Protocol Amendments

Two protocol amendments were made in the study. Protocol amendment No. 1 was dated 29 July 1998. The main change was addition of inclusion criterion related to women with childbearing potential. Protocol amendment No. 2 was dated April 1999. The main changes included following:

- Exclusion criterion related to metformin intake
- Exclusion criterion related to prior treatment restrictions
- Pharmacokinetic sampling
- Baseline laboratory sample timing and liver enzymes and serum bilirubin
- Modification in statistical methods:
  - Clarification of primary endpoint
  - Additional exploratory sensitivity analyses
  - Methods for the secondary/exploratory analyses
  - Clarification of the safety analysis population
- Administrative changes/textual clarifications for patient follow-up and supply handling and some administrative corrections

Study Results

Disposition of patients

The study was conducted at 139 centers in 3 countries. Among the 139 centers, the number of patients enrolled at each center ranged from a single patient to 141 patients.

During blind review of data before database lock, 1 patient was identified as randomized with a treatment number already assigned to another patient. This patient was, therefore, considered not randomized by the sponsor. This patient received study drug but was excluded from all analyses. No VTE, bleeding or SAE were reported in this patient.

Of the 2275 patients were randomized in this study, 1138 were assigned to receive Org31540/SR90107A and 1137 were assigned to receive enoxaparin. The following chart presents the disposition of patients for each treatment group.

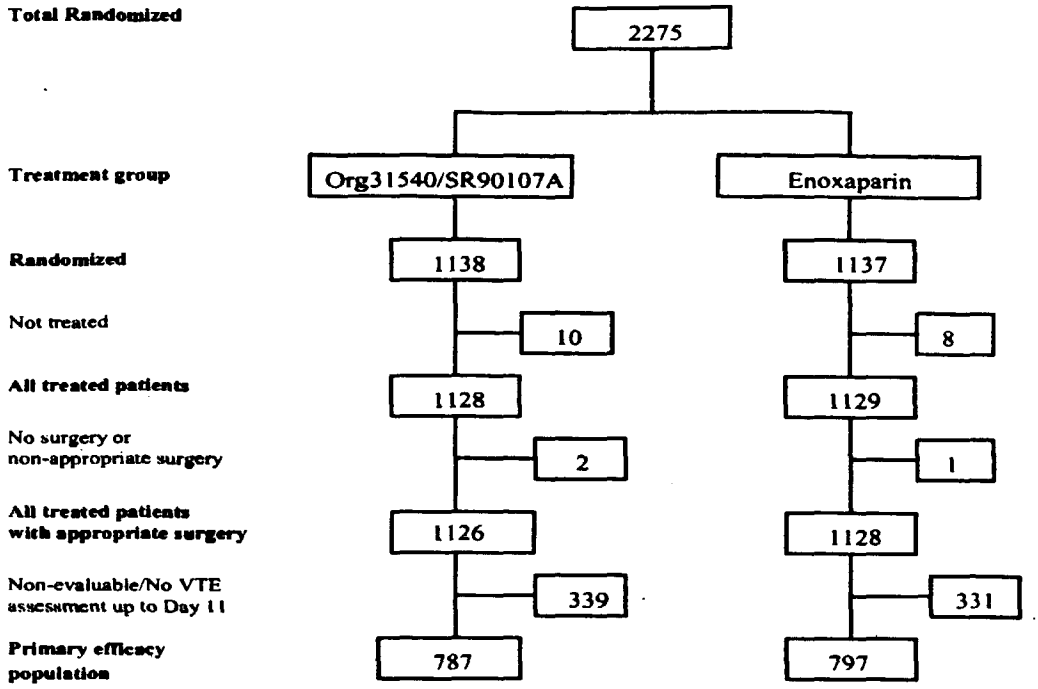


Figure (6.3) 1 - Number of Patients by Treatment Group and Population

Sponsor's figure in NDA Vol. 163, pp. 84

Of the 2275 patients randomized, 18 did not receive any study drug (See Table below). The number of patients who were not treated was similar between the two groups. The main reason for not being treated was inclusion/exclusion criteria not met.

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=1138)	Enoxaparin 30 mg b.i.d. (N=1137)	Total (N=2275)
Inclusion/exclusion criteria not met	5 (0.4%)	6 (0.5%)	11 (0.5%)
Informed consent withdrawn	2 (0.2%)	1 (0.1%)	3 (0.1%)
Adverse event	2 (0.2%)	1 (0.1%)	3 (0.1%)
Other reason (latex allergy)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Total	10 (0.9%)	8 (0.7%)	18 (0.8%)

Sponsor's table in NDA Vol. 163, pp. 62

Adverse events were arrhythmia and "medically unstable" in Org31540/SR90107A group, and increased liver enzyme in enoxaparin group.

A total of 2257 patients (1128 in the Org31540/SR90107A group and 1129 in the enoxaparin group) were randomized and treated (all treated patients population). The number (%) of randomized and treated patients is presented by country and treatment group in the following table.

Number (%) of Randomized and Treated Patients by Country

Country[a] (Number of Centers)	Org31540/SR90107A 2.5 mg o.d.	Enoxaparin 30 mg b.i.d.	Total
United States of America (94)	655	644	1299 (57.6%)
Canada (30)	310	318	628 (27.8%)
Australia (15)	163	167	330 (14.6%)
Total (139)	1128	1129	2257 (100.0%)

NOTE: A patient was considered to be treated when he/she received at least 1 injection of study drug.
[a] Sorted in decreasing order of randomized and treated patients.
Sponsor's table in NDA Vol. 163, pp. 63

A total of 127 (5.6%) of the 2257 randomized and treated patients prematurely stopped study drug (See Table below). The overall rate of treatment discontinuation was similar for both treatment groups.

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=1128)	Enoxaparin 30 mg b.i.d. (N=1129)	Total (N=2257)
Patients who discontinued study drug prematurely	61 (5.4%)	66 (5.8%)	127 (5.6%)
Reason(s) for discontinuation[a]			
Lack of efficacy	4 (0.4%)	2 (0.2%)	6 (0.3%)
Reached endpoint – DVT	3 (0.3%)	2 (0.2%)	5 (0.2%)
Reached endpoint – PE	1 (0.1%)	0 (0.0%)	1 (0.0%)
AE/SAE[b]	33 (2.9%)	35 (3.1%)[c]	68 (3.0%)
Bleeding AE/SAE	14 (1.2%)	17 (1.5%)	31 (1.4%)
Suspicion of drug-induced decrease of platelet count	3 (0.3%)	0 (0.0%)	3 (0.1%)
Other AE/SAE	16 (1.4%)	18 (1.6%)	34 (1.5%)
Subject withdrawn consent	19 (1.7%)	16 (1.4%)	35 (1.6%)
Others	5 (0.4%)	13 (1.2%)	18 (0.8%)
Treatment stopped by physician	0 (0.0%)	5 (0.4%)	5 (0.2%)
Dosing mistakes	3 (0.3%)	5 (0.4%)	8 (0.4%)
Received other anticoagulants	1 (0.1%)	1 (0.1%)	2 (0.1%)
Allergy to contrast dye	0 (0.0%)	1 (0.1%)	1 (0.0%)
Sponsor excluded patient from study	0 (0.0%)	1 (0.1%)	1 (0.0%)
Epidural catheter	1 (0.1%)	0 (0.0%)	1 (0.0%)

a According to Investigator's judgment.
b Including AEs recorded before the first study drug injection (based on data collected in the 'end of treatment' form).
c Including 2 patients who discontinued due to AEs recorded before first study drug injection.
Reviewer's table based on Sponsor's table in NDA Vol. 163, pp. 63 and study EFC2442 Appendix 14.2.1.1.8

The majority of premature discontinuations of study drug were due to non-serious/serious AE. The number of patients who discontinued treatment due to bleeding AE/SAE similar was similar in the two groups.

Most cases of premature treatment discontinuation occurred before Day 5 in each treatment group.

No patients were lost to follow-up during the treatment period. A total of 3 patients in the Org31540/SR90107A group had no information on the final follow-up assessment form.

The randomization code was broken for 7 patients (2 in the Org31540/SR90107A group and 5 in the enoxaparin group). With the exception of one Org31540/SR90107A patient (death), all other code breaks were for technical/administrative reasons (principal investigator's discretion in another Org31540/SR90107A patient; epidural catheter being left in, incorrect opening of injector at 1st dose, missing morning dose on day 3, hospital nursing staff unblinded study medication, and inadvertent administration of one dose in enoxaparin patients).

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 following table summarizes the number (%) of patients who presented with such protocol deviations. The percentages of patients who were excluded from the primary efficacy analysis were similar for both treatment groups (30.2% in Org31540/SR90107A group vs. 29.4% in enoxaparin group). No VTE assessment up to day 11 was the main reason for exclusion in both treatment groups (16.8% in Org31540/SR90107A group and 16.1% in enoxaparin group) followed by non-evaluable venogram.

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

Deviation[a]	Org31540/SR90107A 2.5 mg o.d. (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)	Total (N=2257)
No surgery / Non-appropriate surgery	2 (0.2%)	1 (0.1%)	3 (0.1%)
Non-evaluable venogram up to Day 11	149 (13.2%)	149 (13.2%)	298 (13.2%)
No VTE assessment up to Day 11	190 (16.8%)	182 (16.1%)	372 (16.5%)
Total for exclusion from primary efficacy analysis	341 (30.2%)	332 (29.4%)	673 (29.8%)

[a] Patients were counted only once.
Sponsor's table in NDA Vol. 163, pp. 65

The detailed 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 = 1128)	Enoxaparin 30 mg b.i.d. (N = 1129)	Total (N =2257)
Non-evaluable VTE assessment up to day 11	**149 (13.2%)**	**149 (13.2%)**	**298 (13.2%)**
Both legs assessed-both inadequate	14 (1.2%)	15 (1.3%)	29 (1.3%)
Both legs assessed-operated leg inadequate	14 (1.2%)	18 (1.6%)	32 (1.4%)
Both legs assessed-non-operated leg inadequate	25 (2.2%)	27 (2.4%)	51 (2.3%)
Operated leg assessed only- negative	69 (6.1%)	63 (5.6%)	132 (5.8%)
Operated leg assessed only- inadequate	4 (0.4%)	4 (0.4%)	8 (0.4%)
Non-operated leg assessed only-negative	22 (2.0%)	20 (1.8%)	42 (1.9%)
Non-operated leg assessed only-inadequate	0 (0.0%)	0 (0.0%)	0 (0.0%)
Examination performed before day 5	1 (0.1%)	2 (0.2%)	3 (0.1%)
No VTE assessment up to day 11	**190 (16.8%)**	**182 (16.1%)**	**372 (16.5%)**
VTE assessment after day 11	8 (0.7%)	9 (0.8%)	17 (0.8%)
Reasons for no VTE assessment			
Failed venous access	77 (4.6%)	66 (3.6%)	143 (4.1%)
Subject refuse/withdrew consent	66 (3.4%)	62 (3.1%)	54 (3.2%)
AE/SAE/deaths	6 (0.5%)	5 (0.4%)	11 (0.5%)
Premature treatment discontinuation	3 (0.3%)	11 (1.0%)	14 (0.6%)
Uncooperative/"too ill" for the test	5 (0.4%)	3 (0.3%)	8 (0.4%)
Technical problems	2 (0.2%)	2 (0.2%)	4 (0.2%)
Suspicion of iodine allergy	4 (0.4%)	3 (0.3%)	7 (0.3%)
Increased creatinine	3 (0.3%)	0 (0.0%)	3 (0.1%)
Radiologist/Physician refused	3 (0.3%)	7 (0.6%)	10 (0.4%)
Normal US	5 (0.4%)	5 (0.4%)	10 (0.4%)
Positive US	0 (0.0%)	1 (0.1%)	1 (0.0%)
Symptom assessment only	5 (0.4%)	4 (0.4%)	9 (0.4%)
No reason mentioned	1 (0.1%)	0 (0.0%)	1 (0.0%)
Local but not central	2 (0.2%)	4 (0.4%)	6 (0.3%)
Total	**339 (30.1%)**	**331 (29.3%)**	**670 (29.7%)**

Reviewer's table based on NDA Study EFC2442, Appendix 14.2.1.3

The main reason for non-evaluable venogram was operated leg assessed only with negative finding that was similar between two treatment groups.

The main reasons for no VTE assessment up to day 11 in both treatment groups were failed venous access and subject refusal/withdrew consent. 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, 1 patient was identified as having been randomized with a treatment number already assigned to a previously randomized patient. This patient was considered not randomized and was excluded from all analyses.

The other randomization irregularities consisted of patients randomized out of order to compensate for an unused treatment (practice randomization calls, multiple calls for the same patient, premature calls, telephone clarity problem, and untreated patients). This involved 26 patients (13 in each treatment group). The involved patients experienced few events (Org31540/SR90107A: 1 VTE, 0 major bleeding; enoxaparin: 4 VTE, 0 major bleeding). These irregularities were 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. The most common deviation, which was observed with a similar frequency (2%) in both treatment groups, was receipt of less than 8 injections and not allowed concomitant therapy.

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=1128)	Enoxaparin 30 mg b.i.d. (N=1129)	Total (N=2257)
Meeting exclusion criteria based on current labeling for LMWH[a]	4 (0.4 %)	9 (0.8 %)	13 (0.6 %)
Less than 8 post-operative injections (of placebo or active drug)[b]	23 (2.0 %)	24 (2.1 %)	47 (2.1 %)
Not allowed concomitant therapy[c,d]	24 (2.1 %)	18 (1.6 %)	42 (1.9 %)
Qualifying VTE exam for primary efficacy analysis more than 2 calendar days after the last injection	10 (0.9 %)	3 (0.3 %)	13 (0.6 %)

LMWH = low molecular weight heparin a Patients with more than 1 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. 163, pp. 66

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 2257 randomized and treated patients, 1179 (52.2%) were female and 2116 (93.8%) were Caucasian. The mean age of patients was 65±13 years for both groups. The two treatment groups were similar with regard to demographic and surgical characteristics.

