indication and "the terminology must be specific to the study populations: elective hip replacement surgery, knee replacement surgery, hip fracture surgery".

Therefore, the proposed labeling for patients undergoing major orthopedic surgery is not acceptable. The indicated population should be specified as the patient population studied in the trials.

Efficacy Event:

Study results: Submitted clinical trials demonstrated that fondaparinux sodium 2.5mg SC once daily was superior to enoxaparin sodium 40mg SC once daily for the prophylaxis of DVT. There were no significant differences for the incidence of PE between the two treatments in all submitted pivotal trials.

Proposed indication: "Venous thromboembolic events" (VTE) that includes DVT and PE was used in the proposed labeling.

Even though VTE was a primary efficacy endpoint in clinical trials, only mandatory venography for assessment of DVT was required for all patients in the trials and clinically diagnosed symptomatic PE was used for assessment of PE. The study results showed that the difference in the incidence of VTE between the two treatments was mainly due to difference in the incidence of DVT. There were no differences in the incidence of PE between the two treatments in any of the four pivotal trials.

In the End-Of-Phase II meeting (March 27, 1998), the Agency indicated "In order to support the indication of the prevention of DVT and/or PE, it would be necessary to power/size the proposed studies to independently support both endpoints, DVT and PE".

Using VTE instead of DVT in the labeling may misrepresent the overall study results. For consistency with labeling for previously approved drugs for the same types of indications, the phrase "deep vein thrombosis, which may lead to pulmonary embolism" should be used in the labeling for the indication statement.

B. General Approach to Review of the Efficacy of the Drug

The sponsor has submitted four Phase III trials, two Phase II dose-ranging trials, and two Phase II "Proof of Concept" trials for the proposed indications in three different populations. All four Phase III trials and two dose-ranging Phase II trials were reviewed in detail for the efficacy of the drug. All four Phase III trials were active control, superiority trials and were considered as pivotal trials for the proposed indication.

C. Detailed Review of Trials by Indication

a. Overall Study Designs and Results

The sponsor has submitted four pivotal trials for the proposed indication. These included one pivotal trial (EFC2698) in patients undergoing hip fracture surgery, two trials (63118 and EFC2442) in patients undergoing total elective hip replacement surgery, and one trial (95-002) in patients undergoing major knee surgery.

Four pivotal trials were conducted using a similar design in three different populations. All trials were multicenter, randomized, double-blind, parallel groups with enoxaparin as active control and sized to demonstrated superiority of Org31540/SR90107A. The same dose (2.5 mg SC once daily) of Org31540/SR90107A was used for all four trials. The dose of enoxaparin was 40 mg once daily which was to be started pre-operatively in studies EFC2698 and 63118, 30 mg SC every 12 hours to be started post-operatively in studies EFC2442 and 95-002. The primary efficacy endpoint was the incidence of VTE (adjudicated venographically positive DVT and adjudicated symptomatic non-fatal or fatal PE) up to day 11 for all four trials. Both DVT and PE were adjudicated by the same committee.

The following table summarizes the overall designs of 4 Phase III pivotal trials by the indication:

Summary of Phase III Trial Study Designs

Proposed Indications	Clinical Trials	Study design	Study population		Study treatment	Sample size determination
			Inclusion criteria	Exclusion criteria		
Prophylaxis of DVT in patients undergoing hip fracture surgery	EFC2698 99 centers in 21 countries: 18 European countries, Australia, Argentina, South Africa	Multicenter, randomized, double-blind double dummy, Active controlled study Study period: 11/15/1998-10/22/1999	1.Undergoing standard surgery for fracture of the upper third of the femur, including femoral head and neck, not more than 48 hrs after admission 2. Signed written informed consent 3.Men or women of non-childbearing potential or women of childbearing potential with a negative pregnancy test within 48 hrs prior to surgery or first study drug administration, whichever came first. 4.18 years of age or older.	A. Exclusion criteria for LMWH: 1. Active bleeding 2. Platelet count < 100 x 10^9/L 3. Hypersensitivity to heparin, LMWH, or pork products 4. Acute bacterial endocarditis 5.Bleeding tendency/disorders 6. Ulceration or angiodysplastic gastrointestinal disease 7. Hemorrhagic stroke or recent (<3 mons) brain, spinal, or ophthalmological surgery 8. Planned indwelling intrathecal or epidural catheters for > 6 hrs after the end of surgery 9.Patients for whom anticoagulant therapy was contraindicated or who could not be taken off anticoagulant therapy due to a co-existing condition B. Exclusion criteria related to study procedures (venography): 1. Creatinine level > 2.0 mg/dL (180 µmol/L) in a well-hydrated patient 2. Hypersensitivity to contrast media 3.Use of any contraindicated drug that could not be combined with the injection of contrast medium C. Miscellaneous exclusion criteria: 1. Participation in any other therapeutic drug study or a device study evaluating DVT prophylaxis within 90 days preceding inclusion 2. Previous participation in a study of Org31540/SR90107A 3. Current addictive disorders that could interfere with study participation 4. Bilateral hip surgery done simultaneously or within 2 wks 5. Patients with multiple trauma affecting > 1 organ system (for EFC2698 only) 6. More than 24 hours lapse between trauma (causing hip fracture) and admission to hospital (for EFC2698 only) 7. Administration of heparin, heparinoids, LMWH, oral anticoagulants, dextrans, or fibrinolytic agents during the screening period, i.e., from admission to first study drug administration or surgery, whichever came first	Org31540/SR 90107A: 2.5mg q.d. post-operatively, or pre-operatively if surgery 24-48 hrs after admission for 7±2 days; SC enoxaparin 40mg q.d. pre-operatively for 7±2 days; SC	N=1700 (850 per group) VTE rates: Org31540/SR90107A: 22% enoxaparin: 15% α=0.05 two side power=85% Missing efficacy assessment: 30%
Prophylaxis of DVT in patients undergoing hip replacement surgery	63118 74 centers in 16 European countries	Multicenter, randomized, double-blind double dummy, Active controlled study Study period: 12/4/1998-1/28/2000	1.Undergoing either an elective, primary, total hip replacement (THR) surgery, or a revision of at least one component of a THR 2, 3, 4. Same as EFC2698		Org31540/SR 90107A: 2.5mg q.d. post-operatively for 7±2 days; SC enoxaparin: 40mg q.d. pre-operatively for 7±2 days; SC	N=2200 (1100 per group) VTE rates: Org31540/SR90107A: 5% enoxaparin: 9% α=0.05 two side power=85% Missing efficacy assessment: 30%
	EFC2442 US (94 centers, 58%), Canada (30 centers, 28%), Australia (15 centers, 14%)	Multicenter, randomized, double-blind, Active controlled study Study period: 12/21/1998-1/5/2000	1.Same as study 63118 2, 3, 4. Same as EFC2698 5.Established hemostasis on the calendar day of surgery, no later than 8 hours after closure of the incision.		Org31540/SR 90107A: 2.5mg q.d. post-operatively for 7±2 days; SC enoxaparin 30mg q12 hrs post-operatively for 7±2 days; SC	
Prophylaxis of DVT in patients undergoing knee replacement surgery	95002 US (54 centers, 82%) Canada (10 centers, 18%)	Multicenter, randomized, double-blind, Active controlled study Study period: 12/24/1998-1/17/2000	1.Undergoing either an elective major knee surgery (requiring resection of the distal end of the femur or proximal end of the tibia) or a revision of at least 1 component. Enrollment of patients with surgery limited to an osteotomy was not permitted. 2, 3, 4. Same as EFC2698 5. Same as EFC2442.		Org31540/SR 90107A: 2.5mg q.d. post-operatively for 7±2 days, SC enoxaparin 30mg q12 hrs post-operatively for 7±2 days; SC	N=912 (456 per group) VTE rates: Org31540/SR90107A: 23% enoxaparin: 34% α=0.05 two side power=85% Missing efficacy assessment: 30%

Reviewer's table

The following table summarizes the study results from four pivotal trials by indication.

Three trials (EFC2698, 63118 and 95002) demonstrated superior efficacy of Org31540/SR90107A over enoxaparin for the primary efficacy endpoint (VTE) with a high level of statistical significance (P<0.001). Trial EFC2442 failed to demonstrate superior efficacy of Org31540/SR90107A over enoxaparin for the primary efficacy endpoint (VTE, p=0.09) but showed a significant lower incidence of DVT (p=0.047) up to day 11 in Org31540/SR90107A-treated patients as compared to enoxaparin-treated patients.

The reductions of VTE in the Org31540/SR90107A treatment group were mainly due to reductions of DVT in all three positive trials (EFC2698, 63118 and 95002). The incidence of proximal DVT was also significantly lower in the Org31540/SR90107A group as compared to the enoxaparin group in two trials (EFC2698 and 63118) (p<0.05). In all 4 trials, there were no statistically significant differences in the incidence of PE (symptomatic) up to day 11 between the two treatments.

Summary of Efficacy Results from 4 Pivotal Trials by Indication

Proposed Indications	Clinical Trials	Efficacy Endpoints	Org31540/SR90107A	Enoxaparin	p-Value (Fisher's Test)
Prophylaxis of DVT in patients undergoing hip fracture surgery	EFC2698 Europe, Australia, Argentina, South Africa	VTE	52/626 (8.3%)	119/624 (19.1%)	3×10^{-8}
		DVT	49/624 (7.9%)	117/623 (18.8%)	1×10^{-8}
		Proximal DVT	6/650 (0.9%)	28/646 (4.3%)	0.0001
		PE	3/831 (0.4%)	3/840 (0.4%)	1.0
Prophylaxis of DVT in patients undergoing hip replacement surgery	63118 Europe	VTE	37/908 (4.1%)	85/919 (9.2%)	9×10^{-6}
		DVT	36/908 (4.0%)	83/918 (9.0%)	1×10^{-5}
		Proximal DVT	6/922 (0.7%)	23/927 (2.5%)	0.0021
		PE	2/1129 (0.2%)	2/1123 (0.2%)	1.0
	EFC2442 U.S., Canada, Australia	VTE	48/787 (6.1%)	66/797 (8.3%)	0.09
		DVT	44/784 (5.6%)	65/798 (8.2%)	0.047
		Proximal DVT	14/816 (1.7%)	10/830 (1.2%)	0.42
		PE	5/1126 (0.5%)	1/1126 (0.1%)	0.12
Prophylaxis of DVT in patients undergoing knee-replacement surgery	095-002 U.S., Canada	VTE	45/361 (12.5%)	101/363 (27.8%)	3×10^{-7}
		DVT	45/361 (12.5%)	98/361 (27.1%)	1×10^{-6}
		Proximal DVT	9/368 (2.4%)	20/372 (5.4%)	0.057
		PE	1/517 (0.2%)	4/517 (0.4%)	0.37

Reviewer's table

b. Detailed Review of Individual Trials by Indications

1. For Prophylaxis of DVT in Patients Undergoing Hip Fracture Surgery

Trial EFC2698 - [redacted]

Title of the Study

A multicenter, multinational, randomized, double-blind, comparison study of subcutaneous Org31540/SR90107A versus enoxaparin 40 mg o.d. in the prevention of deep vein thrombosis and symptomatic pulmonary embolism in hip fracture surgery.

Study Period

November 15, 1998 to October 22, 1999

Investigators and Study Centers

The study was carried out by investigators at 99 active centers in 21 countries: 80 centers in 18 European countries, 9 in Australia, 6 in Argentina, 4 in South Africa. There were 7 additional centers (2 in Italy, 1 each in Argentina, New Zealand, Greece, Spain, and the Netherlands) which did not recruit any patients.