Summary of Demographic and Surgical Characteristics - All Treated Patients

Parameter		Org31540/SR90107A 2.5 mg o.d. (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)	Total (N=2257)
Age (years)	n	1128	1129	2257
	Median	67	67	67
	Mean	64.6	64.6	64.6
	SD	12.7	12.6	12.7
	Min - Max	18 - 92	19 - 91	18 - 92
Age [n (%)]	<65	490 (43.4%)	478 (42.3%)	968 (42.9%)
	[65,75[	353 (31.3%)	405 (35.9%)	758 (33.6%)
	≥75	285 (25.3%)	246 (21.8%)	531 (23.5%)
Height (cm)	n	1122	1125	2247
	Median	169	168	168
	Mean	169.2	168.4	168.8
	SD	10.5	10.5	10.5
	Min - Max	132 - 230	124 - 230	124 - 230
Weight (kg)	n	1128	1127	2255
	Median	81	80	80
	Mean	82.3	81.0	81.7
	SD	18.8	19.3	19.0
	Min - Max	36 - 169	35 - 226	35 - 226
BMI (kg/m²) [n (%)]	<30	749 (66.8%)	746 (66.4%)	1495 (66.6%)
	≥30	373 (33.2%)	378 (33.6%)	751 (33.4%)
	Missing	6	5	11
Gender [n (%)]	Male	556 (49.3%)	522 (46.2%)	1078 (47.8%)
	Female	572 (50.7%)	607 (53.8%)	1179 (52.2%)
Race [n (%)]	Caucasian	1059 (93.9%)	1057 (93.6%)	2116 (93.8%)
	Black	50 (4.4%)	46 (4.1%)	96 (4.3%)
	Asian/Oriental	4 (0.4%)	3 (0.3%)	7 (0.3%)
	Other race	15 (1.3%)	23 (2.0%)	38 (1.7%)
Type of surgery [n (%)][a]	Primary	948 (84.0%)	978 (86.6%)	1926 (85.3%)
	Revision	180 (16.0%)	151 (13.4%)	331 (14.7%)
Use of cement [n (%)][a]	Yes	577 (51.2%)	598 (53.0%)	1175 (52.1%)
	No	551 (48.8%)	530 (47.0%)	1081 (47.9%)
	Missing	0	1	1
Type of anaesthesia [n(%)][a]	General only	792 (70.2%)	815 (72.2%)	1607 (71.2%)
	Regional only	288 (25.5%)	263 (23.3%)	551 (24.4%)
	Combination	48 (4.3%)	51 (4.5%)	99 (4.4%)
Duration of surgery (hh:mm)[a]	n	1125	1128	2253
	Median	2:20	2:17	2:18
	Mean	2:29	2:27	2:28
	SD	0:57	0:57	0:57
	Min - Max			

[a] For all treated and operated patients (Org31540/SR90107A, N = 1126; enoxaparin, N = 1128).
Sponsor's table in NDA Vol. 163, pp. 68

As shown in table below, specific medical and surgical history was not significantly different between the two 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=1128)	Enoxaparin 30 mg b.i.d. (N=1129)	Total (N=2257)
Specific medical history			
VTE	52 (4.6%)	63 (5.6%)	115 (5.1%)
Stroke	25 (2.2%)	34 (3.0%)	59 (2.6%)
Myocardial infarction	65 (5.8%)	60 (5.3%)	125 (5.5%)
Cancer	151 (13.4%)	145 (12.8%)	296 (13.1%)
Orthopedic surgery within the previous 12 months			
Any surgery	134 (11.9%)	124 (11.0%)	258 (11.4%)
Hip replacement	78 (6.9%)	70 (6.2%)	148 (6.6%)
Knee replacement	18 (1.6%)	13 (1.2%)	31 (1.4%)
Other surgery	51 (4.5%)	46 (4.1%)	97 (4.3%)

Sponsor's table in NDA Vol. 163, pp. 69

The number (%) of patients who received medications with potential impact on hemostasis within 2 days prior to the day of first study drug injection (active or placebo) was similar for both treatment groups.

Primary efficacy population

The primary efficacy population was similar to the all treated patients population with respect to demographic and surgery characteristics (See Table below). In the primary efficacy population, the 2 treatment groups were also similar.

Summary of Demographic and Surgery Characteristics
-Primary Efficacy Population

Parameter		Org31540/SR90107A 2.5 mg o.d. (N=787)	Enoxaparin 30 mg b.i.d. (N=797)	TOTAL (N=1584)
Age (years)	N	787	797	1584
	Median	67	67	67
	Mean	65.0	65.1	65.1
	SD	12.4	12.4	12.4
	Min – Max	26 - 92	19 - 91	19 - 92
Age [n (%)]	<65	335 (42.6%)	319 (40.0%)	654 (41.3%)
	[65,75[	253 (32.1%)	303 (38.0%)	556 (35.1%)
	≥75	199 (25.3%)	175 (22.0%)	374 (23.6%)
Height (cm)	N	782	794	1576
	Median	169	168	168
	Mean	169.1	168.3	168.7
	SD	10.6	10.3	10.5
	Min – Max	137 - 230	139 - 230	137 - 230
Weight (kg)	n	787	796	1583
	Median	80	79	79
	Mean	81.4	80.1	80.7
	SD	18.2	19.1	18.7
	Min - Max	36 - 164	42 - 226	36 - 226
BMI (kg/m²) [n (%)]	<30	542 (69.3%)	541 (68.2%)	1083 (68.8%)
	≥30	240 (30.7%)	252 (31.8%)	492 (31.2%)
	Missing	5	4	9
Gender [n (%)]	Male	386 (49.0%)	375 (47.1%)	761 (48.0%)
	Female	401 (51.0%)	422 (52.9%)	823 (52.0%)
Race [n (%)]	Caucasian	748 (95.0%)	753 (94.5%)	1501 (94.8%)
	Black	22 (2.8%)	22 (2.8%)	44 (2.8%)
	Asian/Oriental	4 (0.5%)	3 (0.4%)	7 (0.4%)
	Other race	13 (1.7%)	19 (2.4%)	32 (2.0%)
Type of surgery [n (%)]	Primary	668 (84.9%)	691 (86.7%)	1359 (85.8%)
	Revision	119 (15.1%)	106 (13.3%)	225 (14.2%)
Use of cement [n(%)]	Yes	411 (52.2%)	441 (55.4%)	852 (53.8%)
	No	376 (47.8%)	355 (44.6%)	731 (46.2%)
	Missing	0	1	1
Type of anaesthesia [n (%)]	General only	529 (67.2%)	576 (72.3%)	1105 (69.8%)
	Regional only	220 (28.0%)	183 (23.0%)	403 (25.4%)
	Combination	38 (4.8%)	38 (4.8%)	76 (4.8%)
Duration of surgery (hh:mm)	n	786	797	1583
	Median	2:19	2:15	2:15
	Mean	2:28	2:25	2:26
	SD	0:57	0:59	0:58
	Min - Max	[redacted]	[redacted]	[redacted]

Sponsor's table in NDA Vol. 163, pp. 70

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 2 treatment groups were also similar in specific medical and surgical history (See 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=787)	Enoxaparin 30 mg b.i.d. (N=797)	Total (N=1584)
Specific medical history			
VTE	40 (5.1%)	50 (6.3%)	90 (5.7%)
Stroke	18 (2.3%)	25 (3.1%)	43 (2.7%)
Myocardial infarction	49 (6.2%)	47 (5.9%)	96 (6.1%)
Cancer	106 (13.5%)	109 (13.7%)	215 (13.6%)
Orthopedic surgery within the previous 12 months			
Any surgery	99 (12.6%)	84 (10.5%)	183 (11.6%)
Hip replacement	56 (7.1%)	51 (6.4%)	107 (6.8%)
Knee replacement	14 (1.8%)	8 (1.0%)	22 (1.4%)
Other surgery	38 (4.8%)	28 (3.5%)	66 (4.2%)

Sponsor's table in NDA Vol. 163, pp. 71

Extent of exposure

All treated patients

The mean ±SD time between the end of surgery and the first active injection was 7 ±2 hours and 20 ±3 hours in the Org31540/SR90107A and enoxaparin groups, respectively. Most patients in both treatment groups received active study drug at least up to Day 7 ±2, as required by the protocol (See Table below). In accordance with the difference in dosing regimens between the 2 study drugs, the number of active injections differed between the 2 groups.

Summary of Active Treatment - All Treated Patients

	Org31540/SR90107A 2.5 mg o.d. (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)
Number of active injections		
N	1128	1126
Median	7	11
Mean (SD)	6.6 (1.5)	10.6 (3.0)
Min - Max	[redacted]	[redacted]
Last day of active treatment [n (%)][a]		
< Day 5	36 (3.2%)	36 (3.2%)
Day 5 to Day 9	1084 (96.1%)	1077 (95.6%)
> Day 9	8 (0.7%)	13 (1.2%)

[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. 163, pp. 72

Primary efficacy population

The mean ±SD time between the end of surgery and the first active injection was 7 ±2 hours and 20 ±3 hours in the Org31540/SR90107A and enoxaparin groups, respectively.

Overall, the extent of exposure to active study drug for the primary efficacy population, as shown in the table below, was similar to that observed for the all treated patients population.

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

	Org31540/SR90107A 2.5 mg o.d. (N=787)	Enoxaparin 30 mg b.i.d. (N=797)
Number of active injections		
N	787	797
Median	7	11
Mean (SD)	6.6 (1.3)	10.6 (2.8)
Min – Max	[redacted]	[redacted]
Last day of active treatment [n (%)][a]		
< Day 5	12 (1.5%)	11 (1.4%)
Day 5 to Day 9	772 (98.1%)	778 (97.6%)
> Day 9	3 (0.4%)	8 (1.0%)

[a] Day 1 = Day of surgery
Sponsor's table in NDA Vol. 163, pp. 73

Measurements of treatment compliance

As previously shown, the percentage of patients with less than 8 postoperative injections was low and similar between the 2 treatment groups (2.0% in the Org31540/ SR90107A group and 2.1% in the enoxaparin group). In the primary efficacy population, 7 (0.9%) patients who received less than 8 postoperative injections up to the qualifying VTE examination in the Org31540/SR90107A group as compared to 6 (0.8 %) patients in the Exnoxaparin group, besides temporary or permanent discontinuation due to AE or lack of efficacy. Overall, the treatment compliance was similar between the treatment groups.

Four patients in each treatment group received an injection from another kit at some point during the study. No VTE or major bleeding was recorded in these patients except for 1 patient in the Org31540/SR90107A group who had an adjudicated symptomatic VTE on Day 8 after 8 doses of Org31540/SR90107A.

Concomitant medication

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 following table. The use of not allowed or discouraged concomitant medications was similar for both treatment groups.

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

Medication	Org31540/SR90107A 2.5 mg o.d. (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)
Not allowed medication[a]	24 (2.1%)	18 (1.6%)
Heparin (UFH,LMWH)/heparinoid[b]	15 (1.3%)	11 (1.0%)
Anti-Platelet drug other than ASA	0 (0.0%)	1 (0.1%)
Vitamin K antagonist	11 (1.0%)	7 (0.6%)
Discouraged medication[a]	187 (16.6%)	179 (15.9%)
NSAID	156 (13.8%)	143 (12.7%)
ASA	42 (3.7%)	50 (4.4%)

[a] From the day of 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. 163, pp. 75

As shown in the table below, the use of physical therapy during the treatment period was similar for both treatment groups.

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

Physical Therapy	Org31540/SR90107A 2.5 mg o.d. (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)
Elastic stockings only	3 (0.3%)	8 (0.7%)
Physiotherapy only	153 (13.6%)	165 (14.6%)
Both methods	969 (85.9%)	956 (84.7%)

Sponsor's table in NDA Vol. 163, pp. 75

Primary efficacy population

The following tables shows the number of patients who received not allowed or discouraged medications, and physical prophylactic therapy during the treatment period for the primary efficacy population.

As observed in the all treated patients population, the use of not allowed or discouraged concomitant medications as well as physical therapy was similar for both treatment groups in the primary efficacy population.

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

Medication	Org31540/SR90107A 2.5 mg o.d. (N=787)	Enoxaparin 30 mg b.i.d. (N=797)
Not allowed medication[a]	13 (1.7%)	11 (1.4%)
Heparin(UFH,LMWH)/heparinoid[b]	7 (0.9%)	5 (0.6%)
Anti-Platelet drug other than ASA	0 (0.0%)	1 (0.1%)
Vitamin K antagonist	8 (1.0%)	5 (0.6%)
Discouraged medication[a]	107 (13.6%)	108 (13.6%)
NSAID	96 (12.2%)	90 (11.3%)
ASA	13 (1.7%)	27 (3.4%)

[a] From the day of 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. 163, pp. 76

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

Physical Therapy	Org31540/SR90107A 2.5 mg o.d. (N=787)	Enoxaparin 30 mg b.i.d. (N=797)
Elastic stockings only	1 (0.1%)	2 (0.3%)
Physiotherapy only	110 (14.0%)	121 (15.2%)
Both methods	673 (85.5%)	674 (84.6%)

Sponsor's table in NDA Vol. 163, pp. 76

Duration of study participation

The mean duration of participation in the study was similar for both treatment groups for all treated patients (See Table below).

Summary of Duration of Study Participation - All Treated Patients

Duration of Study Participation[a] (Days)	Org31540/SR90107A 2.5 mg o.d. (N=1128)	Enoxaparin 30 mg b.i.d. (N=1129)
Median	43	43
Mean	44.9	44.5
SD	13.7	10.6
Min - Max	[redacted]	[redacted]

a From the first injection (active drug or placebo) to the last visit.
Sponsor's table in NDA Vol. 163, pp. 77

The mean duration of participation in the study was similar between treatment groups and was similar 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=787)	Enoxaparin 30 mg b.i.d. (N=797)
Duration of study participation[a] (in days)	Median	43	43
	Mean	45.0	44.1
	SD	14.2	9.1
	Min - Max	[redacted]	[redacted]
Duration between surgery and qualifying VTE examination (days)	Median	7	7
	Mean	6.9	6.8
	SD	1.4	1.4
	Min - Max	[redacted]	[redacted]

[a] From the first injection (active drug or placebo) to the last visit.
Sponsor's table in NDA Vol. 163, pp. 65

Most patients underwent the qualifying VTE examination between Day 5 and Day11. Only 1 patient (Org31540/SR90107A group) had a qualifying VTE examination before Day 5 (this patient experienced an adjudicated symptomatic proximal DVT on Day 4).

Patients follow-up

Similar follow-up data were observed in both groups for the all treated patients population and primary efficacy population (See Tables below).

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=1128)	Enoxaparin 30 mg b.i.d. (N=1129)
Location at discharge[a]		
Home	636 (56.4%)	642 (56.9%)
Other location than home	492 (43.6%)	487 (43.1%)
- Rehabilitation unit/facility	461 (40.9%)	471 (41.7%)
- Other location	31 (2.7%)	16 (1.4%)
Living situation at follow-up assessment[b]		
Home	1007 (90.0%)	1045 (93.0%)
Home with professional assistance	53 (4.7%)	31 (2.8%)
Rest home	7 (0.6%)	1 (0.1%)
Nursing home	5 (0.4%)	9 (0.8%)
Rehabilitation facility	16 (1.4%)	22 (2.0%)
Other	31 (2.8%)	16 (1.4%)

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. 163, pp. 78

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=787)	Enoxaparin 30 mg b.i.d. (N=797)
Location at discharge[a]		
Home	458 (58.2%)	461 (57.8%)
Other location than home	329 (41.8%)	336 (42.2%)
- Rehabilitation unit/facility	313 (39.8%)	326 (40.9%)
- Other location	16 (2.0%)	10 (1.3%)
Living situation at follow-up assessment[b]		
Home	706 (90.2%)	735 (92.6%)
Home with professional assistance	38 (4.9%)	24 (3.0%)
Rest home	5 (0.6%)	1 (0.1%)
Nursing home	4 (0.5%)	6 (0.8%)
Rehabilitation facility	11 (1.4%)	16 (2.0%)
Other	19 (2.4%)	12 (1.5%)

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. 163, pp. 79

Efficacy Evaluation

Analysis of efficacy

Primary efficacy analysis

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

Results for the primary efficacy endpoint are presented in the table below. The VTE rate up to Day 11 was numerically lower in the Org31540/SR90107A group than that in the enoxaparin group (6.1% versus 8.3%) but the difference did not reach statistical significance (p=0.099). However, the incidence of DVT was significantly lower in the Org31540/SR90107A than that in the enoxaparin group (5.6% vs. 8.3%, p=0.047). There were five non-fatal PE in the Org31540/SR90107A group and one fatal PE in the enoxaparin group. The difference in terms of PE was not statistically significant (p= 0.122).

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 = 787)	Enoxaparin 30 mg b.i.d. (N = 797)	Difference Org31540/SR90107A minus Enoxaparin (%)	Fisher's Exact Test (p)
VTE	48 6.1%	66 8.3%	-2.2%	0.099
DVT	44 (5.6%)	65 (8.2%)	-2.6	0.047
PE	5 (0.6%)	1 (0.1%)	0.5	0.122
Fatal PE	0 (0.0%)	1 (0.1%)	-0.1	
Non-Fatal PE	5 (0.6%)	0 (0.0%)	0.6	

Note: One patient had both DVT and non-fatal PE in Org31540/SR90107A group
p-value for PE was obtained by FDA Statistical Reviewer Dr. Milton C. Fan, Ph.D.
Reviewer's table based on NDA Vol. 163, pp. 80-84 and efficacy datasets

This reviewer further analyzed mortality data from this study. There were 11 deaths (6 in Org31540/SR90107A group and 5 in enoxaparin group) in the study including 4 deaths which occurred up to Day 11 (See table below). Of 11 deaths, three fatal PE were identified (1 in the Org31540/SR90107A group and 2 in the enoxaparin group). There were 4 autopsies (all in the Org31540/SR90107A group) including the case with fatal PE.

Deaths from all causes and PE in the study

	Org31540/SR90107A 2.5 mg o.d. (N = 1128)	Enoxaparin 40 mg o.d. (N = 1129)
Death up to day 11		
All causes	3 (0.3%)	1 (0.1%)
Fatal PE	0 (0.0%)	1 (0.1%)
Death up to day 49		
All causes	6 (0.5%)	3 (0.3%)
Fatal PE	1 (0.1%)	2 (0.2%)
Death after day 49 (up to day 61)		
All deaths	0 (0.0%)	2 (0.2%)
Fatal PE	0 (0.0%)	0 (0.0%)
Total		
All deaths	6 (0.5%)	5 (0.4%)
Fatal PE	1 (0.1%)	2 (0.2%)

Reviewer's table based on NDA study EFC2442 Appendix 14.2.4.2.3 and submitted datasets

For 5 deaths other than PE without autopsy, the SAEs that lead to death were MI in two Org31540/SR90107A patients, malignancy, pneumonia and circulatory failure in 3 enoxaparin patients.

A total of 4 mandatory venographies (1 in the Org31540/SR90107A group and 3 in the enoxaparin group) were performed after Day 11 and were consequently disqualified from the efficacy analysis. The venogram in the Org31540/SR90107A patient was not evaluable, and the venograms in the enoxaparin patients did not reveal any DVTs according to adjudication.

Secondary efficacy analyses

Adjudicated DVT

The number (%) of patients with adjudicated DVT, adjudicated proximal DVT and adjudicated distal only DVT up to Day 11 are summarized by treatment group in the following table. There was a statistically significantly lower rate of any DVT (p=0.047) and distal DVT only (4.3% vs. 6.8%, p=0.037) in the Org31540/SR90107A group than in the enoxaparin group. There was no difference in any proximal DVT between the two treatment groups.

Number (%) of Patients With Adjudicated Examination for Assessment of DVT up to Day 11 - Efficacy Evaluable Patients

	Org31540/SR90107A 2.5 mg o.d.	Enoxaparin 40 mg o.d.	Difference Org31540/SR90107A minus Enoxaparin (%)	Fisher's Exact Test Result (p)
Any DVT	44/784 5.6%	65/796 8.2%	-2.6%	0.047
Any proximal DVT	14/816 1.7%	10/830 1.2%	0.5%	0.42
Distal DVT only	34/796 4.3%	54/800 6.8%	-2.5%	0.037

Reviewer's table based on NDA Vol. 163, pp. 81-2. P-value for distal DVT only was calculated by FDA Statistical Reviewer Dr. Milton C. Fan, Ph.D.

The DVT rates by side of examination (operative/non-operative leg) between the two treatments are presented in the following table. There was a slightly higher incidence of DVT observed in operated leg than in non-operated leg in both groups except for distal DVT only in the Org31540/SR90107A group.

Number (%) and [95% Confidence Intervals] of Patients With Adjudicated Examination for Assessment of DVT up to Day 11 According to Location of DVT - Efficacy Evaluable Patients

Location of DVT	Org31540/SR90107A 2.5 mg o.d.	Enoxaparin 30 mg b.i.d.
Any DVT		
Either side	44 / 784 (5.6)	65 / 796 (8.2)
	[4.1;7.5]	[6.4;10.3]
Operative leg	27 / 876 (3.1)	43 / 883 (4.9)
	[2.0;4.5]	[3.5;6.5]
Non-operative leg	24 / 819 (2.9)	29 / 829 (3.5)
	[1.9;4.3]	[2.4;5.0]
Both sides	7 / 911 (0.8)	7 / 916 (0.8)
	[0.3;1.6]	[0.3;1.6]
Any proximal DVT		
Either side	14 / 816 (1.7)	10 / 830 (1.2)
	[0.9;2.9]	[0.6;2.2]
Operative leg	10 / 898 (1.1)	9 / 908 (1.0)
	[0.5;2.0]	[0.5;1.9]
Non-operative leg	4 / 841 (0.5)	2 / 857 (0.2)
	[0.1;1.2]	[0.0;0.8]
Both sides	0 / 923 (0.0)	1 / 935 (0.1)
	[0.0 ;0.4]	[0.0;0.6]
Distal DVT only		
Either side	34 / 796 (4.3)	54 / 800 (6.8)
	[3.0;5.9]	[5.1;8.7]
Operative leg	17 / 885 (1.9)	34 / 889 (3.8)
	[1.1;3.1]	[2.7;5.3]
Non-operative leg	20 / 831 (2.4)	26 / 833 (3.1)
	[1.5;3.7]	[2.0;4.5]
Both sides	3 / 919 (0.3)	6 / 922 (0.7)
	[0.1;1.0]	[0.2;1.4]

NOTE: Efficacy evaluable patients were defined as all randomized and treated patients who underwent the appropriate surgery and had an adjudicated evaluable DVT assessment at the considered site (entire leg/proximal/ distal) and side (operative/non-operative).
Sponsor's table in NDA Vol. 163, pp. 81

Curative treatment initiated after VTE assessment and prolonged prophylaxis of VTE
The number (%) of patients who had antithrombotic curative treatment initiated based on Investigator assessment of VTE up to Day 11 in the all treated population and in the primary efficacy population is summarized in the tables below.

Consistent with the result in the primary endpoint, there was a statistically non-significant reduction in the rate of patients who initiated antithrombotic curative treatment following VTE assessment in the Org31540/SR90107A treated patients compared to the enoxaparin treated patients for both the all treated patients population and the primary efficacy population.

Number (%) of Treated Patients Who had Antithrombotic Curative Treatment Initiated Based on Investigator Assessment of VTE up to Day 11 -All Treated Patients Who Underwent the Appropriate Surgery With VTE Assessment up to Day 11

Curative treatment[a]	Org31540/SR90107A 2.5 mg o.d. (N [b]=952)	Enoxaparin 30 mg b.i.d. (N [b]=963)
All patients with curative treatment	49 (5.1%)	68 (7.1%)
Heparin (UFH, LMWH)/heparinoids	40 (4.2%)	54 (5.6%)
Vitamin K antagonist without heparin (UFH, LMWH)/heparinoids	5 (0.5%)	6 (0.6%)
Other than Heparin or Vitamin K antagonist	3 (0.3%)	5 (0.5%)
No medication reported	1 (0.1%)	3 (0.3%)

a Patients were only counted once.

b Number of patients with any VTE assessment up to Day 11.
Sponsor's table in NDA Vol. 163, pp. 82

Number (%) of Patients Who had Antithrombotic Curative Treatment Initiated Following the Qualifying VTE Assessment - Primary Efficacy Population

Curative treatment[a]	Org31540/SR90107A 2.5 mg o.d. (N=787)	Enoxaparin 30 mg b.i.d. (N=797)
All patients with curative treatment	45 (5.7%)	63 (7.9%)
Heparin (UFH, LMWH)/heparinoids	37 (4.7%)	49 (6.1%)
Vitamin K antagonist without heparin (UFH, LMWH)/heparinoids	4 (0.5%)	6 (0.8%)
Other than Heparin or Vitamin K antagonist	3 (0.4%)	5 (0.6%)
No medication reported	1 (0.1%)	3 (0.4%)

[a] Patients were only counted once.
Sponsor's table in NDA Vol. 163, pp. 83

During the follow-up period, prolonged prophylaxis of VTE (mainly LMWH and oral anticoagulants) was administered to 27.0% (200/742) of patients in the Org31540/SR90107A group, and 25.2% (185/734) of patients in the enoxaparin group for the primary efficacy population who did not receive curative treatment.

Adjudicated symptomatic events

The following table summarizes the number (%) of patients with adjudicated symptomatic VTE, symptomatic DVT, non-fatal PE and fatal PE by study period (up to Day 11 and up to Day 49) and treatment group.

Number (%) of Patients With Adjudicated Symptomatic VTE up to Day 11 and up to Day 49 - All Treated Patients Who Underwent the Appropriate Surgery

Study Period	Patients with Symptomatic Adjudicated		Org31540/SR90107A 2.5 mg o.d. (N=1126)	Enoxaparin 30 mg b.i.d. (N=1128)	Fisher's Exact p value
up to Day 11	VTE	n (%)	10 (0.9%)	1 (0.1%)	0.0062
		95% CI	[0.4;1.6]	[0.0;0.5]	
	DVT	n (%)	5 (0.4%)	0 (0.0%)	
	Non-fatal PE	n (%)	5 (0.4%)	0 (0.0%)	
	Fatal PE	n (%)	0 (0.0%)	1 (0.1%)	
up to Day 49	VTE	n (%)	29 (2.6%)	13 (1.2%)	0.013
		95% CI	[1.7;3.7]	[0.6;2.0]	
	DVT	n (%)	18 (1.6%)	10 (0.9%)	
	Non-fatal PE	n (%)	11 (1.0%)	2 (0.2%)	
	Fatal PE	n (%)	1 (0.1%)	2 (0.2%)	

Reviewer's table based on Sponsor's table in NDA Vol. 163, pp. 84

The rates of symptomatic VTE up to Day 11 and up to day 49 were statistically significantly higher in the Org31540/SR90107A group as compared to the enoxaparin group (p=0.006 and 0.013, respectively). Of the 11 patients with VTE up to day 11, there was only 1 case of adjudicated fatal PE, which was in the enoxaparin group. For 2 of 5 patients with adjudicated nonfatal PE in the Org31540/SR90107A group, PE was ruled out locally by V/Q scan (later adjudicated positive), and these two patients were not treated for curative treatment with uneventful outcome. One of them continued Org31540/SR90107A for 8 days (symptoms developed on day 5). The other patient who was ajudicated positive for PE had a high probability V/Q scan but a normal spiral CT based on the ajudication. One patient developed symptoms of DVT 3 days after completing the treatment with a negative venogram at the end-of-treatment. In 2 cases, asymptomatic DVT was diagnosed by the investigator on the mandatory venogram with onset of symptoms while the patients were already on curative treatment. Of the 11 cases, 6 patients developed new symptoms that triggered initiation of treatment.

Symptomatic VTEs recorded up to Day 49 were also summarized in the form of cumulative event rate curve, using Kaplan-Meier method. The overall study results are driven by the symptomatic VTEs occurring during the treatment period.

Exploratory analysis for primary efficacy endpoint

Subgroup Analysis

The following table summarizes the number (%) of patients with adjudicated VTE up to Day 11 by covariate and treatment group.

There were inconsistent results among the 3 countries for primary efficacy endpoint. The incidence of VTE up to day 11 was numerically lower in US (5.0% vs. 8.0%, p=0.07) and Australia (4.7% vs. 10.8%, p=0.09) but higher in Canada (8.8% vs. 7.5%, p=0.61) in Org31540/SR90107A group as compared to enoxaparin group. The interaction between

treatment and country was significant at 0.20 significance level (p=0.134, Breslow-Day method, obtained by FDA Statistical Reviewer Dr. Milton C. Fan, Ph.D.). Further analysis performed by Dr. Fan using logistic regression model adjusting for the interaction, the resulting p-value for treatment was 0.069 which still failed to reach statistical significance but was smaller than observed unadjusted p-value of 0.09.

There was no significant heterogeneity of treatment effect across subgroups except for patients with previous VTE and with creatinine less than 0.9 mg/dL (median) before surgery. For patients with previous VTE, the incidence of VTE was much higher in the Org31540/SR90107A group than in the enoxaparin group. For patients with creatinine less than 0.9 mg/dL before surgery, the incidence of VTE was much lower in the Org31540/SR90107A group than in the enoxaparin group.