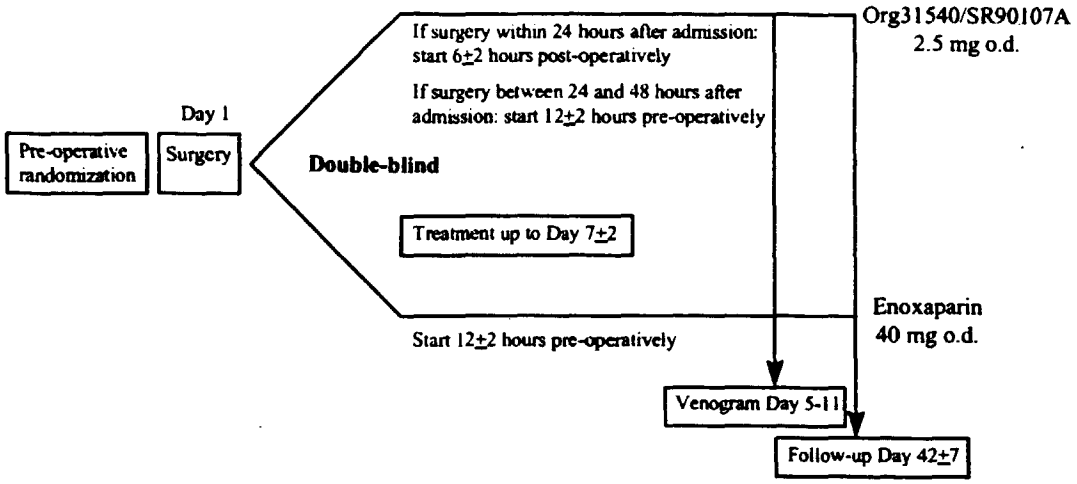
Study Objectives

The objective of this study was to compare the efficacy and safety of a 2.5 mg once daily SC injection of Org31540/SR90107A to once daily SC injections of enoxaparin 40 mg for prevention of DVT and symptomatic PE, in patients undergoing hip fracture surgery.

Overall Study Design

This was a multinational, multicenter, randomized, double-blind, double-dummy, parallel-group study comparing Org31540/SR90107A 2.5 mg once daily SC to enoxaparin 40 mg once daily SC in patients undergoing hip fracture surgery.

The study design is illustrated in the sponsor's Figure below:



Note: Randomization performed within 24 hours after admission and before surgery
Pre-operative injections of study drug were strongly discouraged in case of spinal/epidural anesthesia

Figure (5.1) 1 - Study Design

Sponsor's figure in NDA Vol. 81, pp. 29

All eligible patients were randomly assigned to one of two treatment groups within 24 hours after admission and before surgery. The time of operation could have been up to 48 hours after admission. Org31540/SR90107A 2.5 mg once daily SC was started either 6±2 hours post-operatively if surgery was planned within 24 hours after admission or 12±2 hours pre-operatively if surgery was planned between 24 and 48 hours after admission. enoxaparin 40 mg once daily SC was started 12±2 hours pre-operatively. Pre-operative injections of study drug were strongly discouraged in case of spinal/epidural anesthesia. Treatment duration was 7±2 days. Venogram was performed between day 5 and day 11, but not more than 2 calendar days after the last study treatment administration. A follow-up period was up to Day 42±7. The duration of study participation (randomization through follow-up) was from 35 to 51 days per patient.

Study Population

Inclusion criteria

Patients who satisfied the following inclusion criteria were included in the study:

(1) Undergoing standard surgery for fracture of the upper third of the femur, including femoral head and neck, not more than 48 hours after admission
(2) Signed written informed consent
(3) Men or women of non-childbearing potential (post-menopausal or with hysterectomy or bilateral tubal ligation). Inclusion criteria were extended to women of childbearing potential (protocol amendment no.1 dated 08 April 1999) with a negative pregnancy test within 48 hours prior to surgery or first study drug administration, whichever came first.
(4) 18 years of age or older.

Exclusion criteria

Patients were excluded from study participation if one of the following criteria applied:

1) Exclusion criteria based on current labeling for LMWH:
(1) Active, clinically significant bleeding
(2) Thrombocytopenia or previous history of thrombocytopenia (platelet count below 100 x 10^9/L)
(3) Known hypersensitivity to heparin, LMWH, or pork products
(4) Acute bacterial endocarditis
(5) Documented congenital or acquired bleeding tendency/disorder(s)
(6) Documented current ulceration or angiodysplastic gastrointestinal disease
(7) Hemorrhagic stroke or recent (less than 3 months prior to randomization) brain, spinal, or ophthalmological surgery
(8) Planned indwelling intrathecal or epidural catheters for more than 6 hours after the end of surgery
(9) Patients for whom anticoagulant therapy was contraindicated or who could not be taken off anticoagulant therapy due to a co-existing condition (i.e., prosthetic heart valve implant).

2) Exclusion criteria related to study procedures (venography):
(1) Creatinine level above 2.0 mg/dL (180 µmol/L) in a well-hydrated patient
(2) Documented hypersensitivity to contrast media
(3) Use of any contraindicated drug that could not be combined with the injection of contrast medium. The use of metformin (Glucophage®), initially an exclusion criterion, was allowed, based on the revised labeling for metformin (protocol amendment no.1 dated 08 April 1999). Patients receiving metformin could be included if they consented to its discontinuation for a period of 48 hours prior to and 48 hours following venography and if there was no medical contraindication to the discontinuation.

3) Miscellaneous exclusion criteria:
(1) Participation in any other therapeutic drug study or a device study evaluating DVT prophylaxis within 90 days preceding inclusion
(2) Previous participation in a study of Org31540/SR90107A
(3) Current addictive disorders that could interfere with study participation
(4) Bilateral hip surgery done simultaneously or within 2 weeks
(5) Patients with multiple trauma affecting more than 1 organ system
(6) More than 24 hours time lapse between trauma (causing hip fracture) and admission to hospital
(7) Administration of heparin, heparinoids, LMWH, oral anticoagulants, dextrans, or fibrinolytic agents during the screening period, i.e., from admission to first study drug administration or surgery, whichever came first (protocol amendment no.1 dated 08 April 1999).

Removal of patients from therapy or assessment

Study treatment was stopped prematurely if any of the following occurred or was diagnosed:

- DVT before the scheduled end of the treatment period
- Symptomatic PE before the scheduled end of the treatment period
- Unusual (at Investigators' discretion) symptomatic bleeding meeting the definition of an SAE
- Suspicion of drug-induced decreased platelet count
- Occurrence of an SAE warranting premature termination of study drug administration
- Investigator's opinion that it was in the best interest of the patient to stop study treatment
- Patient's decision to stop participating
- Sponsor's decision to stop the study.

Study Treatments

Patients were randomly assigned to one of 2 treatment groups:

- Org31540/SR90107A group: each patient received Org31540/SR90107A 2.5 mg (0.25 mL) once daily and placebo-enoxaparin (0.4 mL solution placebo matching enoxaparin) once daily.

- enoxaparin group: each patient received enoxaparin 40 mg (0.4 mL) once daily and placebo-Org31540/SR90107A (0.25 mL solution placebo matching Org31540/SR90107A) once daily.

Org31540/SR90107A was supplied by Sanofi-Synthelabo (Notre Dame de Bondeville, France) and was provided as an isotonic 10 mg/mL solution for subcutaneous injection in 0.25 mL prefilled syringes (2:5 mg).

enoxaparin (Lovenox®) was supplied in 0.4 mL (40 mg) pre-filled syringes.

Placebo was supplied by Sanofi-Synthelabo (Paris, France) and was provided in 0.25 mL and 0.4 mL disposable prefilled syringes and contained isotonic sodium chloride for injection.

Randomization process

The sponsor (Department of Statistics of Sanofi-Synthelabo, France) prepared a list of treatment blocks balanced with a block size of 4 (2:2 ratio) and randomly assigned treatment kit numbers (random number of maximum 4 digits) to the Org31540/SR90107A or enoxaparin treatment groups. A treatment kit consisted of an active treatment (Org31540/SR90107A or enoxaparin sodium) and a placebo of the other treatment. The randomization was not stratified by study site (or other factors), but each block was allocated to only one study site. Within a site, the investigator assigned each patient eligible for randomization a sequential patient number. The allocation of a particular treatment kit to a patient was made at the site (locally, not centrally). The

Investigator was instructed to select one of the treatment kits at random from within a block for assignment to each consecutive patient, as he/she was randomized into the study. Each block had to be completed before starting a new one. 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.

Blinding procedures

This was a double-blind, double-dummy study. The placebo was administered in syringes identical to the Org31540/SR90107A (blue) and enoxaparin (yellow) syringes. Sealed coded envelopes containing patient identifiers were maintained at study sites, at affiliate offices, and at Sanofi-Synthelabo, France (Sponsor). The code was to be broken by the Investigators only in exceptional circumstances, when knowledge of the treatment group was essential for treating the patients.

Dosing schedule

Each patient was to receive once daily administrations of study treatment up to Day 7±2. Initiation of treatment was based upon the time lapse between admission and surgery and included 2 possible schedules. When surgery took place within 24 hours after admission, the dosing scheme was as shown in Table below:

Dosing Schedule for Patients Undergoing Surgery Within 24 Hours of Admission

	Dosing Regimens ('Double-Dummy')			
Group	12±2 Hours Pre-Operative[a]	Day 1 6±2 Hours Post-Operative[b]	Day 2[c]	Day 3-9[d] at 8:00 A.M. (±2 Hours)
Org31540/SR90107A	0.4 mL placebo	2.5 mg (0.25 mL)	2.5 mg (0.25 mL)+ 0.4 mL placebo	2.5 mg (0.25 mL)+ 0.4 mL placebo
Enoxaparin	40 mg (0.4 mL)	0.25 mL placebo	40 mg (0.4 mL)+ 0.25 mL placebo	40 mg (0.4 mL)+ 0.25 mL placebo

a To be omitted in patients requiring spinal/epidural anesthesia or catheterization according to precaution/warning in the datasheet of enoxaparin.
b No injection of study drug was allowed within 2 hours of indwelling intrathecal or epidural catheter removal.
c >12 hours after dose of Day 1 for injection of Org31540/SR90107A or placebo-Org31540/SR90107A, and 12-24 hours after surgical closure for injection of enoxaparin or placebo-enoxaparin.
d At least until Day 5.
Sponsor's table in NDA Vol. 81, pp. 32

When surgery took place between 24 and 48 hours after admission, the dosing schedule was as follows:

Dosing Schedule for Patients Undergoing Surgery Between 24 and 48 Hours After Admission

	Dosing Regimens ('Double-Dummy')			
Group	12 ±2 Hours Pre-Operative[a]	Day 1 6 ±2 Hours Post-Operative[b]	Day 2[c]	Day 3-9[d] at 8:00 A.M. (±2 Hours)
Org31540/SR90107A	2.5 mg (0.25 mL)+ 0.4 mL placebo	2.5 mg (0.25 mL)	2.5 mg (0.25 mL)+ 0.4 mL placebo	2.5 mg (0.25 mL)+ 0.4 mL placebo
Enoxaparin	40 mg (0.4 mL)+ 0.25 mL placebo	0.25 mL placebo	40 mg (0.4 mL)+ 0.25 mL placebo	40 mg (0.4 mL)+ 0.25 mL placebo

a To be omitted in patients requiring spinal/epidural anesthesia or catheterization according to precaution/warning in the datasheet of enoxaparin.
b No injection of study drug was allowed within 2 hours of indwelling intrathecal or epidural catheter removal.
c >12 hours after dose of Day 1 for injection of Org31540/SR90107A or placebo-Org31540/SR90107A, and 12-24 hours after surgical closure for injection of enoxaparin or placebo-enoxaparin.
d At least until Day 5.
Sponsor's table in NDA Vol. 81, pp. 33

The protocol called for study treatment to be given up to Day 7±2 or until the mandatory venogram was obtained, whichever came first.