Number (%) of Patients With Adjudicated VTE Up to Day 11 According to Various Baseline Covariates - Primary Efficacy Population

Covariate[a]	Org31540/SR90107A 2.5 mg o.d. (N=787)				Enoxaparin 30 mg b.i.d. (N=797)			
		VTE				VTE		
	N	n	%	95% CI	N	n	%	95% CI
Country								
United States of America	422	21	5.0	[3.1;7.5]	436	35	8.0	[5.7;11.0]
Canada	238	21	8.8	[5.5;13.2]	241	18	7.5	[4.5;11.5]
Australia	127	6	4.7	[1.8;10.0]	120	13	10.8	[5.9;17.8]
Gender								
Male	386	25	6.5	[4.2;9.4]	375	28	7.5	[5.0;10.6]
Female	401	23	5.7	[3.7;8.5]	422	38	9.0	[6.5;12.2]
Race								
Caucasian	748	46	6.1	[4.5;8.1]	753	64	8.5	[6.6;10.7]
Black	22	1	4.5	[0.1;22.8]	22	2	9.1	[1.1;29.2]
Asian	4	0	0.0	[0.0;60.2]	3	0	0.0	[0.0;70.8]
Other races	13	1	7.7	[0.2;36.0]	19	0	0.0	[0.0;17.6]
Age								
<65 years	335	17	5.1	[3.0;8.0]	319	21	6.6	[4.1;9.9]
[65 - 75[years	253	16	6.3	[3.7;10.1]	303	31	10.2	[7.1;14.2]
≥75 years	199	15	7.5	[4.3;12.1]	175	14	8.0	[4.4;13.1]
Obesity								
BMI <30 kg/m^2	542	34	6.3	[4.4;8.7]	541	41	7.6	[5.5;10.1]
BMI ≥30 kg/m^2	240	14	5.8	[3.2;9.6]	252	25	9.9	[6.5;14.3]
Type of anesthesia								
Regional only	220	17	7.7	[4.6;12.1]	183	20	10.9	[6.8;16.4]
Other	567	31	5.5	[3.7;7.7]	614	46	7.5	[5.5;9.9]
Type of surgery								
Primary	668	41	6.1	[4.4;8.2]	691	54	7.8	[5.9;10.1]
Revision	119	7	5.9	[2.4;11.7]	106	12	11.3	[6.0;18.9]
Use of cement								
Yes	411	27	6.6	[4.4;9.4]	441	43	9.8	[7.1;12.9]
No	376	21	5.6	[3.5;8.4]	355	23	6.5	[4.2;9.6]
Duration of surgery[b]								
< median	364	25	6.9	[4.5;10.0]	381	30	7.9	[5.4;11.0]

≥ median	422	23	5.5	[3.5;8.1]	416	36	8.7	[6.1;11.8]
Previous VTE								
Yes	40	7	17.5	[7.3;32.8]	50	6	12.0	[4.5;24.3]
No	747	41	5.5	[4.0;7.4]	747	60	8.0	[6.2;10.2]
Creatinine before surgery[c]								
< median	302	18	6.0	[3.6;9.3]	324	37	11.4	[8.2;15.4]
≥ median	448	30	6.7	[4.6;9.4]	438	27	6.2	[4.1;8.8]

a Per covariate, only non missing observations were taken into account.
b Median for duration of surgery was 2:15:00.
c Median for creatinine before surgery was 0.9 mg/dL.
Sponsor's table in NDA Vol. 163, pp. 88-9

Sensitivity Analysis

There were 339 (30.1%) patients in the Org31540/SR90107A group and 331 (29.3%) patients in the enoxaparin group who had non-evaluable/no VTE assessment for primary efficacy endpoint in the study for all treated patients with appropriate surgery population. These patients were considered as missing patients in the study.

The following tables present the results of the best case, realistic case, and worst case scenario analyses. These results were consistent with those observed for the primary efficacy analysis.

Sensitivity Analysis on the Primary Efficacy Endpoint - All Treated Patients Who Underwent the Appropriate Surgery

Scenario	Org31540/SR90107A 2.5 mg o.d. (N=1126)	Enoxaparin 30 mg b.i.d. (N=1128)	Difference and 95%CI	Fishers Exact p-Value
Best case scenario	48 (4.3%)	66 (5.9%)	-1.6% [-4.04 ; 0.41]	0.102
Realistic scenario	77 (6.8%)	93 (8.2%)	-1.4% [-4.21 ; 0.96]	0.231
Worst case scenario	387 (34.4%)	397 (35.2%)	-0.8% [-5.05 ; 3.17]	0.691

*p-values were obtained by FDA Statistical Reviewer Dr. Milton C. Fan, Ph.D.
Sponsor's table in NDA Vol. 163, pp. 93

Sensitivity Analysis on the Primary Efficacy Endpoint - All randomized patients

Scenario	Org31540/SR90107A 2.5 mg o.d. (N=1126)	Enoxaparin 30 mg b.i.d. (N=1128)	Difference and 95%CI	Fishers Exact p-Value
Best case scenario	48 (4.3%)	66 (5.9%)	-1.6% [-4.04 ; 0.41]	0.085
Realistic scenario	77 (6.8%)	93 (8.2%)	-1.4% [-4.21 ; 0.96]	0.206
Worst case scenario	387 (34.4%)	397 (35.2%)	-0.8% [-5.05 ; 3.17]	0.793

*p-values were obtained by FDA Statistical Reviewer Dr. Milton C. Fan, Ph.D.
Sponsor's table in NDA Amendment No.4, Attachment No. 2, submitted on 5/1/2001

Drug-drug and drug-disease interactions

The primary efficacy endpoint was further analyzed according to specific concomitant medications, i.e., not allowed or discouraged medications as well as medications which were reported to have an interaction with heparin, according to US PDR 1999.

The following table presents the VTE rate up to Day 11 according to these types of medications. No apparent interactions were found with the concomitant medications examined.

Number (%) of Patients With Adjudicated VTE up to Day 11 According to Selected Concomitant Medications - Primary Efficacy Population

WHO Preferred Drug Name / Concomitant Intake	Org31540/SR90107A 2.5 mg o.d. (N=787)				Enoxaparin 30 mg b.i.d. (N=797)			
		VTE				VTE		
	N	n	%	95% CI	N	n	%	95% CI
Heparin(UFH, LMWH)/heparinoid								
With	7	2	28.6	[3.7;71.0]	5	1	20.0	[0.5;71.6]
Without	780	46	5.9	[4.3;7.8]	792	65	8.2	[6.4;10.3]
Anti-Platelet drug other than ASA								
With	0	0	NA	NA	1	0	0.0	[0.0;97.5]
Without	787	48	6.1	[4.5;8.0]	796	66	8.3	[6.5;10.4]
Vitamin K antagonist								
With	8	3	37.5	[8.5;75.5]	5	0	0.0	[0.0;52.2]
Without	779	45	5.8	[4.2;7.7]	792	66	8.3	[6.5;10.5]
NSAID								
With	96	4	4.2	[1.1;10.3]	90	7	7.8	[3.2;15.4]
Without	691	44	6.4	[4.7;8.5]	707	59	8.3	[6.4;10.6]
ASA								
With	13	2	15.4	[1.9;45.4]	27	3	11.1	[2.4;29.2]
Without	774	46	5.9	[4.4;7.8]	770	63	8.2	[6.3;10.3]
Penicillins								
With	18	0	0.0	[0.0;18.5]	23	3	13.0	[2.8;33.6]
Without	769	48	6.2	[4.6;8.2]	774	63	8.1	[6.3;10.3]
Cephalosporins								
With	683	44	6.4	[4.7;8.6]	693	62	8.9	[6.9;11.3]
Without	104	4	3.8	[1.1;9.6]	104	4	3.8	[1.1;9.6]
Anti-histamines and phenothiazines								
With	345	21	6.1	[3.8;9.2]	343	29	8.5	[5.7;11.9]
Without	442	27	6.1	[4.1;8.8]	454	37	8.1	[5.8;11.1]
Cardiac-glycosides								
With	10	0	0.0	[0.0;30.8]	16	1	6.3	[0.2;30.2]
Without	777	48	6.2	[4.6;8.1]	781	65	8.3	[6.5;10.5]
Macrolide antibiotics								
With	2	0	0.0	[0.0;84.2]	5	0	0.0	[0.0;52.2]
Without	785	48	6.1	[4.5;8.0]	792	66	8.3	[6.5;10.5]
Tetracyclines -								
With	1	0	0.0	[0.0;97.5]	2	0	0.0	[0.0;84.2]
Without	786	48	6.1	[4.5;8.0]	795	66	8.3	[6.5;10.4]
Other antibiotics								
With	42	2	4.8	[0.6;16.2]	47	5	10.6	[3.5;23.1]
Without	745	46	6.2	[4.6;8.2]	750	61	8.1	[6.3;10.3]
Vitamin C								
With	185	6	3.2	[1.2;6.9]	190	19	10.0	[6.1;15.2]
Without	602	42	7.0	[5.1;9.3]	607	47	7.7	[5.7;10.2]

Note: As per protocol, forbidden medications did not take into account heparin flush up to 200 IU/day.
Sponsor's table in NDA Vol. 163, pp. 94-5

As regards drug-disease interactions, only the effects of obesity (BMI) and previous VTE were analyzed. No other drug-disease interaction was examined.

Reviewer's Summary

Study EFC2442 was a multicenter, randomized, double-blind, parallel-group study comparing Org31540/SR90107A 2.5 mg once daily SC (n=1138) to enoxaparin 30 mg every 12 hours SC (n=1137) in 2275 patients undergoing either an elective primary total hip replacement surgery, or a revision of hip replacement surgery.

Administration of drugs was started post-operatively in all patients in both treatment groups. Org31540/SR90107A was started 7±2 hours as compared to 20±3 hours for enoxaparin after surgical closure. The average treatment duration was 7±2 days.

The primary efficacy endpoint was a composite endpoint of VTE up to Day 11 that included adjudicated venographically positive DVT and adjudicated symptomatic non-fatal or fatal PE. Among 2275 randomized patients in the study, 670 (29.7%) patients had missing primary efficacy endpoint due to non-evaluable venography/no VTE assessment up to day 11. The percentage of patients missing efficacy data were similar in the two treatment groups [339 (30.1%) in the Org31540/SR90107A group and 331 (29.3%) in the enoxaparin group]. The missing rate associated with venography procedure in this study was comparable to other studies in patients undergoing elective hip replacement surgery (21-29% in studies in NDA 20-164/000, Lovenox, FDA Medical Officer's Review, page 63 and 102; 31% in studies in NDA 20-287/S-008, Fragmin, FDA Medical Officer's Review, page 15).

Study EFC2442 failed to demonstrate superiority of Org31540/SR90107A 2.5 mg once daily SC over enoxaparin 30 mg every 12 hours SC for primary efficacy endpoint of VTE up to Day 11 in patients undergoing primary elective total hip replacement, or a revision of component(s) of a THR. However, the study showed that patients treated with Org31540/SR90107A 2.5 mg once daily SC had a numerically lower incidence of VTE up to day 11 than those treated with enoxaparin 30 mg every 12 hours SC (6.1% vs. 8.3%, p=0.099). In addition, there was a significantly lower incidence of any DVT (5.6% vs. 8.3%, p=0.047) and distal DVT only (4.3% vs. 6.8%, p=0.037) in the Org31540/SR901 treatment group as compared to the enoxaparin treatment group. There was no difference in the incidence of PE and proximal DVT up to day 11 between the two treatment groups. For symptomatic VTE, there was a statistically significantly higher incidence in Org31540/SR901 group as compared to that in enoxaparin group up to day 11 (p=0.006) and up to day 49 (p=0.013).

Results were inconsistent among 3 countries for the primary efficacy endpoint. The incidence of VTE up to day 11 was numerically lower in US (5.0% vs. 8.0%, p=0.07) and Australia (4.7% vs. 10.8%, p=0.09) but higher in Canada (8.8% vs. 7.5%, p=0.61) in Org31540/SR90107A group as compared to enoxaparin group. After adjusting for the interaction between treatment and country, the p-value for treatment was 0.069, which still failed to reach statistical significance but was smaller than observed unadjusted p-value of 0.09.

There was no significant heterogeneity of treatment effect across subgroups except for patients with previous VTE and with creatinine less than 0.9 mg/dL (median) before surgery. For patient with previous VTE, the incidence of VTE was much higher in the Org31540/SR90107A group than in the enoxaparin group. For patients with creatinine less than 0.9 mg/dL before surgery, the incidence of VTE was much lower in the Org31540/SR90107A group than in the enoxaparin group.

Trial DRI2643

Title of the Study

A multicenter, randomized, parallel, double-blind, dose ranging study of subcutaneous Org31540/SR90107A with an assessor blind, comparative control group of subcutaneous LMWH in the prevention of deep vein thrombosis after elective total hip replacement.

Study Period

November 1, 1996 to March 3, 1998

Investigators and Study Centers

The study was carried out by investigators at 70 centers in the United States (50), Canada (10) and Australia (10).

Study Objective

The primary objective of the study was to determine the optimum dose of a once-daily subcutaneous injection of Org31540/SR90107A starting postoperatively and continuing for a minimum of 5 days for venous thromboembolic event (VTE) prophylaxis as compared with a twice daily subcutaneous injection of a low molecular weight heparin (LMWH) in patients undergoing elective total hip replacement.

Overall Study Design

This study was a Phase II, multicenter, randomized, parallel, dose ranging study of Org31540/SR90107A (0.75mg, 1.5mg, 3.0mg, 6.0mg, and 8.0mg) once daily SC post-operatively with comparative control group of enoxaparin 30mg twice daily SC post-operatively in patients undergoing elective total hip replacement. The Org31540/SR90107A dose groups were double-blind but the comparative control group of enoxaparin was assessor blind only.

The total duration of the treatment for each patient was a minimum of 5 treatment days and until the final venogram was obtained up to a maximum of 10 days (Day 1 to Day 10). The follow-up duration was 30±2 days (Day 11 to Day 40±2).

Study Population

Inclusion criteria

- Undergoing elective primary hip replacement or a revision of a primary procedure
- Written informed consent
- Males or females of non-childbearing potential (post-menopausal greater than one year or with hysterectomy or bilateral tubal ligation for at least six months prior to enrollment)
- 18 years of age or older

Exclusion criteria

- Any major orthopedic surgery less than 12 months prior to enrollment amended to any major orthopedic surgery during the 3 months prior to enrollment in order to harmonize the exclusion criteria to those in a concurrent total knee replacement study (Protocol Amendment no. 4 dated March 26, 1997)
- Body weight less than 45 kg or more than 135 kg
- Known congenital or acquired bleeding tendency, or bleeding tendency revealed by one or more of the following preoperative tests: thrombocytes < 130 $x10^9$/L, prothrombin time (PT) < 65% of control or international normalized ratio (INR) > 1.3, and ratio activated partial thromboplastin time (aPTT)/control > 1.2
- Serum creatinine level above the upper limit of normal range amended to serum creatinine level above 1.6 mg/dL (Protocol Amendment no. 1 dated Oct. 20, 1996)
- Systolic blood pressure (SBP) > 180 mmHg or diastolic blood pressure (DBP) > 110 mmHg
- Previous (i.e., < three months) ischemic or hemorrhagic cerebral stroke or myocardial infarction (MI)
- Participation in another clinical investigational drug study or clinical study evaluating methods for DVT prophylaxis within the last 90 days
- Any contraindication to heparin (standard or LMWH) or heparinoids
- Treatment during a period of one week before the start of the study with the following medications: heparin (Standard or LMWH) or heparinoids, antiplatelet drugs (e.g., ticlopidine, aspirin), oral anticoagulants (vitamin K antagonists), fibrinolytic agents, dextrans, and antiplatelet antibodies
- Known progressive malignant disease
- Known drug-addictive disorder or alcoholism
- Confirmed Pulmonary Embolism (PE) or DVT within the last 12 months
- Patients with a known recent (≤ 4 weeks) or present history of gastrointestinal bleeding or peptic ulcer
- Known sensitivity to iodine or contrast dyes
- Unusual difficulties in applying epidural or spinal anesthesia, e.g., more than two attempts or a bloody tap (Protocol Amendment no. 2 dated Dec. 03, 1996). This exclusion criterion was added following the occurrence of an epidural hematoma in a patient for whom general anesthesia was administered after five unsuccessful punctures for an epidural anesthesia.

Removal of patients from therapy or assessment

Study treatment was prematurely stopped if:

- DVT or PE occurred before the scheduled end of the treatment period
- A major bleeding complication occurred
- A severe thrombocytopenia occurred
- The investigator considered it necessary in the interest of the patient
- The patient wished to terminate his/her participation in the study

Study Treatments

Org31540/SR90107A was administered as a once daily subcutaneous injection for a minimum of 5 treatment days and until the final venogram was obtained up to a maximum of 10 days. The tested doses were 0.75 mg, 1.5 mg, 3.0 mg, 6.0 mg and 8.0 mg. Org31540/SR90107A was provided as an isotonic 10 mg/mL injectable solution of the decasodium salt (conversion factor for acid = 1.146) in 0.15 mL, 0.30 mL, 0.60 mL and 0.80 mL prefilled syringes.
Enoxaparin (Lovenox®) was administered as a 30 mg twice daily subcutaneous injection. Enoxaparin was provided in 0.3 mL (30 mg) prefilled syringes.

Efficacy Endpoints

Primary endpoint was the incidence of patients with adjudicated mandatory venogram positive for DVT and/or symptomatic adjudicated PE.

Secondary endpoint was the incidence of each VTE (proximal and/or distal DVT and PE) taken separately.

All venograms and lung scans performed during the study were evaluated blindly by independent experts of the Central Independent Adjudication Committee (CIAC). The criteria for DVT and PE used in this study were the same as in Studies 63118 and EFC2442.

Safety Assessment

The incidences of major bleeding and minor bleeding were evaluated blindly by the CIAC.

Major bleeding was defined as:

- bleeding at critical site, i.e., intracranial, retroperitoneal, intraocular, spinal or pericardial
- bleeding index > 2. The bleeding index was calculated within 48 hours of bleed as follows: units of RBC transfused + pre-bleed hemoglobin value (g/dL) – post-bleed hemoglobin value(g/dL)
- required medical intervention or surgical intervention at the operative site

Other safety variables included adverse events (AEs), clinical examination, and laboratory and coagulation parameters.

Statistical Methods

Sample size determination
A total of 140 patients per Org31540/SR90107A group was estimated to obtain a 95 % CI of ±1.5 mg for a dose that would be associated with a VTE incidence of 7.5 %. In addition, 140 patients per group were estimated to allow detection of a difference between the lowest Org31540/SR90107A tested dose and the recommended dose(s) with sufficient power.

The sample size of the enoxaparin group was calculated to allow demonstration that the Org31540/SR90107A selected dose was at least as effective as enoxaparin (unilateral equivalence, VTE incidence of 7.5 % with Org31540/SR90107A and of 12 % with enoxaparin, non-inferiority margin = 3 %).

Stopping rule
The criteria used to terminate a dose group were following:
- The lower limit of the 95% CI for the VTE rate was >15%.
- The lower limit of the 95% CI for the major bleeding event rate was >3%.

Analyzed populations
All treated patients: all randomized and treated (at least one dose) patients.

pITT population: subpopulation of all treated patients including patients who underwent hip replacement surgery with an adjudicated evaluable bilateral (or positive unilateral) scheduled venogram performed between Day 5 and Day 10 (or before Day 5 with DVT) or a symptomatic adjudicated PE but no more than 24 hours after last dose.

Per protocol population: subpopulation of pITT population excluding patients with major protocol deviations as regards study treatment (less than 5 days of treatment and first injection not on time), and forbidden concomitant treatment or physical methods.

Efficacy analyses
The primary analysis was a logistic regression among Org31540/SR90107A doses based on the per protocol population. Pairwise comparisons between the lowest Org31540/SR90107A dose (0.75 mg) and the other completed doses (1.5 mg, 3.0 mg) using Fisher's exact tests as well as 95 % exact CI on differences and relative risks were performed as secondary analyses. Pairwise comparisons between enoxaparin group and the three completed Org31540/SR90107A groups using Fisher's exact tests as well as 95% exact CI on differences and relative risks were also performed as secondary analyses. Similar analyses were performed for the pITT population.

Safety analyses

Bleeding events are presented according to two study periods, i.e., the treatment period (from Day 1 to 2 calendar days after the last study drug injection) and the follow-up period (from 3 calendar days after the last study drug injection to Day 42).

All AEs were summarized by organ class and preferred term according to two study periods, i.e., the treatment period and the follow-up period. Related AEs (i.e. AEs with a relation to the study drug reported as likely or unknown by the investigators) were also summarized by organ class and preferred term on these two periods.

Protocol Amendments

The protocol was amended 4 times and modified twice.
Amendment no. 1: October 20, 1996, before the first randomization
Amendment no. 2: December 03, 1996
Amendment no. 3: January 29, 1997
Amendment no. 4: March 26, 1997
Modification no. 1: December 1, 1997
Modification no. 2: February 17, 1998

The main changes resulting from amendments and modification requests are summarized below:

- Increase in expected number of study centers and redefinition of block size (Amendment no. 3).
- Modification of three exclusion criteria (Amendment no. 1, 2 and 4).
- Termination of 6.0 mg and 8.0 mg treatment assignment (Modification Request no. 1)
- Exclusion of in-dwelling intrathecal and epidural catheters during treatment (Amendment no. 3).

Study Results

Disposition of patients

A total of 950 patients were randomized into one of the five Org31540/SR90107A groups or the enoxaparin group. Among them, 17 did not receive any treatment (8 in Org31540/SR90107A groups and 9 in the enoxaparin group). The main reasons for not being treated were inclusion/exclusion criteria not met (6 patients), informed consent not signed or withdrawn (4 patients), and technical problem (3 patients).

A total of 933 patients received at least one dose of study drug. The number of treated patients is presented by country and dose group in the table below.

Number (%) of treated patients by country and dose group

Country (number of centers)	Org31540/SR90107A					Enoxaparin	Total
	0.75 mg	1.5 mg	3.0 mg	6.0 mg	8.0 mg		
Australia (10)	23	24	23	7	3	33	113 (12.1)
Canada (10)	33	35	34	11	9	50	172 (18.4)
United States (50)	128	129	120	54	40	177	648 (69.5)
Total (70)	184 (19.7)	188 (20.2)	177 (19.0)	72 (7.7)	52 (5.6)	260 (27.9)	933 (100.0)

Sponsor's table in NDA Vol. 2, pp. 54

The 8.0 mg and 6.0 mg dose groups enrollment were terminated early based on the pre-defined stopping rule for major bleeding events (>3%). The decision to terminate the 8.0 mg dose group was made on July 8, 1997 after six out of 38 treated patients (15.8 %, 95% CI: [6.0 % - 31.3 %]) were adjudicated as having experienced a major bleeding event. The decision to terminate the 6.0 mg dose group was made on August 01, 1997 when nine out of 53 treated patients (17.0 %, 95% CI: [8.1 % - 29.8 %]) were adjudicated as having experienced a major bleeding event.

A total of 94 (10.1 %) patients discontinued study drug with higher incidences in the 6.0 mg (16.7 %) and 8.0 mg (25.0 %) groups than in the four other groups (between 7.3 % in the 3.0 mg group and 10.4 % in the enoxaparin group). In the 6.0 mg, 8.0 mg and enoxaparin groups, study drug was prematurely discontinued mainly because of adverse events (13.9% and 16.7%, respectively).

The disposition of patients is presented by group in the Sponsor's Figure.

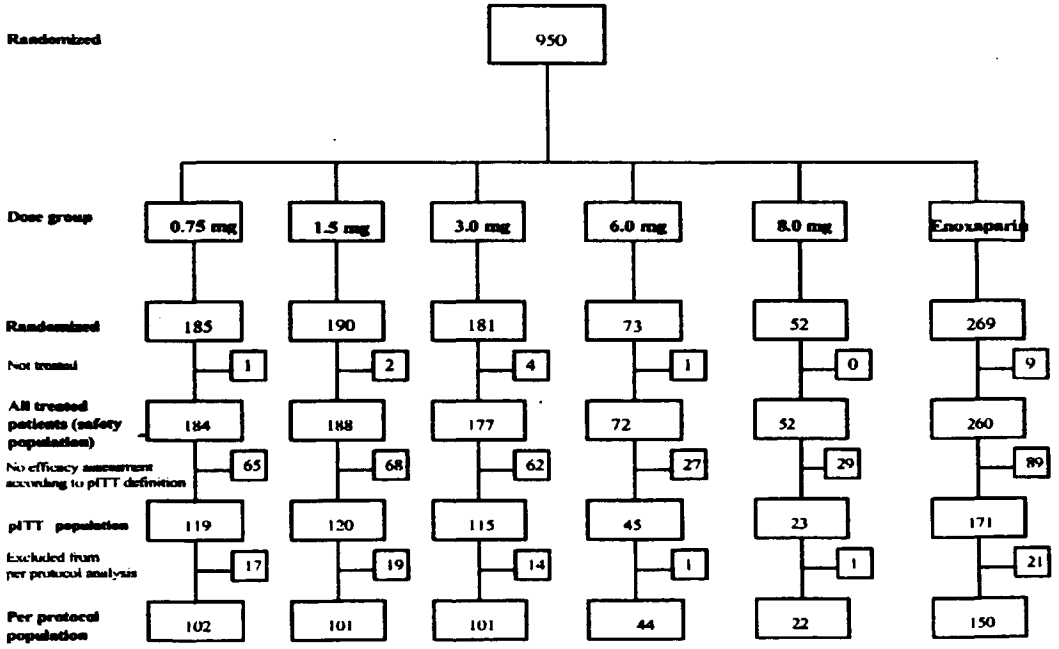


Figure (6.3) 1 - Number of patients by treatment group and population

Sponsor's figure in NDA Vol. 2, pp. 61

Protocol Deviations

The incidences of patients with protocol deviations leading to their exclusion from the pITT and per protocol populations are provided by reason for exclusion and dose group in the table below.

Number (%) of patients per dose group with reasons for exclusion from pITT and per protocol populations - All treated patients

Population Deviation		Org31540/SR90107A					Enoxaparin (N=260)	Total (N=933)
		0.75 mg (N=184)	1.5 mg (N=188)	3.0 mg (N=177)	6.0 mg (N=72)	8.0 mg (N=52)		
PITT	No DVT assessment[1]	23 (12.5)	28 (14.9)	23 (13.0)	14 (19.4)	8 (15.4)	37 (14.2)	133 (14.3)
	Non-evaluable efficacy Assessment[1,2]	27 (14.7)	28 (14.9)	30 (16.9)	8 (11.1)	10 (19.2)	44 (16.9)	147 (15.8)
	Evaluable venography outside the window[1,3]	15 (8.2)	12 (6.4)	9 (5.1)	5 (6.9)	11 (21.2)	8 (3.1)	60 (6.4)
	Total for exclusion from pITT	65 (35.3)	68 (36.2)	62 (35.0)	27 (37.5)	29 (55.8)	89 (34.2)	340 (36.4)
Per protocol	Less than 5 days of treatment[4]	11 (6.0)	6 (3.2)	5 (2.8)	0 (0.0)	7 (13.5)	7 (2.7)	36 (3.9)
	First injection not on time[5]	14 (7.6)	10 (5.3)	6 (3.4)	1 (1.4)	1 (1.9)	16 (6.2)	48 (5.1)
	Forbidden concomitant Medication	9 (4.9)	10 (5.3)	12 (6.8)	0 (0.0)	4 (7.7)	16 (6.2)	51 (5.5)
	Other mechanical device than elastic stockings[6]	5 (2.7)	5 (2.7)	3 (1.7)	0 (0.0)	0 (0.0)	4 (1.5)	17 (1.8)
	Total for exclusion from per protocol[7]	82 (44.6)	87 (46.3)	76 (42.9)	28 (38.9)	30 (57.7)	110 (42.3)	413 (44.3)

1: with no PE confirmed 24 hours after last dose of study drug
2: i.e., venogram inadequate for interpretation or unilateral venogram unless a DVT was adjudicated
3: before Day 5 (without DVT), after Day 10 or more than 24 hours after last dose
4: with no VTE confirmed
5: less than 4 hours or more than 8 hours following closure of surgical incision for Org31540/SR90107A or not within 12 to 24 hours after closure of the surgical incision for enoxaparin
6: if used after the first study drug administration
7: patients presenting with several protocol deviations were counted once only
Sponsor's table in NDA Vol. 2, pp. 56

The percentages of patients presenting with a protocol deviation leading to exclusion from the pITT population were similar for the 0.75 mg, 1.5 mg, 3.0 mg, 6.0 mg and enoxaparin groups (34.2 % to 37.5 %). The percentage was higher in the 8.0 mg group (55.8 %). This unbalance between the 8.0 mg group and the five other groups was mainly

due to evaluable venographies performed within the [Day 5 - Day 10] interval but more than 24 hours after the last study drug injection (17.3 % versus 2.8 % to 6.5 %). This difference could be explained by the high incidence of treatment discontinuation due to bleeding events in the 8.0 mg group. In case of such bleeding, the venography could not easily be performed within the 24 hours following the last dose administration.