In cases of unusual bleeding during surgery or unusual difficulties in applying epidural or spinal anesthesia (e.g., more than 2 attempts or a bloody tap), administration of study medication was to be reconsidered due to the increased risk of bleeding or aggravation of existing bleeding complications (this recommendation was added following protocol amendment no. 1 dated 08 April 1999).

Drug administration

Study treatments were administered as deep SC injections, while patients were lying down. Sites of administration were alternated, between the left and right anterolateral and left and right posterolateral abdominal wall. The 2 daily subcutaneous injections (enoxaparin and placebo-Org31540/SR90107A or Org31540/SR90107A and placebo-enoxaparin) were administered at 2 different injection sites.

Prior and concomitant therapy

During the screening period and during the drug administration period, and until the mandatory venogram had been obtained, patients could not be treated with any of the following medications:

- Heparins (UFH or LMWH), heparinoids, and hirudin (except arterial and/or venous line UFH flushes up to 200 IU/day and UFH up to 1500 IU for priming cell-saver equipment during surgery).
- Antiplatelet drugs (e.g., ticlopidine, clopidogrel, or GPIIb-IIIa platelet antagonists)
- Oral anticoagulants (vitamin K antagonists)
- Fibrinolytic agents
- Dextrans.

The use of intermittent pneumatic compression (IPC) of the legs and/or feet was prohibited during administration of study treatment and until the mandatory venogram had been obtained. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin was discouraged.

Other physical methods for prophylaxis of DVT, which included the use of elastic stockings and early mobilization, were strongly recommended during the treatment portion of the study (Day 1-Day 11).

Efficacy Assessment

Primary efficacy endpoint

The primary efficacy endpoint was a composite endpoint of VTE up to Day 11 that included:

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

The VTE conclusion is the worst result considering both DVT result and PE result, and derived as follows:

Primary efficacy end-point derived from DVT and PE outcomes

VTE Assessment		Adjudicated symptomatic PE (Non-fatal or fatal)		
		+	-	Not evaluated for PE
Adjudicated Venogram proved DVT	+	VTE (+)	VTE (+)	VTE (+)
	-	VTE (+)	VTE (-)	VTE (-)
	Non-evaluable or missing	VTE (+)	Non-Evaluable	Non-Evaluable

Reviewer's table

Assessment of DVT and PE

A mandatory bilateral venogram was required to be performed between Day 5 and Day 11 (not more than 2 calendar days after the last dose but as close as possible to the last study drug injection) in all patients to rule out the presence of asymptomatic DVT. If signs and/or symptoms occurred between scheduled evaluations, diagnostic tests were carried out. All venograms, scheduled or unscheduled, were sent to the Central Independent Adjudication Committee (CIAC) for blind review and adjudication.

- **Mandatory bilateral venography**

Venography was performed according to the method of Rabinov and Paulin (Arch Surg 1972; 104:134-44). For consistency between centers, it was required to obtain thigh to ankle films visualizing the whole deep venous system of the lower extremities including the iliofemoral segment, with a minimum of 2 views (in perpendicular directions). An adequate volume (i.e., 75-100 mL) of contrast medium was injected into each foot vein. All mandatory venograms (original films or a copy) were sent to the Sponsor and forwarded to the blinded CIAC for independent review. This central evaluation of DVTs was performed by a panel of at least 2 independent reviewers who were unaware of the

treatment allocation. Central adjudication was based on the assessment of the venograms for intra-luminal filling defects (ILFDs).
An ILFD was defined as follows:

- An area of reduced or absent filling at least partially surrounded with contrast medium which was constant in more than 1 film, or
- A lack of filling in a vessel in which there was a cut-off which had the configuration of a thrombus, with filling of that vessel seen more proximally.

Any ILFD above the trifurcation of the calf veins was considered proximal DVT. Any ILFD confined to the calf was considered distal DVT.

Each patient was categorized by the CIAC as:

- Having no DVT: if the proximal and distal veins in both legs were negative, i.e., all deep veins were visualized and there was no ILFD
- Having any DVT: if any of the proximal or distal veins in either leg had an ILFD
- Having no proximal DVT: if the proximal veins in both legs were negative
- Having proximal DVT: if any of the proximal veins in either leg had an ILFD
- Non-evaluable: if venogram was inadequate, unilateral and negative (except if the patient was 1-legged), not available, or not done.

In order to make decisions about patient care, the mandatory venogram was reviewed by the local hospital radiologist; the Investigator then determined if the result warranted treatment and the treatment decision was recorded in the CRF. Any VTE was treated according to local hospital practice.

- **Unscheduled diagnostic tests for symptomatic DVT or PE**

To confirm or rule out symptomatic DVT or PE during the treatment period and the follow-up period, the following diagnostic tests were recommended; all corresponding films/recordings were sent to the CIAC for blind review and adjudication:

Symptomatic DVT –Ultrasonography/Venography
If a patient experienced clinical signs or symptoms of a DVT before or following surgery up to Day 4, or outside the mandatory venography period (i.e., Day 5-Day 11), the Investigator could perform a compression ultrasonography. If the results were negative for DVT, then the patient could continue in the study; if the results were positive for DVT, a confirmatory bilateral venography had to be performed within 2 calendar days of symptom onset. If the results of venography were negative for DVT, then the patient could continue in the study and another venogram had to be performed at the end of the treatment period; if the results were positive for DVT, the patient had reached a study endpoint and study treatment had to be discontinued. Ultrasound data were sent to the CIAC, when needed, for adjudication to provide additional information. Adjudication of compression ultrasonography involved mainly the assessment of the proximal region.

Symptomatic PE –Ventilation/perfusion (V/Q) lung scan/ Pulmonary angiography

This examination was performed in case of clinical suspicion of PE. V/Q lung scan criteria and suggested further testing were as follows:

- High probability defects were considered as evidence of a PE; in this case, a study endpoint had been reached and study treatment was discontinued
- Non-high probability defects with a positive venography were considered as evidence of a PE
- Non-high probability defects with a negative venography were considered as no evidence of a PE and the patient could continue study treatment
- If non-high probability defects were observed and no venography was available, a pulmonary angiography had to be performed. Spiral computed tomography (CT)-scan was an alternative investigation when pulmonary angiography could not be performed.
- If no defects were observed, then the patient could continue study treatment.

- **Additional assessments**

In cases of DVT, PE or another thrombotic event (MI or stroke), a blood sample for the assessment of platelet count (local laboratory testing) was immediately drawn, and a serum sample was collected and frozen for central analysis of specific antiplatelet antibodies (sampling repeated after 3 days). For each event, investigator was required to provide the sponsor with a clinical summary, including a 30-day follow-up.

Secondary efficacy endpoints

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

Safety Assessment

Bleeding events

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.

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

Deaths
The CIAC reviewed the source documents and autopsy report (if available) to determine the cause of death as:
- Fatal PE
- Hemorrhagic death
- Death not associated with VTE or bleeding

Other safety variables included transfusion requirements, adverse events (AEs)/serious AEs (SAEs), and changes in laboratory parameters.

Laboratory evaluation included platelet counts, hemoglobin, hematocrit, hemostasis parameters (i.e., aPTT and prothrombin time, in case of bleeding), creatinine, AST, ALT, total bilirubin, and antiplatelet antibodies.

Statistical Methods

Sample size determination

The incidence of VTEs under enoxaparin had been cited as 22% in a small hip fracture study (less than 150 patients per group) from published literature. Therefore, the VTE rate was set at 22% for enoxaparin in the sample size calculation, and a risk reduction of about 30% with Org31540/SR90107A treatment was targeted. With 600 evaluable (non-missing efficacy assessment) patients per group, the power to detect a significant difference (with a 2-sided α of 0.05) between the enoxaparin group (22%) and the Org31540/SR90107A group (15%) 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.

Analysis population

Safety analysis-"all treated patients" population
All treated patients population was defined as all randomized patients who received at least one dose of study drug (placebo or active drug).

Efficacy analysis-"primary efficacy" population
Primary efficacy population was defined as all randomized patients who satisfied the following criteria:
- Received at least one dose of study drug (placebo or active drug)
- Underwent the appropriate surgery (i.e., hip fracture surgery of the upper third of the femur)
- Had a non-missing evaluation for the parameter analyzed.

A patient was considered to have a non-missing evaluation if:

- An adjudicated and evaluable bilateral venogram performed between Day 5 and Day 11 was available (a unilateral venogram was considered adequate if positive, and inadequate if negative unless the patient was one-legged)

- 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 (adjudication results) had occurred up to Day 11

(in any of the 3 latter cases, the primary efficacy endpoint was considered to have been reached).

The analysis of the primary efficacy endpoint was supplemented by exploratory 'sensitivity' analyses including treated patients who underwent the appropriate surgery with missing VTE evaluation.

Analysis of primary efficacy endpoint

- **Primary analysis**

The analysis of the primary efficacy endpoint (i.e., the VTE rate up to Day 11) consisted of the comparison of the 2 groups using a 2-sided Fisher's exact test. Ninety-five percent exact CI on the difference between the 2 treatment groups was calculated. Point estimates and 95% CI per treatment group were computed. No adjustment on p-values was performed for multiplicity of tests.

- **Exploratory analyses**

- Subgroup analysis

These included the analysis of the primary efficacy endpoint by country, gender, race, age, obesity, previous VTEs, type of anesthesia, type of hip fracture, type of surgery, use of cement, and duration of surgery. Two additional covariates (baseline plasma creatinine and use of other antithrombotic medication between trauma and the day before the first study drug injection) were added during blind review of data. For each subgroup, point estimates and 95% CIs per treatment group, as well as 95% exact CIs on the differences, were computed.

Logistic regression analysis was performed on the primary efficacy endpoint in order to test the influence of the pre-defined covariates. The analysis consisted first of selection of significant covariates ($p<0.25$) using a forward selection procedure with a logistic regression model (logit link function). The treatment group was then added to the same model restricted to the selected covariates in order to test the treatment effect adjusted for these covariates. Each treatment by covariate interaction was tested on the selected binary covariates on contingency tables by the Breslow-Day's test for homogeneity of the odds ratios (race was not introduced in the model as a covariate since the majority of patients were Caucasians).

- Sensitivity analyses

The analysis of the primary efficacy endpoint was supplemented by a 'best case' analysis including all treated patients who underwent the appropriate surgery and considering the patients with missing evaluations as successes, i.e., having no VTE. In addition, 2 other scenarios ('realistic' and 'worst case') were added following protocol modification request no. 1 dated 08 April 1999.

- 'Realistic' scenario: The VTE rate for patients with missing primary efficacy endpoint in any of the 2 groups was assumed to be the observed VTE rate in the worst group
- 'Worst' scenario: All missing evaluations were classified as a VTE.

For each scenario, 95% exact CIs on the differences between the 2 treatment groups were calculated.