The reason for stopping study drug before receiving 5 days of Org31540/SR90107A 8.0 mg was mainly due to bleeding event occurrence.

Other protocol deviations

Other protocol deviations included randomization irregularities (15/933, 9 in Org31540/SR90107A, 6 in enoxaparin), use of forbidden previous medication [4.8 %, ASA was the most prescribed drug (4.4 %)], platelet count <130 G/L before inclusion (2.8 %), PT with INR>1.3 before inclusion (2.6%), missing first dose in Org31540/SR90107A groups (2.8%) due to failure to uncap auto-injector, temporary interruptions of study treatment (9.2% in enoxaparin group and 2.3% in Org31540/SR90107A groups), study treatment after the venography (6.5 in enoxaparin group and 3.1% in Org31540/SR90107A groups). These irregularities were considered by the Sponsor of no significance to the overall results of the study.

Demographic and baseline characteristics

All treated patients

Demographic data and characteristics of surgery are presented by dose group for all treated patients in the following table. No statistically significant differences were observed among the six groups for any of the demographic and surgery characteristics. While no statistically significant differences were observed for median or mean age, a slightly greater incidence of patients over 65 years of age was observed in the 8 mg group.

Table (6.4.1) 1 - Summary of demographic and surgery characteristics - All treated patients

Parameter		Org31540/SR90107A 0.75 mg (N=184)	1.5 mg (N=188)	3.0 mg (N=177)	6.0 mg (N=72)	8.0 mg (N=52)	Enoxaparin (N=260)	Total (N=933)
Age (in years)	N	184	188	177	72	52	260	933
	Median	66	67	66	67	72	66	67
	Mean	64.4	65.1	63.8	65.4	66.2	64.5	64.6
	S.D.	12.1	12.1	11.2	10.2	14.1	12.0	11.9
	Min	18	37	32	41	32	26	18
	Max	89	91	85	84	92	86	92
Age n (%)	< 65 years	78 (42.4)	78 (41.5)	83 (46.9)	31 (43.1)	12 (23.1)	107 (41.2)	389 (41.7)
	≥65 years	106 (57.6)	110 (58.5)	94 (53.1)	41 (56.9)	40 (76.9)	153 (58.8)	544 (58.3)
Height (in cm)	N	182	185	172	71	52	255	917
	Median	170	169	170	171	170	170	170
	Mean	170.1	169.1	169.8	170.2	169.5	170.4	169.9
	S.D.	11.0	10.0	11.1	10.4	11.5	10.0	10.5
	Min	145	147	140	150	140	146	140
	Max	197	191	193	198	201	193	201
Weight (in kg)	N	183	186	175	72	52	259	927
	Median	80	78	80	78	80	81	80
	Mean	81.8	80.1	81.3	81.4	79.8	82.2	81.3
	S.D.	17.6	17.8	17.5	18.9	18.3	17.4	17.7
	Min	45	45	46	49	46	45	45
	Max	127	135	132	127	118	134	135
Gender n (%)	Male	102 (55.4)	100 (53.2)	97 (54.8)	37 (51.4)	27 (51.9)	137 (52.7)	500 (53.6)
	Female	82 (44.6)	88 (46.8)	80 (45.2)	35 (48.6)	25 (48.1)	123 (47.3)	433 (46.4)
Race n (%)	Caucasian	164 (89.1)	172 (91.5)	164 (92.7)	68 (94.4)	48 (92.3)	236 (90.8)	852 (91.3)
	Black	17 (9.2)	11 (5.9)	13 (7.3)	3 (4.2)	4 (7.7)	17 (6.5)	65 (7.0)
	Oriental/Asian	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	3 (0.3)
	Other race	3 (1.6)	4 (2.1)	0 (0.0)	1 (1.4)	0 (0.0)	5 (1.9)	13 (1.4)
Type of surgery n (%)	Primary	157 (85.3)	157 (83.5)	147 (83.5)	61 (84.7)	42 (80.8)	225 (86.5)	789 (84.7)
	Revision	27 (14.7)	31 (16.5)	29 (16.5)	11 (15.3)	10 (19.2)	35 (13.5)	143 (15.3)
Use of cemented prosthesis n (%)	No	90 (48.9)	81 (43.1)	79 (44.6)	35 (48.6)	17 (32.7)	109 (41.9)	411 (44.1)
	Yes	94 (51.1)	107 (56.9)	98 (55.4)	37 (51.4)	35 (67.3)	151 (58.1)	522 (55.9)
Type of anesthesia n (%)	General only	129 (70.1)	124 (66.0)	124 (70.1)	56 (77.8)	35 (67.3)	184 (70.8)	652 (69.9)
	Local only	40 (21.7)	46 (24.5)	39 (22.0)	13 (18.1)	14 (26.9)	56 (21.5)	208 (22.3)
	Mixed	15 (8.2)	18 (9.6)	14 (7.9)	3 (4.2)	3 (5.8)	20 (7.7)	73 (7.8)
Duration of surgery (h: min)	N	184	188	176	72	52	259	931
	Median	2:15	2:30	2:20	2:30	2:34	2:21	2:25
	Mean	2:31	2:35	2:36	2:41	2:37	2:31	2:34
	S.D.	1:01	0:52	0:59	1:03	0:46	0:51	0:55
	Min	[redacted]						
	Max							

Sponsor's table in NDA Vol. 2, pp. 63

The treated population consisted of a population with a majority of males (53.6 %), mainly of Caucasian origin (91.3 %), with a mean age of 64.6 ± 11.9 years. The patients received mainly general anesthesia (77.7 %). The most common procedure performed was a cemented prosthesis (55.9 %) for patients undergoing primary hip replacement (84.7 %). The majority of the treated patients (84.1 %) had hip arthrosis.

The most frequent risk factors for VTE (at study start or in the past) were intake of estrogen, cancer, obesity, varicose veins, arterial or venous thromboembolic problems, and smoking habits. A total of 2.0 % of patients had cancer present at study start. No statistically significant differences were observed among the six groups for any of these risk factors.

Per protocol patients

Demographic data and characteristics of surgery are presented by dose group for the per protocol population in the following table. There were no relevant differences between the per protocol and the pITT population.

Table (6.4.3) 1 - Summary of demographic and surgery characteristics - Per protocol patients

Parameter		Org31540/SR90107A 0.75 mg (N=102)	1.5 mg (N=101)	3.0 mg (N=101)	6.0 mg (N=44)	8.0 mg (N=22)	Enoxaparin (N=150)	Total (N=520)
Age (in years)	N	102	101	101	44	22	150	520
	Median	66	67	67	67	72	67	67
	Mean	64.7	64.5	63.7	65.8	69.6	64.6	64.7
	S.D.	11.5	12.8	11.6	9.9	11.8	12.2	11.9
	Min	18	37	37	44	32	26	18
	Max	89	91	85	84	92	85	92
Age n (%)	< 65 years	46 (45.1)	44 (43.6)	46 (45.5)	17 (38.6)	3 (13.6)	59 (39.3)	215 (41.3)
	≥65 years	56 (54.9)	57 (56.4)	55 (54.5)	27 (61.4)	19 (86.4)	91 (60.7)	305 (58.7)
Height (in cm)	N	101	99	99	44	22	146	511
	Median	170	168	170	169	172	170	170
	Mean	170.3	169.0	171.2	168.5	172.3	170.4	170.2
	S.D.	11.4	10.0	10.8	9.3	11.6	9.5	10.3
	Min	145	149	146	150	150	150	145
	Max	197	191	193	185	201	193	201
Weight (in kg)	N	101	99	100	44	22	149	515
	Median	80	77	81	76	87	80	80
	Mean	82.4	79.9	81.2	78.0	83.9	80.8	80.9
	S.D.	18.0	18.4	16.8	13.9	18.4	16.4	17.1
	Min	45	45	46	55	48	50	45
	Max	127	135	121	115	111	132	135
Gender n (%)	Male	58 (56.9)	52 (51.5)	61 (60.4)	19 (43.2)	12 (54.5)	74 (49.3)	276 (53.1)
	Female	44 (43.1)	49 (48.5)	40 (39.6)	25 (56.8)	10 (45.5)	76 (50.7)	244 (46.9)
Race n (%)	Caucasian	96 (94.1)	89 (88.1)	93 (92.1)	43 (97.7)	22 (100.0)	138 (92.0)	481 (92.5)
	Black	5 (4.9)	8 (7.9)	8 (7.9)	1 (2.3)	0 (0.0)	7 (4.7)	29 (5.6)
	Oriental/Asian	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	2 (0.4)
	Other race	1 (1.0)	3 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.7)	8 (1.5)
Type of surgery n (%)	Primary	90 (88.2)	88 (87.1)	85 (84.2)	34 (77.3)	17 (77.3)	129 (86.0)	443 (85.2)
	Revision	12 (11.8)	13 (12.9)	16 (15.8)	10 (22.7)	5 (22.7)	21 (14.0)	77 (14.8)
Use of cemented prothesis n (%)	No	48 (47.1)	38 (37.6)	42 (41.6)	22 (50.0)	4 (18.2)	59 (39.3)	213 (41.0)
	Yes	54 (52.9)	63 (62.4)	59 (58.4)	22 (50.0)	18 (81.8)	91 (60.7)	307 (59.0)
Type of anesthesia n(%)	General only	72 (70.6)	62 (61.4)	73 (72.3)	37 (84.1)	13 (59.1)	102 (68.0)	359 (69.0)
	Local only	23 (22.5)	31 (30.7)	24 (23.8)	6 (13.6)	8 (36.4)	37 (24.7)	129 (24.8)
	Mixed	7 (6.9)	8 (7.9)	4 (4.0)	1 (2.3)	1 (4.5)	11 (7.3)	32 (6.2)
Duration of surgery (h: min)	N	102	101	101	44	22	150	520
	Median	2:15	2:31	2:25	2:32	2:40	2:20	2:25
	Mean	2:26	2:37	2:35	2:50	2:43	2:33	2:35
	S.D.	0:51	0:49	0:53	1:14	0:55	0:55	0:55
	Min							
	Max							

Sponsor's table in NDA Vol. 2, pp. 65

No statistically significant differences were observed among the six groups for any of the risk factors for VTE (Table below). Only 1.9 % of patients had cancer present at the start of the study. The risk factors reported as "others" included hypertension, diabetes, osteoarthritis, hip replacement, etc. No relevant modifications were observed for any of these risk factors in comparison with all treated patients.

Risk factors for VTE - Per protocol patients

Risk factors	Org31540/SR90107A					Enoxaparin (N=150)	Total (N=520)
	0.75 mg (N=102)	1.5 mg (N=101)	3.0 mg (N=101)	6.0 mg (N=44)	8.0 mg (N=22)		
	n (%[a])	n (%[a])	n (%[a])	n (%[a])	n (%[a])	n (%[a])	n (%[a])
Smoking Habit	36 (35.3)	46 (45.5)	47 (46.5)	14 (31.8)	8 (36.4)	55 (36.7)	206 (39.6)
Intake of estrogen	18 (17.6)	16 (15.8)	12 (11.9)	9 (20.5)	4 (18.2)	32 (21.3)	91 (17.5)
All cancer	15 (14.7)	9 (8.9)	16 (15.8)	9 (20.5)	5 (22.7)	21 (14.0)	75 (14.4)
Cancer at study start	4 (3.9)	1 (1.0)	2 (2.0)	0	0	3 (2.0)	10 (1.9)
Obesity[b]	17 (16.7)	15 (14.9)	8 (7.9)	6 (13.6)	4 (18.2)	11 (7.3)	61 (11.7)
Varicose veins	17 (16.7)	14 (13.9)	11 (10.9)	8 (18.2)	1 (4.5)	10 (6.7)	61 (11.7)
Arterial or Venous Thromboembolic problems	11 (10.8)	7 (6.9)	12 (11.9)	6 (13.6)	2 (9.1)	17 (11.3)	55 (10.6)
Rheumatoid Arthritis	3 (2.9)	6 (5.9)	2 (2.0)	4 (9.1)	1 (4.5)	8 (5.3)	24 (4.6)
Severe Heart Failure	2 (2.0)	0	0	0	0	0	2 (0.4)
Others	5 (4.9)	2 (2.0)	5 (5.0)	3 (6.8)	1 (4.5)	2 (1.3)	18 (3.5)

a: percentages are computed with total non-missing answers
b: investigator's judgment
Sponsor's table in NDA Vol. 2, pp. 66

Extent of exposure

All treated patients

The extent of exposure (number of days from first injection to last injection) is summarized by dose group in the table below. No differences were observed among the six groups.

Extent of exposure (days) by dose group - All treated patients

Extent of exposure (number of days)	Org31540/SR90107A					Enoxaparin
	0.75 mg o.d.	1.5 mg o.d.	3.0 mg o.d.	6.0 mg o.d.	8.0 mg o.d.	30 mg b.i.d.
	(N = 184)	(N = 188)	(N = 177)	(N = 72)	(N = 52)	(N = 260)
Median	6	7	6	7	7	6
Mean (S.D.)	6.5 (1.8)	6.7 (1.8)	6.6 (1.8)	6.6 (2.1)	6.2 (2.1)	6.0 (1.8)
Min - Max						

o.d.: once daily, b.i.d.: twice a day
Sponsor's table in NDA Vol. 2, pp. 67

The mean duration between the end of surgery and the first injection was 5.6-6.0 hours for the five Org31540/SR90107A groups and 19 hours for enoxaparin.

Per protocol patients

As was the case for the all-treated population, no differences in the extent of exposure (in day) until efficacy assessment were observed among the six treatment groups in the per protocol population (See Table below).

Extent of exposure (in day) by dose group until efficacy assessment -Per protocol patients

Extent of exposure (number of days)	Org31540/SR90107A					Enoxaparin 30 mg b.i.d. (N = 150)
	0.75 mg o.d.	1.5 mg o.d.	3.0 mg o.d.	6.0 mg o.d.	8.0 mg o.d.	
	(N = 102)	(N = 101)	(N = 101)	(N = 44)	(N = 22)	
Median	7	7	6	7	7	6
Mean (S.D.)	6.9 (1.5)	7.1 (1.5)	6.7 (1.5)	7.1 (1.6)	6.8 (1.4)	6.0 (1.5)
Min - Max						

o.d.: once daily, b.i.d.: twice a day
Sponsor's table in NDA Vol. 2, pp. 68

Concomitant medications

Concomitant antithrombotic drugs were administered to a greater percentage of patients in the enoxaparin group (21.9 %) than in the five Org31540/SR90107A groups (from 5.8 % in the 8.0 mg group to 13.6 % in the 0.75 mg group). The difference may be due to the fact that extended prophylaxis of VTE was started in the evening of the same day as last morning injection for patients included in the enoxaparin group whereas it was started the day after for the majority of patients included in the Org31540/SR90107A groups.

The use of discouraged concomitant medications (i.e., NSAID) was slightly higher in the 8.0 mg and enoxaparin groups (28.8 % and 28.5 %, respectively) than in the four other groups (from 18.1 % in the 6.0 mg group to 22.8 % in the 0.75 mg group). The most common indication was postoperative pain.

During the follow-up period, a slightly greater percentage of patients was treated with an antithrombotic drug (vitamin K antagonist or heparin class) in the 0.75 mg (39.1 %), 1.5 mg (35.6 %), 3.0 mg (35.0 %) and enoxaparin (34.6 %) groups than in the 6.0 mg (27.8 %) and 8.0 mg (28.8 %) groups. The incidences of patients receiving anti-anemic preparations ranged from 6.8 % (3.0 mg group) to 15.4 % (8.0 mg group) for the Org31540/SR90107A groups and was 8.8 % for the enoxaparin group.

Elastic stockings were the most common physical method used for prophylaxis of DVT (97.5 % of all patients) and were used for a period greater than 5 days by the majority of patients (70.5%). Elevation of the foot was also used for a period greater than 5 days for the majority of patients in the six groups (66%). The majority of patients were mobilized on Day 2 (51.2%). There was no significant difference in the percentage of patients using physical methods among all six groups.

The same trends for concomitant medication and physical method were observed for the per protocol population as observed for all treated population.

Efficacy Evaluation

Primary endpoint

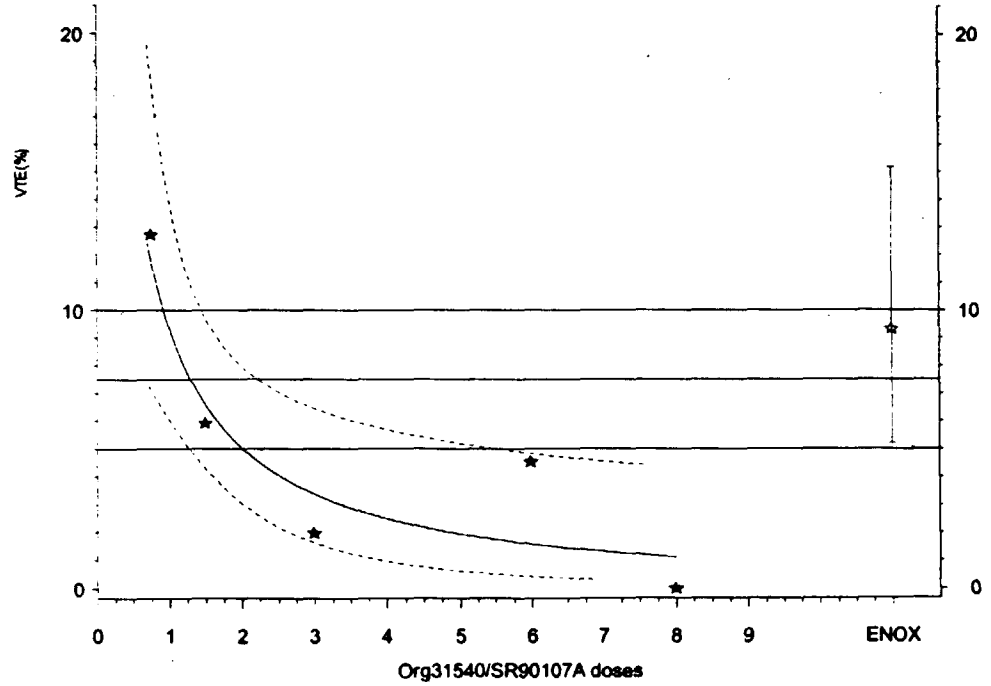
The incidences of patients with VTE and the 95 % CIs are presented by dose group for the per protocol population in Table below.

Number (%) of patients with VTE - Per protocol patients

VTE	Org31540/SR90107A					Enoxaparin (N=150)
	0.75 mg (N=102)	1.5 mg (N=101)	3.0 mg (N=101)	6.0 mg (N=44)	8.0 mg (N=22)	
n (%)	13 (12.7)	6 (5.9)	2 (2.0)	2 (4.5)	0 (0.0)	14 (9.3)
95 % CI	[6.96; 20.81]	[2.21; 12.48]	[0.24; 6.97]	[0.56; 15.47]	[0; 15.44]	[5.2; 15.16]

One outcome event in both the 1.5 mg and 6.0 mg groups occurred in patients included in center 12 who did not receive study drug
Sponsor's table in NDA Vol. 2, pp. 73

The incidence of VTE was fitted across all Org31540/SR90107A doses using a logit model (See Figure below). The incidence of VTE decreased with the increase of the Org31540/SR90107A doses (p = 0.003).



★: observed incidence for Org31540/SR90107A groups, and probit estimation with 95 % CI fiducial limit
☆: observed incidence for enoxaparin group and 95 % CI
Ref: Appendix 13.2.2.1.2.3.1

Figure (7.1.1.1) 1 - Plot of the incidence of patients with VTE per Org31540/SR90107A dose - Per protocol patients

Sponsor's figure in NDA Vol. 2, pp. 74

In the pairwise comparison between the completed groups, the results showed a statistically significant lower incidence of VTE in the 3.0 mg dose group as compared to the enoxaparin group (p=0.019) and the 0.75 mg dose group (p=0.005).

The incidences of patients with VTE and the 95 % CIs are presented by dose for the pITT population in the table below.

Number (%) of patients with VTE - pITT patients

Total VTE	Org31540/SR90107A					Enoxaparin (N=171)
	0.75 mg (N=119)	1.5 mg (N=120)	3.0 mg (N=115)	6.0 mg (N=45)	8.0 mg (N=23)	
n (%)	14 (11.8)	8 (6.7)	2 (1.7)	2 (4.4)	0 (0.0)	16 (9.4)
95 % CI	[6.58; 18.95]	[2.92; 12.71]	[0.21; 6.14]	[0.54; 15.15]	[0; 14.82]	[5.44; 14.75]

One outcome event in both the 1.5 mg and 6.0 mg groups occurred in patients included in center 12 who did not receive study drug
Sponsor's table in NDA Vol. 2, pp. 75

As for the per protocol population analysis, a statistically significant dose-dependent effect was observed for Org31540/SR90107A (p = 0.0024).

The pairwise comparison also showed a statistically significant lower incidence of VTE in the 3.0 mg dose group as compared to enoxaparin group (p=0.011) and the 0.75 mg group (p=0.003).

Secondary efficacy endpoints

Per protocol patients

The incidences of patients with total DVT, proximal DVT and distal DVT and the corresponding 95 % CIs are presented by dose group in following table.

Number (%) of patients with DVT - Per protocol patients

DVT		Org31540/SR90107A					Enoxaparin (N = 150)
		0.75 mg (N = 102)	1.5 mg (N = 101)	3.0 mg (N = 101)	6.0 mg (N = 44)	8.0 mg (N = 22)	
Total DVT	n (%)	11 (10.8)	6 (5.9)	2 (2.0)	2 (4.5)	0 (0.0)	14 (9.3)
	95% CI	[5.51; 18.48]	[2.21; 12.48]	[0.24; 6.97]	[0.56; 15.47]	[0; 15.44]	[5.2; 15.16]
Total proximal DVT	n (%)	3 (2.9)	5 (5.0)	1 (1.0)	1 (2.3)	0 (0.0)	5 (3.3)
	95% CI	[0.6; 8.36]	[1.63; 11.18]	[0.03; 5.39]	[0.06; 12.02]	[0; 15.44]	[1.09; 7.61]
Isolated	n	3	5	1	1	0	3
with distal	n	0	0	0	0	0	2
Total distal DVT	n (%)	8 (7.8)	1 (1.0)	1 (1.0)	1 (2.3)	0 (0.0)	11 (7.3)
	95% CI	[3.45; 14.87]	[0.03; 5.39]	[0.03; 5.39]	[0.06; 12.02]	[0; 15.44]	[3.72; 12.74]
Isolated	n	8	1	1	1	0	9

Sponsor's table in NDA Vol. 2, pp. 77

A statistically significant lower incidence of total DVT was observed in the 3.0 mg group as compared to the 0.75 mg group (p = 0.0185) and enoxaparin group (p= 0.0189). Only two (2.0 %) patients, both in the Org31540/SR90107A 0.75 mg group, experienced a PE.

Intent-to-treat patients

The incidences of patients with total DVT, proximal DVT and distal DVT and the corresponding 95 % CIs are presented by dose group for the pITT population in table below.

Number (%) of patients with DVT - pITT patients

DVT		Org31540/SR90107A					Enoxaparin (N = 171)
		0.75 mg (N = 119)	1.5 mg (N = 120)	3.0 mg (N = 115)	6.0 mg (N = 45)	8.0 mg (N = 23)	
Total DVT	n (%)	12 (10.1)	8 (6.7)	2 (1.7)	2 (4.4)	0 (0.0)	16 (9.4)
	95% CI	[5.32; 16.95]	[2.92; 12.71]	[0.21; 6.14]	[0.54; 15.15]	[0; 14.82]	[5.44; 14.75]
Total proximal DVT	n (%)	3 (2.5)	6 (5.0)	1 (0.9)	1 (2.2)	0 (0.0)	5 (2.9)
	95% CI	[0.52; 7.19]	[1.86; 10.57]	[0.02; 4.75]	[0.06; 11.77]	[0; 14.82]	[0.96; 6.69]
isolated	n	3	5	1	1	0	3
with distal	n	0	1	0	0	0	2
Total distal DVT	n (%)	9 (7.6)	3 (2.5)	1 (0.9)	1 (2.2)	0 (0.0)	13 (7.6)
	95% CI	[3.52; 13.87]	[0.52; 7.13]	[0.02; 4.75]	[0.06; 11.77]	[0; 14.82]	[4.11; 12.65]
isolated	n	9	2	1	1	0	11

Sponsor's table in NDA Vol. 2, pp. 78

The statistical results observed for the pITT analysis of patients with DVT are similar to those observed for the per protocol analysis.

All treated patients

The incidences of treated patients with symptomatic confirmed VTE during the all study period and the corresponding 95 % CIs are presented by dose group in the table below.

Number (%) of patients with symptomatic confirmed VTE throughout the study - All treated patients

Symptomatic Confirmed VTE		Org31540/SR90107A					Enoxaparin (N=260)
		0.75 mg (N=184)	1.5 mg (N=188)	3.0 mg (N=177)	6.0 mg (N=72)	8.0 mg (N=52)	
VTE	n (%)	3 (1.6)	0 (0.0)	5 (2.8)	2 (2.8)	1 (1.9)	7 (2.7)
	95 % CI	[0.34; 4.69]	[0; 1.94]	[0.92; 6.47]	[0.34; 9.68]	[0.05; 10.26]	[1.09; 5.47]
DVT	n	1	0	3	2	0	4
Non fatal PE	n	2	0	3	0	1	2
Fatal PE	n	0	0	0	0	0	1

Sponsor's table in NDA Vol. 2, pp. 78

The occurrence of symptomatic confirmed VTEs was reported during the treatment period for four patients (two PEs in the 0.75 mg group, and one distal DVT in the 6.0 mg and enoxaparin groups). For the 14 other patients, the VTEs were confirmed during the follow-up period (between Day 17 and Day 38) including a fatal PE in the enoxaparin group. Among these 14 patients, 12 had mandatory evaluable venographies at the end of the treatment period which were adjudicated as "no DVT". Two patients (one with a PE in the 8.0 mg group and one with a proximal DVT in the enoxaparin group) did not have evaluable assessment at the end of treatment.

Adjustment for covariates

The incidences of patients with VTE are presented by sub-population (gender, age category and race) and dose group for per protocol patients and Intent-to-treat patients. Gender and race were no statistically significant factor whereas the incidence of patients with VTE increased with age (p = 0.042). No obvious treatment-covariate interactions were observed.

Sensitivity analysis

A worse case scenario analysis considering patients excluded from the pITT analysis (i.e., with no DVT assessment, non-evaluable efficacy assessment or with venography not performed on time) as failures was performed. The incidences of patients with a failure in efficacy assessment and the corresponding 95 % CIs are presented by dose group in the table below. The 3.0mg dose group had a lowest incidence of VTE among all dose groups and also lower than enoxaparin group.

Number (%) of patients with VTE or a failure in efficacy assessment
All treated patients

Total failures	Org31540/SR90107A					Enoxaparin (N = 260)
	0.75 mg (N = 184)	1.5 mg (N = 188)	3.0 mg (N = 177)	6.0 mg (N = 72)	8.0 mg (N = 52)	
n (%)	79 (42.9)	76 (40.4)	64 (36.2)	29 (40.3)	29 (55.8)	105 (40.4)
95 % CI	[35.68; 50.42]	[33.35; 47.81]	[29.08; 43.7]	[28.88; 52.5]	[41.33; 69.53]	[34.37; 46.62]

Sponsor's table in NDA Vol. 2, pp. 80

Reviewer's Summary

Study DRI2643 was a phase II, multicenter, randomized, parallel, dose ranging study of Org31540/SR90107A (0.75mg, 1.5mg, 3.0mg, 6.0mg, and 8.0mg) once daily SC with comparative control group of enoxaparin 30mg twice daily SC in 950 patients undergoing elective total hip replacement. The main objective of this Phase II study was to determine the optimum dose of a once daily subcutaneous injection of Org31540/SR90107A starting postoperatively for VTE prophylaxis for the Phase III studies in patients undergoing elective total hip replacement surgery.

During the study, two highest dose groups (6.0mg and 8.0 mg) were terminated early due to the pre-specified stopping rule for major bleeding (15.8% with 95%CI of 6.0%-31.3% and 17.0% with 95%CI of 8.1%-29.8%, respectively).

The study demonstrated a statistically significant dose response within the selected dose range for the per protocol population (p=0.003) and for pITT (p=0.0024) population. The study also demonstrated that the 3.0 mg Org31540/SR90107A dose group had a statistically significantly lower incidence of VTE as compared to the 0.75 mg Org31540/SR90107A dose group (p=0.005 for the per protocol population and p= 0.003 for the pITT population), and the enoxaparin group (2.0 % versus 9.3 %, p = 0.019 for the per protocol population, and 1.7% versus 9.4 % p = 0.011 for pITT population).