- Drug-drug interactions

No specific drug-drug interaction analysis was planned in the protocol. However, the primary efficacy endpoint was further analyzed according to selected concomitant medications which were reported to have a potential interaction with UFH. Point estimates and 95% CIs per treatment group, as well as 95% exact CIs on the differences were computed for the 2 groups of patients who received or who did not receive such medication.

Analysis of secondary efficacy endpoints

In order to analyze all available data, analysis of DVT by location was performed on treated patients who underwent the appropriate surgery, with available data for the parameter considered:

- DVT 'on either side' evaluated the rate of DVT (any, proximal, or distal only) on patients with an evaluable bilateral examination (either positive or negative), or with a DVT on a unilateral examination
- DVT 'on operative leg' evaluated the rate of DVT (any, proximal, or distal only) on patients with an evaluable examination on the operative leg
- DVT 'on non-operative leg' evaluated the rate of DVT (any, proximal, or distal only) on patients with an evaluable examination on the non-operative leg
- DVT 'on both sides' evaluated the rate of bilateral DVT (any, proximal, or distal only) on patients with an evaluable bilateral examination, or with a negative unilateral examination.

Adjudicated symptomatic VTEs (symptomatic DVT, non-fatal or fatal PE) were analyzed on treated patients who underwent the appropriate surgery.

Point estimates and 95% CI per treatment group were calculated for all secondary efficacy endpoints. Before unblinding of data, the statistical analysis plan specified that treatment group comparisons for secondary efficacy parameters were restricted to any DVT on either side (up to Day 11), any proximal DVT on either side (up to Day 11), and all symptomatic VTEs (up to Day 11 and up to Day 49). The analysis consisted of the comparison of the 2 treatment groups using a Fisher's exact test. Ninety-five percent exact CIs on the differences between the 2 treatment groups were calculated.

Symptomatic VTEs were also summarized in the form of cumulative event rate curve, using Kaplan-Meier method for the time to the first event. Comparisons between the 2 treatment groups were performed using Log-rank and Wilcoxon tests. Kaplan-Meier estimates at Day 11 and Day 49 were calculated.

Safety analyses

All analyses of AEs considered 2 periods of time, the period between the first injection (active or not) and Day 11, and the period between the first injection and Day 49. When an event began in the first period and became serious or led to death after Day 11, the event was not counted as serious or death during the first period.

Major and minor bleeding
Patients with adjudicated bleeding events were summarized using counts and percentages using the following categories of results: major bleeding (associated or not with minor bleeding), minor bleeding only, and any major or minor bleeding. The analysis was performed according to 2 periods of time, as described above. If date/time of onset of at least one of the events was between the first injection and Day 11 then the adjudicated event was counted in both periods. When there was more than one form of bleeding adjudication in the same period of time, the worst outcome was taken into account in the analysis.

Fisher's exact tests were used to compare bleeding incidences between the 2 treatment groups. Ninety-five percent exact CIs on the differences were computed.

The main safety endpoint (major bleeding) was further analyzed according to the same covariates (except for prior VTE) and specific concomitant medications as those used for the primary efficacy endpoint, with the same statistical methods.

Transfusion requirements and other bleeding related criteria
Summaries on 'more than expected' blood loss occurring at least once from surgery or at least once post-operatively were computed. No statistical comparison was performed.

Interim analyses

An unblinded interim analysis as planned in the protocol was carried out when half of the planned number of patients (850 patients) were randomized and when adjudication of the efficacy and safety endpoints were available and validated for those patients. Following the interim analysis which became available on 06 July 1999, the DMC recommended to continue the study as planned without any increase of the sample size. The sponsor proposed no statistical type-I error adjustment for the final analysis according to simulations performed during protocol development in order to measure the impact of sample size reassessment.

Study Committees

Three study committees evaluated study documents, definitions, assessment criteria, and patient safety for 4 simultaneously conducted Org31540/SR90107A Phase III trials (EFC2698, 63118, EFC2442 and 95002), to ensure cross-study consistency. The responsibilities and composition of the committees are described below. A statistical center independent of the Sponsor, also described below, conducted the interim analysis.

Steering Committee
Steering committee was responsible for approving final protocol, naming members of the Central Independent Adjudication Committee (CIAC) and the Data Monitoring Committee (DMC), amending the protocol during the course of the study, when needed, and reviewing the statistical analysis plan, when needed, prior to unblinding of data.

It was composed of four experts (2 in Europe and 2 in North America) in the field of thrombosis prevention in orthopedic surgery, and two representatives of Sanofi-Synthelabo (the Sponsor) and 2 representatives of Organon (the development partner).

Data Monitoring Committee (DMC)
The DMC had the responsibilities of providing the Steering Committee with recommendations on patient health and safety. DMC members were regularly updated as to the rate of venous thromboembolic event (VTE) occurring during the study (per the adjudication of the respective committee), the incidence of major bleeding events (per the adjudication of the respective committee), and all serious adverse events (SAEs) occurring during the study.

The DMC regularly reviewed summary tables provided in A or B treatment code. These tables were composed by a statistician independent of the Sponsor and independent of the DMC. The DMC could request, if needed, unblinded information without knowledge of the Sponsor, in order to make appropriate safety recommendations.

It was composed of three independent surgeon experts in the field of thrombosis and hemostasis.

Central Independent Adjudication Committee (CIAC)
The CIAC was responsible for efficacy and safety assessment, including proposing deep vein thrombosis (DVT) criteria to the Steering Committee, adjudicating (blindly) venograms for DVT occurrence on an ongoing basis, adjudicating tests for symptomatic pulmonary embolism (PE), adjudicate causes of deaths (VTE and hemorrhagic deaths), proposing criteria for major bleeding events to the Steering Committee, evaluating (blindly) all 'unusual' bleeding events on an ongoing basis.

It was composed of 8 venography and bleeding experts of the
[ ]

The — was responsible for providing the DMC with appropriate data for their blind review, providing, if appropriate due to safety concerns, the DMC with unblinded data upon its request, and interim analysis.

It was composed of one statistician independent of the Sponsor —

Protocol Amendment

There was a protocol amendment titled "protocol modification request no. 1" dated 08 April 1999. The main changes are listed below.

- Inclusion criterion related to women of childbearing potential
- Exclusion criterion related to metformin intake
- Exclusion criterion related to prior treatment restrictions
- Administration of study drug and risk of post-surgical bleeding
- Time window for surgery
- In statistical methods:
  - Additional exploratory sensitivity analyses
  - Clarification of methods for the secondary/exploratory analyses
- Administrative changes/Textual clarifications following discrepancies between table footnotes and text/Other textual clarifications.

Changes in planned analyses during blind review

Chi-square test was actually used instead of Fisher's exact test for all categorical data except for main efficacy and safety criteria, because of computer resources and acceptable use of asymptotic tests with more than 1000 patients.

Concomitant medication
During blind review of data, it appeared that anticoagulants started on the day of last injection or the day of venography for continuation of VTE prophylaxis (authorized per protocol) would be considered wrongly as concomitant medication because the start time of medication was not captured in the 'Medication Record' form. Thus the definition of concomitant medication was changed to *'any medication administered within the first day of treatment and the day before the last day of treatment or the day before the qualifying VTE examination - whichever occurs last - both extreme dates included'* for analyses on the all treated patients population and to *'any medication administered within the first day of treatment and the day before the qualifying VTE examination'* for analyses on the primary efficacy population.

Efficacy analyses
Sensitivity analyses were performed on all treated patients having undergone the appropriate surgery (instead of all randomized patients, as specified in protocol modification request no. 1 dated 08 April 1999).

The primary efficacy endpoint was further analyzed according to specific concomitant medications, i.e., all medications which were reported to have an interaction with heparin, according to US PDR 1999.

Safety analyses
Major bleeding was further analyzed according to the same baseline covariates (except for previous VTE) and specific concomitant medications as those used for the primary efficacy endpoint, with the same statistical methods.

Details concerning time periods to consider in the analysis of transfusion requirements were given during blind review of data because the way transfusion data were recorded in the CRF did not allow the analysis planned in the protocol (actual time of transfusions was not to be recorded in the CRF; therefore, it could not always be determined if a transfusion was given before or after the first study drug administration).

The safety ranges were defined for clinical laboratory parameters including platelet count, hemoglobin, hematocrit, bilirubin, AST and/or ALT.

Changes in planned analyses after breaking the blind

Pre-treatment medications
An error in the statistical plan was noted in comparison to modification request no. 1 dated 08 April 1999. Antiplatelet drugs other than aspirin were considered as not allowed medication when used as previous medication between trauma and the day before the first injection. In order to give a full picture of pre-treatment medications with a potential impact on hemostasis, pre-treatment medications were summarized according to 2 categories: 'Not allowed per protocol modification' and 'other medication with potential impact on hemostasis'. In the latter category, aspirin, antiplatelet drug other than aspirin and NSAID were included.

Extent of exposure
The last day of active treatment was summarized according to the categories: <Day 5, Day 5 to Day 9, and >Day 9, and compared using Wilcoxon rank sum test in order to have comparable statistics between the 4 Phase III orthopedic studies.

Concomitant medication
The statistical analysis plan did not specify at the time the blind was broken that heparin flushes would not be considered as not allowed medication, as stated in the protocol. This omission had no effect on the result since no heparin flushes were recorded as concomitant treatment. Patients who initiated antithrombotic curative treatment following VTE assessment were compared between the 2 groups using Chi-square test.

Major bleeding
Patients re-operated after a major bleeding event at surgical site were identified in a separate listing.

Clinical laboratory parameters
Hematocrit: The threshold of 30% was changed to 24% in order to have consistency between hemoglobin and hematocrit.

Study Results

Disposition of patients

A total of 1714 patients were enrolled at 99 centers from 21 countries in the study. Among the 99 centers, the number of patients enrolled at each center ranged from a single patient to 74 patients.

During blind review of data before database lock, 3 patients were identified as having been 'randomized' with treatment numbers already assigned to previously randomized patients. These patients were considered not randomized by the sponsor; they received study drug (1 in Org31540/SR90107A group and 2 in enoxaparin group) but were excluded from all analyses. No VTE, bleeding or SAE were reported in these patients.

Of the remaining 1711 patients randomized in this study, 849 were assigned to receive Org31540/SR90107A and 862 were assigned to receive enoxaparin. The following figure presents the disposition of patients for each treatment group.

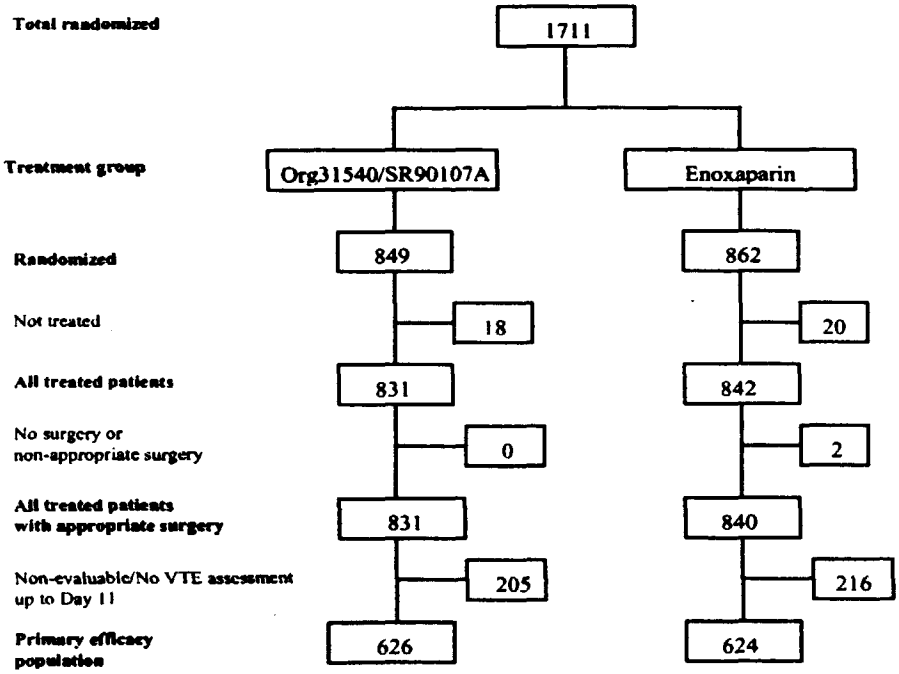


Figure (6.3) 1 - Number of Patients by Treatment Group and Population

Sponsor's figure in NDA Vol. 81, pp. 70

Of the 1711 patients randomized, 38 did not receive any study drug. There was a similar number of patients who were not being treated in both treatment groups. The following table summarizes the reasons for not being treated by treatment group. The main reason was the inclusion/exclusion criteria not met which was equally distributed in both groups.

Number (%) of Randomized Non-Treated Patients by Reason for Not Being Treated

Reason For Not Being Treated	Org31540/SR90107A 2.5 mg o.d. (N = 849)	Enoxaparin 40 mg o.d. (N = 862)	Total (N = 1711)
Inclusion/exclusion criteria not met	13 (1.5%)	13 (1.5%)	26 (1.5%)
Informed consent withdrawn	2 (0.2%)	4 (0.5%)	6 (0.4%)
Technical problem	1 (0.1%)	2 (0.2%)	3 (0.2%)
Adverse event[a]	2 (0.2%)	1 (0.1%)	3 (0.2%)
Total	**18 (2.1%)**	**20 (2.3%)**	**38 (2.2%)**

a Adverse event: death for all 3 patients
Sponsor's table in NDA Vol. 81, pp. 65

A total of 1673 patients (831 in the Org31540/SR90107A group and 842 in the enoxaparin group) were randomized and treated ("all treated patients" population). The number (%) of randomized and treated patients by country and treatment group is presented in the table below.

Number (%) of Randomized and Treated Patients by Country

Country[a] (Number of Centers)	Org31540/SR90107A 2.5 mg o.d.	Enoxaparin 40 mg o.d.	Total	
Australia (9)	106	104	210	(12.6%)
Czech Republic (7)	105	105	210	(12.6%)
Denmark (6)	68	74	142	(8.5%)
Sweden (4)	54	53	107	(6.4%)
France (9)	50	55	105	(6.3%)
The Netherlands (10)	48	49	97	(5.8%)
Belgium (8)	43	36	79	(4.7%)
Spain (5)	36	39	75	(4.5%)
Greece (3)	36	34	70	(4.2%)
Hungary (3)	34	34	68	(4.1%)
Italy (4)	34	33	67	(4.0%)
Switzerland (2)	34	33	67	(4.0%)
Portugal (6)	29	35	64	(3.8%)
Germany (3)	27	26	53	(3.2%)
United Kingdom (2)	26	25	51	(3.0%)
Poland (4)	24	26	50	(3.0%)
Norway (2)	23	26	49	(2.9%)
Argentina (6)	24	20	44	(2.6%)
Finland (1)	13	13	26	(1.6%)
South Africa (4)	11	14	25	(1.5%)
Austria (1)	6	8	14	(0.8%)
Total (99)	**831**	**842**	**1673**	**(100.0%)**

NOTE: A patient was considered to be treated when he/she received at least one injection of study drug.
a Sorted in decreasing order of randomized and treated patients
Sponsor's table in NDA Vol. 81, pp. 66

A total of 122 (7.3%) of the 1673 randomized and treated patients prematurely discontinued study drug. There were more patients who discontinued treatment prematurely in enoxaparin group (8.0%) as compared to Org31540/SR90107A group

(6.6%). The following table summarizes the number (%) of patients who permanently discontinued study drug prematurely by primary reason and treatment group.

Number (%) of Patients Who Discontinued Study Drug Prematurely by Primary Reason for Discontinuation - All Treated Patients

Premature Treatment Discontinuation/Reason for Stopping	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)	Total (N = 1673)
Patients who discontinued study drug Prematurely	**55 (6.6%)**	**67 (8.0%)**	**122 (7.3%)**
Reason(s) for discontinuation[a]			
Lack of efficacy	**1 (0.1%)**	**2 (0.2%)**	**3 (0.2%)**
Reached endpoint – DVT	1 (0.1%)	1 (0.1%)	2 (0.1%)
Reached endpoint – PE	0 (0.0%)	1 (0.1%)	1 (0.1%)
AE/SAE[b]	**30 (3.6%)**	**32 (3.8%)**	**62 (3.7%)**
Bleeding AE/SAE	11 (1.3%)	3 (0.4%)	14 (0.8%)
Suspicion of drug-induced decrease of platelet count	2 (0.2%)	4 (0.5%)	6 (0.4%)
Suspicion of PE (not confirmed afterwards)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Other AE/SAE	16 (1.9%)	26 (3.1%)	42 (2.5%)
Violation of inclusion/exclusion criteria	**8 (1.0%)**	**14 (1.7%)**	**22 (1.3%)**
Violate inclusion criteria #1-more than 48 hours from trauma	8 (1.0%)	12 (1.4%)	20 (1.2%)
No hip fracture	0 (0.0%)	1 (0.1%)	1 (0.1%)
Stroke 2 months ago	0 (0.0%)	1 (0.1%)	1 (0.1%)
Dosing mistakes	**5 (0.6%)**	**3 (0.4%)**	**8 (0.5%)**
By error-only 4 days of treatment	3 (0.4%)	2 (0.2%)	5 (0.3%)
Medication was stopped without reason	1 (0.1%)	0 (0.0%)	1 (0.1%)
Erroneous injection	0 (0.0%)	1 (0.1%)	1 (0.1%)
Received 2 treatment number	1 (0.1%)	0 (0.0%)	1 (0.1%)
Received other anticoagulant/dextran	**2 (0.2%)**	**1 (0.1%)**	**3 (0.2%)**
Withdrawn	**9 (1.1%)**	**14 (1.7%)**	**23 (1.4%)**
Subject withdrawn consent	7 (0.8%)	11 (1.3%)	18 (1.1%)
Physician refuse to give treatment	2 (0.2%)	1 (0.1%)	3 (0.2%)
Early discharge	0 (0.0%)	2 (0.2%)	2 (0.1%)

a According to the Investigator's judgment

b Including AEs recorded before the first study drug injection (based on data collected in the 'end of treatment' form)

Reviewer's table based on sponsor's table in NDA Vol. 82, pp. 67 and Appendix 14.2.1.1.8 in NDA Vol. 85, pp. 1331-1337

The majority of premature discontinuations of study drug were due to non-serious/serious AEs (3.5% in Org31540/SR90107A group vs. 3.8% in enoxaparin group). There had been more patients who discontinued treatment prematurely due to bleeding AE/SAE in Org31540/SR90107A group (11, 1.3%) as compared to those in enoxaparin group (3, 0.4%). On the other hand, there were more patients who discontinued treatment due to other AE/SAE, violation of inclusion criteria #1 (surgery after 48 hours from trauma), and subject withdrawn consent in enoxaparin group as compared to those in Org31540/SR90107A group.

Most cases of premature treatment discontinuation occurred before Day 5 in both treatment groups.

A total of 4 patients, 2 in the Org31540/SR90107A group, and 2 in the enoxaparin group had no information on the final follow-up assessment form.

The randomization code was broken for 2 patients in emergency situations due to SAEs (allergic reaction and sepsis with disseminated intravascular coagulation, respectively) during the treatment period. Both patients were in the Org31540/SR90107A group.

Protocol deviations

Protocol deviations leading to exclusion from primary efficacy analysis

All randomized and treated patients who presented with any of the following deviations were excluded from the primary efficacy analysis:

- Non-appropriate or no surgery
- Missing VTE evaluation up to Day 11, i.e., non-evaluable or no VTE assessment up to Day 11.

The number (%) of patients who presented with such protocol deviations is summarized in the table below. The percentages of patients who were excluded from the primary efficacy analysis were similar for both treatment groups (24.7% in Org31540/SR90107A group vs. 25.9% in enoxaparin group).

Number (%) of Patients by Reason for Exclusion From Primary Efficacy Analysis -All Treated Patients

Deviation[a]	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)	Total (N = 1673)
No surgery/Non-appropriate surgery	0 (0.0%)	2 (0.2%)	2 (0.1%)
Non-evaluable venography up to day 11	73 (8.8%)	87 (10.3%)	160 (9.6%)
No VTE assessment up to day 11	132 (15.9%)	129 (15.3%)	261 (15.6%)
Total for exclusion from primary Efficacy analysis	205 (24.7%)	218 (25.9%)	423 (25.3%)

a Patients were counted only once
Reviewer's table based on NDA Vol. 86, pp. 1372-1410

The main reason for exclusion from primary efficacy analysis was no VTE assessment up to day 11 in both treatment groups. There was slightly lower percentage of non-evaluable venography assessment in Org31540/SR90107A group (8.8%) than in enoxaparin group (10.3%).

The detail reasons for non-evaluable/ no VTE assessment up to day 11 are summarized in the following table:

Reasons for Non-Evaluable/No VTE Assessment up to Day 11- All Treated Patients

Non-evaluable /No VTE assessment up to day 11	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)	Total (N =1673)
Non-evaluable VTE assessment up to day 11	**73 (8.8%)**	**87 (10.3%)**	**160 (9.6%)**
Both legs assessed-both inadequate	16 (1.9%)	13 (1.5%)	29 (1.7%)
Both legs assessed-operated leg inadequate	14 (1.7%)	12 (1.4%)	26 (1.6%)
Both legs assessed-non-operated leg inadequate	12 (1.4%)	19 (2.3%)	31 (1.9%)
Operated leg assessed only- negative	16 (1.9%)	29 (3.4%)	45 (2.7%)
Operated leg assessed only- inadequate	3 (0.4%)	5 (0.6%)	8 (0.5%)
Non-operated leg assessed only-negative	9 (1.1%)	8 (1.0%)	17 (1.0%)
Non-operated leg assessed only-inadequate	2 (0.2%)	0 (0.0%)	2 (0.1%)
Examination performed before day 5	1 (0.1%)	1 (0.1%)	2 (0.1%)
No VTE assessment up to day 11	**132 (15.9%)**	**129 (15.3%)**	**261 (15.6%)**
VTE assessment after day 11	10 (1.2%)	14 (1.7%)	24 (1.4%)
Reasons for no VTE assessment			
Failed venous access	38 (4.6%)	30 (3.6%)	68 (4.1%)
Subject refuse/withdrew consent	28 (3.4%)	26 (3.1%)	54 (3.2%)
SAE/deaths	12 (1.4%)	18 (2.1%)	30 (1.8%)
Premature treatment discontinuation	15 (1.8%)	14 (1.7%)	29 (1.7%)
Uncooperative/"too ill" for the test	7 (0.8%)	10 (1.2%)	17 (1.0%)
Technical problems	5 (0.6%)	5 (0.6%)	10 (0.6%)
Suspicion of iodine allergy	3 (0.4%)	1 (0.1%)	4 (0.2%)
Problematic venous system	1 (0.1%)	1 (0.1%)	2 (0.1%)
Increased creatinine	3 (0.4%)	0 (0.0%)	3 (0.2%)
Normal US/ Spiral CT	2 (0.2%)	1 (0.1%)	3 (0.2%)
Symptomatic assessment only	0 (0.0%)	1 (0.1%)	1 (0.1%)
Monoclonal antibodies	2 (0.2%)	0 (0.0%)	2 (0.1%)
No reason mentioned	5 (0.6%)	7 (0.8%)	12 (0.7%)
Local but not central	1 (0.1%)	1 (0.1%)	2 (0.1%)
Total	**205 (24.7%)**	**216 (25.7%)**	**421 (25.2%)**

Reviewer's table based on NDA Vol. 86, pp. 1372-1410

The majority of patients with non-evaluable VTE assessment up to day 11 were due to both legs assessed with both or one leg inadequate in both treatment groups. Noted that there were few patients with operated-leg assessed only with negative finding in Org31540/SR90107A group (1.9%) as compared to enoxaparin group (3.4%).

The main reasons for no VTE assessment up to day 11 in both treatment groups were failed venous access, subject refusal/withdrew consent, SAE/death, premature treatment discontinuation (majority were due to violation of inclusion/exclusion criteria), uncooperative/"too ill" for the test, and technical problem. There were slightly more patients who had no VTE assessment due to failed venous access and subject refusal/withdraw consent in Org31540/SR90107A group (4.6% and 3.4%, respectively) as compared to enoxaparin group (3.6% and 3.1% respectively).

Other protocol deviations

As previously described, 3 patients were identified as having been 'randomized' with a treatment number already assigned to previously randomized patients. These patients were considered not randomized and were excluded from all analyses by the sponsor.

The other randomization irregularities consisted of starting a different treatment block before completion of the previous one. There were 56 patients in Org31540/SR90107A group and 50 patients in enoxaparin group who received treatment from a different block prior to completion of the previous block. These patients experienced few events (Org31540/SR90107A group: 4 VTEs, 1 major bleeding; enoxaparin group: 6 VTEs, 1 major bleeding). These irregularities are considered by the sponsor of no significance to the overall results of the study.

The following table summarizes the main protocol deviations other than those leading to exclusion from the primary efficacy analysis.

Number (%) of Patients With Selected Protocol Deviations Other Than Those Leading to Exclusion From Primary Efficacy Analysis- All Treated Patients

Deviation	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)	Total (N =1673)
Period between admission to hospital and surgery >48 hours	30 (3.6%)	34 (4.0%)	64 (3.8%)
Meeting exclusion criteria based on current labeling for LMWH[a]	2 (0.2%)	5 (0.6%)	7 (0.4%)
Less than 8 post-operative injections (of placebo or active drug)[b]	19 (2.3%)	25 (3.0%)	44 (2.6%)
Not allowed concomitant therapy[c,d]	47 (5.7%)	40 (4.8%)	87 (5.2%)
Qualifying VTE examination for primary efficacy analysis more than 2 calendar days after the last injection	6 (0.7%)	6 (0.7%)	12 (0.7%)

a Patients with more than one protocol deviation were counted once
b Unless discontinuation due to AE or lack of efficacy
c From the day of the first injection up to the day before the qualifying VTE examination or the day before the last injection, whichever came last
d As per protocol, did not take into account heparin flush up to 200 IU/day
Sponsor's table in NDA Vol. 81, pp. 69

The most common deviation was use of not allowed concomitant therapy with a higher rate in Org31540/SR90107A group (5.7%) as compared to enoxaparin group (4.8%). The difference between the two groups was not statistically significant (p=0.4).

One patient in the Org31540/SR90107A group and 3 patients in the enoxaparin group did not provide written informed consent but received study medication. The reason informed consent was not obtained was not specified in the CRF.

Demographic and baseline characteristics

All treated patients

The following table presents demographic data and characteristics of surgery by treatment group for the all treated patients population.

Of the 1673 randomized and treated patients, 1262 (75%) were female and 1658 (99.2%) were Caucasian. The mean age of patients was 77±12 years for both groups. Org31540/SR90107A group had slightly more female (p=0.05) and fewer patients with BMI ≥30 (p=0.09) than enoxaparin group. The 2 treatment groups were similar with respect to other demographic characteristics.

There were slightly more patients with subtrochanteric fracture in enoxaparin group than that in Org31540/SR90107A group (p=0.04). The 2 treatment groups were similar in type of surgery, type of anesthesia, use of cement, or duration of surgery. The time between trauma and start of surgery was also similar for both treatment groups (mean time ±SD: 25±16 hours in each treatment group).

Summary of Demographic and Surgical Characteristics - All Treated Patients

Parameter		Org31540/SR9010A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)	Total (N = 1673)
Age (years)	n	827	839	1666
	Median	79	79	79
	Mean	76.8	77.3	77.0
	SD	12.3	12.6	12.4
	Min – Max	17 - 97	19 - 101	17 - 101
Age [n (%)]	<65	111 (13.4%)	104 (12.4%)	215 (12.9%)
	[65,75]	154 (18.6%)	151 (18.0%)	305 (18.3%)
	≥75	562 (68.0%)	584 (69.6%)	1146 (68.8%)
	Missing	4	3	7
Height (cm)	N	777	784	1561
	Median	164	165	165
	Mean	164.2	164.8	164.5
	SD	8.9	9.3	9.1
	Min – Max	140 - 195	140 - 197	140 - 197
Weight (kg)	N	798	801	1599
	Median	65	63	64
	Mean	64.3	64.2	64.2
	SD	13.1	13.8	13.5
	Min – Max	30 - 125	35 - 115	30 - 125
BMI (kg/m^2) [n (%)]	<30	732 (94.6%)	722 (92.4%)	1454 (93.5%)
	≥30	42 (5.4%)	59 (7.6%)	101 (6.5%)
	Missing	57	61	118
Gender [n (%)]	Male	187 (22.5%)	224 (26.6%)	411 (24.6%)
	Female	644 (77.5%)	618 (73.4%)	1262 (75.4%)
Race [n (%)]	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%)
Type of fracture [n (%)]	Cervical only	400 (48.1%)	388 (46.3%)	788 (47.2%)
	Trochanteric[a]	373 (44.9%)	368 (43.9%)	741 (44.4%)
	Subtrochanteric	58 (7.0%)	82 (9.8%)	140 (8.4%)
	Missing	0	3	3
Type of surgery [n (%)][b]	Total prosthesis	56 (6.7%)	58 (6.9%)	114 (6.8%)
	Half prosthesis	193 (23.2%)	183 (21.8%)	376 (22.5%)
	Other[c]	582 (70.0%)	600 (71.3%)	1182 (70.7%)
Use of cement [n (%)][b]	Yes	176 (21.2%)	183 (21.8%)	359 (21.5%)
	No	655 (78.8%)	658 (78.2%)	1313 (78.5%)
Type of anaesthesia [n (%)][b]	General only	262 (31.5%)	276 (32.8%)	538 (32.2%)
	Regional only	554 (66.7%)	548 (65.2%)	1102 (65.9%)
	Combination	15 (1.8%)	17 (2.0%)	32 (1.9%)
Duration of surgery (hh:mm)[b]	n	830	841	1671
	Median	1:35	1:35	1:35
	Mean	1:41	1:44	1:43
	SD	0:39	0:44	0:42
	Min- Max			

[a]Not associated with any subtrochanteric fracture
[b]For all treated and operated patients (Org31540/SR9010A, N=831; enoxaparin, N=841)
[c]The category 'other' included nailing, screwing, plate, and any type of combined surgery
Sponsor's table in NDA Vol. 81, pp. 72

The following table presents the specific medical and surgical histories which were risk factors for VTE in the 2 treatment groups.

Number (%) of Patients With Specific Medical and Surgical History -All Treated Patients

Specific Medical and Surgical History	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)	Total (N = 1673)
Specific medical history			
VTE	29 (3.5%)	32 (3.8%)	61 (3.6%)
Stroke	65 (7.8%)	61 (7.2%)	126 (7.5%)
Myocardial infarction	50 (6.0%)	47 (5.6%)	97 (5.8%)
Cancer	79 (9.5%)	74 (8.8%)	153 (9.1%)
Orthopedic surgery within the previous 12 months			
Any surgery	33 (4.0%)	26 (3.1%)	59 (3.5%)
Hip replacement	4 (0.5%)	2 (0.2%)	6 (0.4%)
Knee replacement	1 (0.1%)	4 (0.5%)	5 (0.3%)
Hip fracture	15 (1.8%)	10 (1.2%)	25 (1.5%)
Other surgery	17 (2.0%)	13 (1.5%)	30 (1.8%)

Sponsor's table in NDA Vol. 81, pp. 73

There was no statistically significant difference in specific medical and surgical history listed above between treatment groups ($p>0.05$).

The number (%) of patients who received medications with potential impact on hemostasis between trauma and the day before the first study drug injection was shown in the following table. There were slightly more patients who received medications with potential impact on hemostasis in the Org31540/SR90107A group than in the enoxaparin group.

Number (%) of Patients Who Took Medications With Potential Impact on Hemostasis Between Trauma and the Day Before the First Study Drug Injection -All Treated Patients

Medication	Org31540/SR90107A 2.5 mg o.d. (N= 831)	Enoxaparin 40 mg o.d. (N= 842)
Total medication with potential impact on hemostasis	144 (17.3%)	134 (15.9%)
Not allowed medication per amendment	32 (3.9%)	28 (3.3%)
Heparin(UFH, LMWH)/heparinoids	27 (3.2%)	24 (2.9%)
Vitamin K antagonist	4 (0.5%)	3 (0.4%)
Dextran	1 (0.1%)	1 (0.1%)
Other medication with potential impact on hemostasis	117 (14.1%)	114 (13.5%)
Antiplatelet drugs other than ASA	7 (0.8%)	9 (1.1%)
ASA	74 (8.9%)	68 (8.1%)
NSAID	41 (4.9%)	43 (5.1%)

Sponsor's table in NDA Vol. 81, pp. 74

Primary efficacy population

The following table presents demographic data and characteristics of surgery by treatment group for the primary efficacy population.

The primary efficacy population was similar to the all treated patients population with respect to demographic and surgical characteristics. Org31540/SR90107A group remained to have slightly more female (p=0.05) and fewer patients with subtrochanteric fracture (p=0.07) than enoxaparin group. Other demographic and surgical characteristics were also similar between 2 treatment groups in the primary efficacy population.

Summary of Demographic and Surgical Characteristics -Primary Efficacy Population

Parameter		Org31540/SR90107A 2.5 mg o.d. (N = 626)	Enoxaparin 40 mg o.d. (N = 624)	Total (N = 1250)
Age (years)	n	622	622	1244
	Median	79	79	79
	Mean	76.4	77.3	76.9
	SD	12.4	11.9	12.2
	Min - Max	17 - 97	19 - 99	17 - 99
Age [n (%)]	<65	90 (14.5%)	80 (12.9%)	170 (13.7%)
	[65,75[	123 (19.8%)	115 (18.5%)	238 (19.1%)
	≥75	409 (65.8%)	427 (68.6%)	836 (67.2%)
	Missing	4	2	6
Height (cm)	n	588	586	1174
	Median	164	165	165
	Mean	164.2	164.8	164.5
	SD	9.0	9.1	9.0
	Min - Max	140 - 195	140 - 194	140 - 195
Weight (kg)	n	601	597	1198
	Median	65	63	64
	Mean	64.4	64.0	64.2
	SD	13.1	13.6	13.4
	Min - Max	30 - 125	35 - 115	30 - 125
BMI (kg/m²) [n (%)]	<30	554 (94.7%)	544 (93.2%)	1098 (93.9%)
	≥30	31 (5.3%)	40 (6.8%)	71 (6.1%)
	Missing	41	40	81
Gender [n (%)]	Male	144 (23.0%)	174 (27.9%)	318 (25.4%)
	Female	482 (77.0%)	450 (72.1%)	932 (74.6%)
Race [n (%)]	Caucasian	622 (99.4%)	619 (99.2%)	1241 (99.3%)
	Black	1 (0.2%)	1 (0.2%)	2 (0.2%)
	Asian/Oriental	3 (0.5%)	2 (0.3%)	5 (0.4%)
	Other race	0 (0.0%)	2 (0.3%)	2 (0.2%)
Type of fracture [n (%)]	Cervical only	305 (48.7%)	289 (46.5%)	594 (47.6%)
	Trochanteric[a]	278 (44.4%)	274 (44.1%)	552 (44.2%)
	Subtrochanteric	43 (6.9%)	59 (9.5%)	102 (8.2%)
	Missing	0	2	2
Type of surgery [n (%)]	Total prosthesis	47 (7.5%)	45 (7.2%)	92 (7.4%)
	Half prosthesis	142 (22.7%)	127 (20.4%)	269 (21.5%)
	Other[b]	437 (69.8%)	452 (72.4%)	889 (71.1%)
Use of cement [n (%)]	Yes	133 (21.2%)	130 (20.8%)	263 (21.0%)
	No	493 (78.8%)	494 (79.2%)	987 (79.0%)
Type of anaesthesia [n (%)]	General only	203 (32.4%)	207 (33.2%)	410 (32.8%)
	Regional only	410 (65.5%)	406 (65.1%)	816 (65.3%)

	Combination	13 (2.1%)	11 (1.8%)	24 (1.9%)
Duration of surgery (hh:mm)	n	626	624	1250
	Median	1:35	1:35	1:35
	Mean	1:41	1:42	1:42
	SD	0:38	0:41	0:40
	Min - Max			

[a]Not associated with any subtrochanteric fracture
[b]The category 'other' included nailing, screwing, plate, and any type of combined surgery
Sponsor's table in NDA Vol. 81, pp. 75

The primary efficacy population was similar to the all treated patients population with respect to specific medical and surgical history. In the primary efficacy population, the two treatment groups were also similar as shown in the table below.

Number (%) of Patients With Specific Medical and Surgical History -Primary Efficacy Population

Specific Medical and Surgical History	Org31540/SR90107A 2.5 mg o.d. (N = 626)	Enoxaparin 40 mg o.d. (N = 624)	Total (N = 1250)
Specific medical history			
VTE	21 (3.4%)	21 (3.4%)	42 (3.4%)
Stroke	51 (8.1%)	45 (7.2%)	96 (7.7%)
Myocardial infarction	33 (5.3%)	33 (5.3%)	66 (5.3%)
Cancer	59 (9.4%)	57 (9.1%)	116 (9.3%)
Orthopedic surgery within the previous 12 months			
Any surgery	20 (3.2%)	20 (3.2%)	40 (3.2%)
Hip replacement	3 (0.5%)	1 (0.2%)	4 (0.3%)
Knee replacement	1 (0.2%)	3 (0.5%)	4 (0.3%)
Hip fracture	8 (1.3%)	8 (1.3%)	16 (1.3%)
Other surgery	11 (1.8%)	9 (1.4%)	20 (1.6%)

Sponsor's table in NDA Vol. 81, pp. 76

The number (%) of patients who received medications with potential impact on hemostasis between trauma and the day before the first study drug injection in primary efficacy population is summarized in the following table. No apparent difference was observed between the two treatment groups.

Number (%) of Patients Who Took Medications With Potential Impact on Hemostasis Between Trauma and the Day Before the First Study Drug Injection -Primary Efficacy Population

Medication	Org31540/SR90107A 2.5 mg o.d. (N = 626)	Enoxaparin 40 mg o.d. (N = 624)
Total medication with potential impact on hemostasis	106 (12.8%)	93 (11.0%)
Not allowed medication per amendment	22 (2.6%)	18 (2.1%)
Heparin(UFH, LMWH)/heparinoids	18 (2.2%)	16 (1.9%)
Vitamin K antagonist	4 (0.5%)	1 (0.1%)
Dextran	0 (0.0%)	1 (0.1%)
Other medication with potential impact on hemostasis	87 (10.5%)	81 (9.6%)
Antiplatelet drugs other than ASA	7 (0.8%)	6 (0.7%)
ASA	54 (6.5%)	46 (5.5%)
NSAID	29 (3.5%)	32 (3.8%)

Sponsor's table in NDA Vol. 81, pp. 77

Extent of exposure

All treated patients

Table below summarizes the number (%) of patients who received active pre-operative injections according to the type of anesthesia.

Number (%) of Patients With Active Pre-Operative Injections by Type of Anesthesia - All Treated and Operated Patients

Patients With	Org31540/SR90107A 2.5 mg o.d.	Enoxaparin 40 mg o.d.
General anesthesia only	50/262 (19.1%)	95/276 (34.4%)
Regional anesthesia only or combination	49/569 (8.6%)	124/565 (21.9%)
Total with active pre-operative injections	99/831 (11.9%)	219/841 (26.0%)

NOTE: Treated and operated patients (Org31540/SR90107A, N=831; enoxaparin, N=841)
Sponsor's table in NDA Vol. 81, pp. 77
Reviewer's note: The number of treated and operated patients should be 840 for the enoxaparin group.

The majority of patients in both groups started treatment post-operatively. A total of 11.9% of patients in Org31540/SR90107A group and 26% in enoxaparin group received active pre-operative treatment. Among those, 4 patients in the Org31540/SR90107A group and 8 patients in the enoxaparin group received more than one active pre-operative injection (maximum: 3 injections) due to surgery delayed for more than 24 hours following admission.

Overall, mean time (±SD) between the last active pre-operative injection and start of surgery was similar for both groups (16±8 hours and 17±14 hours in the Org31540/SR90107A and enoxaparin groups, respectively). Mean time (±SD) between the end of surgery and the first active post-operative injection was 6±2 hours and 18±5 hours in the Org31540/SR90107A and enoxaparin groups, respectively.

The following table presents a summary of active treatment. Most patients in both treatment groups received active study drug at least up to Day 7±2, as required by the protocol. The number of active injections differed between the two groups (7.2±1.9 in Org31540/SR90107A vs. 6.5±1.9 in enoxaparin). This difference may be due to the different dosing schedule for the two treatments because one additional dose of Org31540/SR90107A was given in Day 1 of surgery.

Summary of Active Treatment- All Treated Patients

	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)
Number of active injections		
N	829	840
Median	7	7
Mean (SD)	7.2 (1.9)	6.5 (1.9)
Min-Max	[redacted]	[redacted]
Last day of active treatment [n (%)] [a]		
<Day 5	42 (5.1 %)	49 (5.8 %)
Day 5 to Day 9	741(89.4 %)	739 (88.0 %)
>Day 9	46 (5.5 %)	52 (6.2 %)

a Day 1 = Day of surgery (or day of first study drug injection for non-operated patients), taking into account all treated patients who received active injections
Sponsor's table in NDA Vol. 81, pp. 78

Primary efficacy population

Overall, the extent of exposure to active study drug for the primary efficacy population, as shown in Table below was similar to that observed for the all treated patients population. The majority of patients in both groups started treatment post-operatively. A total of 10.9% of patients in Org31540/SR90107A group and 25.6% in enoxaparin group received active pre-operative treatment in primary efficacy population.

The number (%) of patients who received pre-operative active injections is summarized according to the type of anesthesia (See Table below).

Number (%) of Patients With Pre-Operative Active Injection by Type of Anesthesia - Primary Efficacy Population

Patients With	Org31540/SR90107A 2.5 mg o.d.	Enoxaparin 40 mg o.d.
General anesthesia only	33/203 (16.3%)	73/207 (35.3%)
Regional anesthesia only or combination	35/423 (8.3%)	87/417 (20.9%)
Total with pre-operative active injections	68/626 (10.9%)	160/624 (25.6%)

Sponsor's table in NDA Vol. 81, pp. 79

Overall, mean time (±SD) between the last active pre-operative injection and start of surgery was 14±6 hours and was identical in both groups. Mean time (±SD) between the end of surgery and the first active post-operative injection was 6±2 hours and 18±5 hours, in the Org31540/SR90107A and enoxaparin groups, respectively.

As observed in all treated patients population, the number of active injections up to the qualifying VTE examination differed between the two treatment groups (7.4±1.6 in Org31540/SR90107A vs. 6.7±1.6 in enoxaparin) (See Table below).

Summary of Active Treatment up to the Qualifying VTE Examination -Primary Efficacy Population

	Org31540/SR90107A 2.5 mg o.d. (N=626)	Enoxaparin 40 mg o.d. (N= 624)
Number of active injections		
N	626	624
Median	7	7
Mean (SD)	7.4 (1.6)	6.7 (1.6)
Min-Max	[redacted]	[redacted]
Last day of active treatment [n (%)][a]		
<Day 5	11 (1.8%)	4 (0.6%)
Day 5 to Day 9	585 (93.5%)	589 (94.4%)
>Day 9	30 (4.8%)	31 (5.0%)

a Day 1 = Day of surgery
Sponsor's table in NDA Vol. 81, pp. 79

Measurements of treatment compliance

Besides temporary or permanent discontinuation of treatment due to AE or lack of efficacy, the percentage of patients with less than 8 postoperative injections in all treated patients was comparable between the two treatment groups [19 (2.3 %) in Org31540/SR90107A group and 25 (3.0%) in enoxaparin group]. For primary efficacy population, there were 4 (0.6%) patients in Org31540/SR90107A group and 1 (0.2%) patient in enoxaparin group who received less than 8 post-operative injections up to the qualifying VTE examination.

Four patients in each treatment group received an injection from another kit at some point during the study. One patient in the enoxaparin group who experienced a major bleed (hematoma of the thigh) on Day 4 (after 4 days on treatment); on this day, an injection of Org31540/SR90107A was given by mistake instead of enoxaparin.

Concomitant medications

All treated patients

The percentage of patients receiving not allowed or discouraged concomitant medications from the day of the first injection up to the day before the qualifying VTE examination or the day before the last injection, whichever came last, is presented in the table below. There were slightly more patients taking not allowed and discouraged medication in Org31540/SR90107A group than in enoxaparin group but the differences were not statistically significant (p=0.4 for both categories).

Number (%) of Patients Who Received Not Allowed or Discouraged Concomitant Medications - All Treated Patients

Medication	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)
Not allowed medication[a]	47 (5.7%)	40 (4.8%)
Heparin (UFH, LMWH)/heparinoids[b]	35 (4.2%)	32 (3.8%)
Antiplatelet drug other than ASA	9 (1.1%)	6 (0.7%)
Vitamin K antagonist	4 (0.5%)	2 (0.2%)
Dextran	2 (0.2%)	1 (0.1%)
Discouraged medication[a]	229 (27.6%)	215 (25.5%)
NSAID	148 (17.8%)	148 (17.6%)
ASA	96 (11.6%)	84 (10.0%)

a From the day of the first injection up to the day before the qualifying VTE examination or the day before the last injection, whichever came last
b As per-protocol, did not take into account heparin flush up to 200 IU/day
Sponsor's table in NDA Vol. 81, pp. 81

The use of physical therapy during the treatment period was similar for both treatment groups (See Table below).

Number (%) of Patients With Physical Therapy During Treatment Period -All Treated Patients

Physical Therapy	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)
Elastic stockings only	14 (1.7%)	14 (1.7%)
Physiotherapy only	359 (43.3%)	354 (42.3%)
Both methods	380 (45.8%)	386 (46.2%)

Sponsor's table in NDA Vol. 81, pp. 81

Primary efficacy population

As observed for the all treated patients population, in the primary efficacy population, the use of not allowed or discouraged concomitant medications were slightly higher in the Org31540/SR90107A group than in the enoxaparin group. Again, the differences were not statistically significant (p=0.7 and 0.3, respectively).

Number (%) of Patients Who Received Not Allowed or Discouraged Concomitant Medications - Primary Efficacy Population

Medication	Org31540/SR90107A 2.5 mg o.d. (N = 626)	Enoxaparin 40 mg o.d. (N = 624)
Not allowed medication[a]	23 (3.7%)	21 (3.4%)
Heparin (UFH, LMWH)/heparinoids[b]	17 (2.7%)	19 (3.0%)
Antiplatelet drug other than ASA	5 (0.8%)	2 (0.3%)
Vitamin K antagonist	2 (0.3%)	1 (0.2%)
Dextran	1 (0.2%)	0 (0.0%)
Discouraged medication[a]	141 (22.5%)	126 (20.2%)
NSAID	101 (16.1%)	92 (14.7%)
ASA	47 (7.5%)	43 (6.9%)

a From the day of the first injection up to the day before the qualifying VTE examination
b As per-protocol, did not take into account heparin flush up to 200 IU/day
Sponsor's table in NDA Vol. 81, pp. 82

As observed for the all treated patients population, physical therapy was similar for both treatment groups (See table below).

Number (%) of Patients With Physical Therapy During Treatment Period -Primary Efficacy Population

Physical Therapy	Org31540/SR90107A 2.5 mg o.d. (N = 626)	Enoxaparin 40 mg o.d. (N = 624)
Elastic stockings only	9 (1.4%)	10 (1.6%)
Physiotherapy only	261 (41.7%)	273 (43.8%)
Both methods	303 (48.4%)	285 (45.7%)

Sponsor's table in NDA Vol. 81, pp. 82

Duration of participation in the study

The following table summarizes the duration of study participation for all treated patients. The mean duration of participation was similar for both treatment groups.

Summary of Duration of Study Participation - All Treated Patients

Duration of Study Participation[a] (Days)	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)
Median	44	44
Mean	44.5	44.4
SD	13.0	11.4
Min - Max	[redacted]	[redacted]

a From first injection (active drug or placebo) to last visit
Sponsor's table in NDA Vol. 81, pp. 83

For the primary efficacy population, the mean duration of study participation was similar between treatment groups, and was comparable to that observed for the all treated

patients population. Additionally, the mean time between surgery and the qualifying VTE examination was similar between the 2 treatment groups.

Summary of Duration of Study Participation, and Duration between Surgery and the Qualifying VTE Examination - Primary Efficacy Population

Parameter		Org31540/SR90107A 2.5 mg o.d. (N = 626)	Enoxaparin 40 mg o.d. (N = 624)
Duration of study participation[a] (days)	Median	44	44
	Mean	44.7	44.5
	SD	11.6	9.8
	Min - Max	[redacted]	[redacted]
Duration between surgery and the qualifying VTE examination (days)	Median	8	8
	Mean	7.7	7.6
	SD	1.6	1.6
	Min - Max	[redacted]	[redacted]

a From first injection (active drug or placebo) to last visit
Sponsor's table in NDA Vol. 81, pp. 84

Most patients underwent the qualifying VTE examination between Day 5 and Day11. Only 2 patients one in each treatment had a qualifying VTE examination before Day 5 (these patients experienced a fatal PE before Day 5).

Patients follow-up

The following table summarizes location at discharge and living situation at follow-up assessment for the all treated patients population. Similar follow-up data were observed in both groups.

Number (%) of Patients by Location at Discharge and Living Situation at Follow-Up Assessment - All Treated Patients

Parameter	Org31540/SR90107A 2.5 mg o.d. (N = 831)	Enoxaparin 40 mg o.d. (N = 842)
Location at discharge[a]		
Home	377 (45.9%)	366 (43.8%)
Other location than home	445 (54.1%)	470 (56.2%)
Rehabilitation unit/facility	324 (39.4%)	330 (39.5%)
Other location	121 (14.7%)	140 (16.7%)
Missing	9	6
Living situation at follow-up assessment[b]		
Home	447 (56.6%)	465 (58.5%)
Home with professional assistance	36 (4.6%)	35 (4.4%)
Rest home	34 (4.3%)	32 (4.0%)
Nursing home	40 (5.1%)	42 (5.3%)
Rehabilitation facility	157 (19.9%)	145 (18.2%)
Other	76 (9.6 %)	76 (9.6 %)

a Percentages were based on non-missing information b Percentages were based on patients with a follow-up form available, excluding death up to Day 49 and missing
Sponsor's table in NDA Vol. 81, pp. 85

The similar percentage of patients by location at discharge and living situation at follow-up assessment was observed between 2 treatment groups for the primary efficacy population (See Table below).

Number (%) of Patients by Location at Discharge and Living Situation at Follow-Up Assessment - Primary Efficacy Population

Parameter	Org31540/SR90107A 2.5 mg o.d. (N = 626)	Enoxaparin 40 mg o.d. (N = 624)
Location at discharge[a]		
Home	297 (48.0%)	289 (46.5%)
Other location than home	322 (52.0%)	332 (53.5%)
Rehabilitation unit/facility	245 (39.6%)	241 (38.8%)
Other location	77 (12.4%)	91 (14.7%)
Missing	7	3
Living situation at follow-up assessment[b]		
Home	344 (57.0%)	356 (58.9%)
Home with professional assistance	32 (5.3%)	30 (5.0%)
Rest home	19 (3.1%)	23 (3.8%)
Nursing home	32 (5.3%)	32 (5.3%)
Rehabilitation facility	117 (19.4%)	107 (17.7%)
Other	60 (9.9%)	56 (9.3%)

a Percentages were based on non-missing information
b Percentages were based on patients with a follow-up form available, excluding death up to Day 49 and missing data
Sponsor's table in NDA Vol. 81, pp. 86

Efficacy Evaluation

Analysis of efficacy

Primary efficacy analysis

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

The following table presents the results of the comparison of the rate of adjudicated VTE between the Org31540/SR90107A group and the enoxaparin group.

Number (%) of Patients With Adjudicated VTE With a Qualifying Examination up to Day 11 - Primary Efficacy Population

Endpoints	Org31540/SR90107A 2.5 mg o.d. (N = 626)	Enoxaparin 40 mg o.d. (N = 624)	Difference Org31540/SR90107A minus Enoxaparin (%)	Fisher's Exact Test (p)
VTE	52 8.3%	119 19.1%	-10.8	2.6×10^{-8}
DVT	49 (7.8%)	117 (18.8%)	-11.0	1×10^{-8}
PE	3 (0.5%)	3 (0.5%)	0.0	1.0
Fatal PE	3 (0.5%)	2 (0.3%)	0.2	
Non-Fatal PE	0 (0.0%)	1 (0.2%)	-0.2	

Note: one patient had both DVT and PE in the enoxaparin group.
p-value for PE was obtained by FDA Statistical Reviewer Dr. Mushfiqur Rashid, Ph.D.
Reviewer's table based on NDA Vol. 81, pp. 145-153 and efficacy datasets

The VTE rate up to Day 11 was statistically significantly lower in the Org31540/SR90107A group than in the enoxaparin group (8.3% versus 19.1%, $p=2.6 \times 10^{-8}$). This highly significant difference in VTE rate was mainly due to difference in DVT component between the two groups (7.8% vs. 18.6%, $p=1 \times 10^{-8}$). There was no difference in the incidence of PE up to Day 11 between the two groups.

This reviewer further analyzed mortality data from this study. There were 93 deaths in the study including 33 deaths occurred up to Day 11. The number of all-cause deaths and deaths due to PE were similar between two treatments. The number of patients who died of all causes and PE in the study is summarized in the table below.

Deaths from all causes and PE in the study

	Org31540/SR90107A 2.5 mg o.d. (N = 849)	Enoxaparin 40 mg o.d. (N = 862)
Death up to day 11		
All causes	15 (1.8%)	18 (2.1%)
Fatal PE	4 (0.5%)	2 (0.2%)
Death up to day 49		
All causes	43 (5.1%)	44 (5.1%)
Fatal PE	9 (1.1%)	7 (0.8%)
Death after day 49 (up to day 60)		
All deaths	2 (0.2%)	4 (0.5%)
Fatal PE	0 (0.0%)	0 (0.0%)
Total		
All deaths	45 (5.3%)	48 (5.6%)
Fatal PE	9 (1.1%)	7 (0.8%)

Reviewer's table based on NDA study EFC2698 Appendix 14.2.4.2.4 and datasets

Central Independent Adjudication Committee (CIAC) classified the cause of death into only three categories: fatal PE, hemorrhagic death, and death not associated with VTE or bleeding.

Of those 93 deaths, 22 (23.6%) had autopsies (8 in the Org31540/SR90107A group and 14 in the enoxaparin group) and only one case of fatal PE (in the enoxaparin group) was identified from the autopsy. Of the remaining 71 deaths without autopsy, the SAE's that leading to deaths were summarized by treatment in the table below. The number of SAE's leading to death was similar in the two groups except for more patients who died of cardiac diseases in the Org31540/SR90107A group as compared to the enoxaparin group.

SAE's that leading to deaths by treatment

SAEs that leading to deaths	Org31540/SR90107A 2.5 mg o.d. (N = 849)	enoxaparin 40 mg o.d. (N = 862)
Fatal PE	9	6
Cardiac/M.I.	7	4
Pneumonia	6	6
CVA	3	4
Heart failure	2	4
Unknown origin	4	2
Cancer	1	4
Sepsis	2	0
Liver cirrhosis	0	1
Anemia	1	1
Respiratory insufficiency	0	1
Arteritis	0	1
Surgical site reaction	1	0
Intraoperative death, asystole	0	1
"Not bleeding"	1	0
Total	37	34

Reviewer's table based on NDA study EFC2698 Appendix 14.2.4.2.4 and datasets

A total of 18 mandatory venographies (7 in the Org31540/SR90107A group and 11 in the enoxaparin group) were performed after Day 11 and were consequently disqualified from all efficacy analyses. Adjudication of these examinations revealed only 1 asymptomatic proximal DVT reported on Day 15 in the Org31540/SR90107A group versus a total of 4 asymptomatic DVTs (2 proximal and 2 distal only [i.e., confined to the calf]) recorded between Day 12 and Day 14 in the enoxaparin group.

Secondary efficacy analyses

Adjudicated DVT

The number (%) of patients with adjudicated DVT, adjudicated proximal DVT and adjudicated only distal DVT up to Day 11 is summarized by treatment group in the table below.

There were statistically significantly lower incidence rates of any DVT, proximal DVT and distal DVT in the Org31540/SR90107A group than in the enoxaparin group. The incidence rate of any proximal DVT was much lower than distal DVT only in both treatment groups.