Study DRI2643 provided the basis for dose selection for Phase III studies (63118 and EFC2442) in patients undergoing hip replacement surgery. The result of a significant dose response relationship in this study supported the efficacy of the drug in patients undergoing hip replacement surgery.

3. For Prophylaxis of DVT in Patients Undergoing Knee Replacement Surgery

Trial 095-002 - [redacted]

Title of the study

A multicenter, multinational, randomized, double-blind comparison of subcutaneous Org31540/SR90107A with enoxaparin in the prevention of deep vein thrombosis and symptomatic pulmonary embolism after elective major knee surgery or a revision.

Study Period

December 24, 1998 to January 17, 2000

Investigators and Study Centers

The study was carried out by investigators at 64 centers in United States (54) and Canada (10).

Study Objectives

The objective of this study was to demonstrate superior efficacy of a once-daily, postoperative, subcutaneous (SC) injection of 2.5 mg Org31540/SR90107A compared to twice-daily, post-operative, SC injection of 30 mg enoxaparin in the prevention of venous thromboembolic events (DVT and PE) in patients undergoing elective major knee surgery or a revision of component(s).

Overall Study Design

This was a multicenter, multinational, randomized, double-blind, parallel-group study comparing a 2.5 mg o.d. SC injection of Org31540/SR90107A with enoxaparin 30 mg b.i.d. SC in patients undergoing elective major knee surgery.

The study design of 95-002 was the same as in Study EFC2442 except for a different study population. The dose regimen, dose schedule and blinding method was identical to EFC2442. The randomization was performed post-operatively. The efficacy and safety evaluations were the same as in the other 3 Phase III studies (EFC2698, 63118 and EFC2442) and were adjudicated by the same CIAC.

Study Population

Inclusion criteria

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

- Undergoing either an elective major knee surgery or a revision of at least 1 component. (Elective major knee surgery was defined as surgery requiring resection of the distal end of the femur or proximal end of the tibia. Enrollment of patients with surgery limited to an osteotomy was not permitted.)
- Signed written informed consent
- Men or women of non-childbearing potential (post-menopausal or with a hysterectomy or a bilateral tubal ligation). This inclusion criterion was modified to allow inclusion of women of childbearing potential using highly effective birth control (method with a failure rate of <1% per year when used consistently and correctly) and with a negative serum pregnancy test at screening and within 48 hours prior to randomization (Protocol amendment No. 1 dated 10 November 1998)
- 18 years of age or older
- Established hemostasis on the calendar day of surgery, no later than 8 hours after incision closure.

Exclusion criteria

The exclusion criteria were the same as in Study EFC2698 except for criteria 3): (5) and (6) related to trauma.

Study Treatments

Patients were randomly assigned to 1 of 2 treatment groups:

- Org31540/SR90107A group: each patient received Org31540/SR90107A 2.5 mg once daily in the morning and 1 placebo injection in the evening

- Enoxaparin group: each patient received enoxaparin 30 mg twice a day.

The administration of Org31540/SR90107A started 6 ±2 hours after surgery closure on Day 1 and that of enoxaparin in the morning of Day 2, but at least 12 hours after the Day 1 dose (placebo).

Dosing schedule

Each patient was to receive twice daily administration of study treatment up to Day 7±2. Each patient received study treatment once on the operative day, Day 1, and twice daily thereafter until the mandatory venogram was obtained. The following table presents the dosing schedule for treatment days.

Dosing Schedule

Group	Operative Day	Subsequent Treatment Period			
	Day 1: 6 ±2 hours after surgical closure	Day 2, AM between 8-12:00[a]	Day 2, PM 20:00 ±2 hours	Day 3-9, AM 8:00 ±2 hours	Day 3-9, PM[b] 20:00 ±2 hours
Org31540/ SR90107A	2.5 mg (0.25 mL)	2.5 mg (0.25mL)	placebo	2.5 mg(0.25mL)	placebo
Enoxaparin	Placebo	30 mg (0.3mL)	30 mg (0.3mL)	30 mg (0.3mL)	30 mg (0.3mL)

a The morning injection on Day 2 was at least 12 hours after the Day 1 dose and less than 24 hours post-surgical closure.
b Patients were required to receive injections for 7±2 days, including the day of surgery, and until the final (positive unscheduled or mandatory) venogram was obtained.
Sponsor's table in NDA Vol. 209, pp. 29

Study treatment was to be given up to Day 7±2 or until the mandatory venogram was obtained, whichever came first. After the venogram was performed, the patient could receive an evening dose on the day of venography. Patients were not to receive study drug on the day after the mandatory venogram. Extended VTE prophylaxis could be started the day after the venogram was obtained.

Randomization Process

Treatments were allocated according to one pre-specified central randomization list produced by the Biostatistics Department (Sponsor: Organon, Inc., USA). Randomization was balanced with a block size of four, with a 2:2 ratio of Org31540/SR90107A and enoxaparin treatments. Within the list of consecutive patient numbers, in each block of four coded as A, B, C, and D, two codes (e.g. A and D) were assigned to Org31540/SR90107A, and two remaining codes were assigned to enoxaparin. The central randomization was not stratified by center (or other factors), but whole blocks were allocated to each center. The patients received a 4-digit treatment code number (in this study treatment code numbers are identical to patient numbers) when the clinical site personnel called the Interactive Voice Response System (IVRS). A patient was considered as randomized as soon as a study treatment box was assigned and the investigator had reported the treatment number and randomization date on the "Treatment Assignment" form of the Case Report Form booklet. Randomized patients who did not start or complete treatment were not to be replaced.

Determination of sample size

Based on the Phase II knee replacement study (95-001), the DVT and/or PE rate was 17.7% with a 95% CI of (10%, 29%) for the 3.0 mg Org31540/SR90107A group and 28.8% with a 95% CI of (19%, 42%) for the 1.5 mg Org31540/SR90107A group. In the current study, a dose of 2.5mg Org31540/SR90107A was to be used. Based on publications and a Phase II knee replacement study, it was assumed that the DVT rate for enoxaparin is between 25% and 34%. A sample size of 319 evaluable subjects per group would allow detection of a difference of 23% and 34% between Org31540/SR90107A and enoxaparin (based on 2-sided chi-square test with continuity correction, and using a type-I error of 5% and 85% power). About 912 patients were to be randomized, assuming an approximate 30% non-evaluable rate.

Interim analyses

As planned in the protocol, an interim analysis was carried out when half of the planned number of patients (i.e., 500 patients) were randomized and when adjudication of the primary efficacy criterion was available and validated for those patients. No statistical type-I error adjustment for the final analysis was proposed by the sponsor.

Protocol Amendments

There were 2 protocol amendments made in the study. Protocol amendments No. 1 was dated 10 November 1998 and the main change was addition of inclusion criterion related to women with childbearing potential. Protocol Amendment No. 2 was dated 08 April 1999 and the major changes were following:

- Exclusion criterion related to metformin intake
- Exclusion criterion related to prior treatment restrictions
- Pharmacokinetic sampling
- Baseline laboratory sample timing and liver enzymes and serum bilirubin
- Modification in statistical methods:
    - Clarification of primary endpoint
    - Additional exploratory sensitivity analyses
    - Methods for the secondary/exploratory analyses
    - Clarification of the safety analysis population
- Administrative changes/textual clarifications for patient follow-up and supply handling and some administrative corrections

Study Results

Disposition of patients

A total of 1049 patients were enrolled at 64 centers in United States (54 centers) and Canada (10 centers). Among the 64 centers, the number of patients enrolled at each center ranged from a single patient to 93 patients.

Of the 1049 patients randomized, 526 were assigned to receive Org31540/SR90107A and 523 were assigned to receive enoxaparin. The following chart presents the disposition of patients for each treatment group.

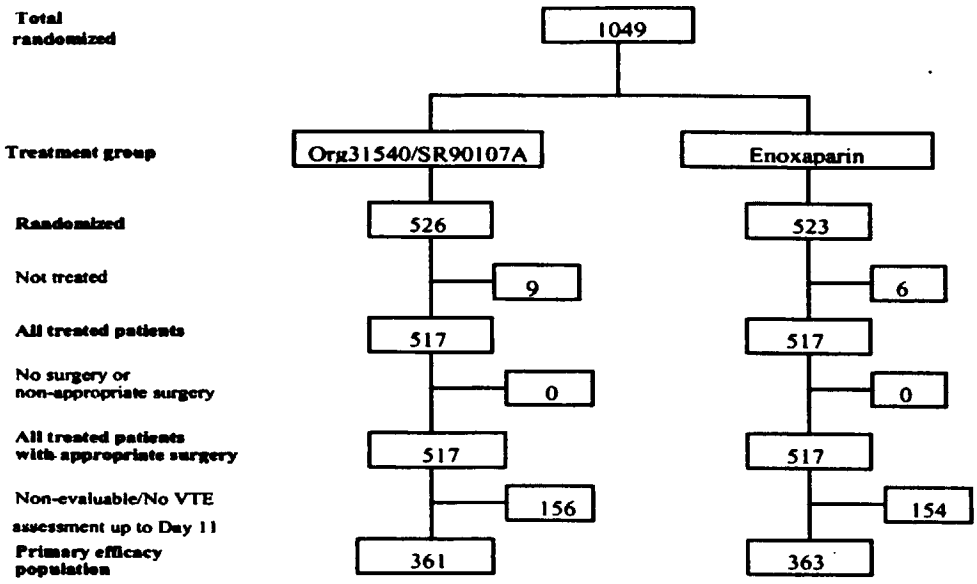


Figure (6.3) 1 - Number of patients by population

Sponsor's figure in NDA Vol. 209, pp. 65

Of the 1049 patients randomized, 15 did not receive any study drug. The following table summarizes the number (%) of randomized, non-treated patients by treatment group and reason for not being treated. The number of patients who were not treated was similar between the two groups. The main reason for not being treated was inclusion/exclusion criteria not met.

Number (%) of randomized and non-treated patients by reason for not being treated

Reason for not being treated	Org31540/SR90107A 2.5 mg o.d. (N = 526)	Enoxaparin 30 mg b.i.d. (N = 523)	Total (N = 1049)
Inclusion/exclusion criteria not met	3 (0.6)	2 (0.4)	5 (0.5)
Informed consent withdrawn	1 (0.2)	2 (0.2)	3 (0.3)
Other reason	5 (1.0)	3 (0.6)	8 (0.8)
Coumadin given prior to randomization	1 (0.2)	0 (0.0)	1 (0.1)
Physician withdrew patients	1 (0.2)	1 (0.2)	2 (0.2)
Protocol had not been approved	1 (0.2)	0 (0.0)	1 (0.1)
Surgery cancelled	0 (0.0)	1 (0.2)	1 (0.1)
Post-operative bleeding	1 (0.2)	1 (0.2)	2 (0.2)
Total	9 (1.7)	6 (1.1)	15 (1.4)

Reviewer's table based on sponsor's table in NDA Vol. 209, pp. 61 and study 95-002 Appendix 14.2.1.1.2

A total of 1034 patients (517 in the Org31540/SR90107A group and 517 in the enoxaparin group) were randomized and treated. The number (%) of randomized and treated patients is presented by treatment group and country in the table below.

Number (%) of randomized and treated patients by country

Country[a] (number of centers)	Org31540/SR90107A 2.5 mg o.d. (N = 517)	Enoxaparin 30 mg b.i.d. (N = 517)	Total (N = 1034)
	n	n	n (%)
United States (54)	423	424	847 (81.9)
Canada (10)	94	93	187 (18.1)
Total (64)	517	517	1034 (100.0)

NOTE: A patient was considered to be treated when he/she received at least 1 injection of either active drug or placebo.
[a] Sorted in decreasing order of randomized and treated patients
Sponsor's table in NDA Vol. 209, pp. 61

A total of 72 (7.0%) of the 1034 randomized and treated patients permanently stopped study drug prematurely, including 36 (7.0%) patients in each treatment group (See table below).

Number (%) of patients who permanently 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 = 517)	Enoxaparin 30 mg b.i.d. (N = 517)	Total (N = 1034)
	n (%)	n (%)	n (%)
Total	36 (7.0)	36 (7.0)	72 (7.0)
Reason for discontinuation[a]			
Lack of efficacy	2 (0.4)	6 (1.2)	8 (0.8)
Reached endpoint – DVT	1 (0.2)	4 (0.8)	5 (0.5)
Reached endpoint – PE	1 (0.2)	2 (0.4)	3 (0.3)
AE/SAE[b]	20 (3.9)	13 (2.5)[c]	33 (3.2)
Bleeding AE/SAE	7 (1.4)	2 (0.4)	9 (0.9)
Suspicion of drug-induced decrease in platelet count	2 (0.4)	0 (0.0)	2 (0.2)
Other AE/SAE	11 (2.1)	11 (2.1)	22 (2.1)
Subject withdrew consent	8 (1.4)	11 (2.1)	18 (1.7)
Other reasons	7 (1.4)	6 (1.2)	13 (1.3)
Dosing mistakes	4 (0.8)	0 (0.0)	4 (0.4)
Allergy to contrast dye	0 (0.0)	1 (0.2)	1 (0.1)
Received other anticoagulants	0 (0.0)	1 (0.2)	1 (0.1)
Protocol violation	1 (0.2)	0 (0.0)	1 (0.1)
Discharge/Drop-out	1 (0.2)	3 (0.6)	4 (0.4)
Sponsor excluded subject from study	0 (0.0)	1 (0.2)	1 (0.1)

[a] According to the Investigator's judgment
[b] Including event recorded before the first study drug injection and based solely on data collected in the End of Treatment Form
[c] Including 1 patient who discontinued solely due to an AE that was present before first study drug injection

Reviewer's table based on Sponsor's table in NDA Vol. 209, pp. 62 and study 95-002 Appendix 14.2.1.1.6

In both treatment groups, the majority of patients who permanently discontinued study drug prematurely were due to AEs/SAEs followed by subject withdrew consent. There were slightly more patients who discontinued treatment due to AEs/SAEs in the Org31540/SR90107A group as compared to those in the enoxaparin group (3.9% vs. 2.5%).

In both treatment groups, most patients who permanently discontinued study drug prematurely did so before Day 5.

No patients were lost to follow-up during the treatment period. A total of 7 patients, 3 in the Org31540/SR90107A group and 4 in the enoxaparin group had no information on the final Follow-up Assessment Form.

The randomization code for 2 patients in the enoxaparin group was broken. One of them had a serum creatinine concentration >2.0 mg/dL and thus should have been excluded from the study. The Sponsor advised that the randomization code be broken with unclear reason. The other patient had cardiac arrest with pulmonary embolism, resulting in death.

Protocol deviations

The numbers (%) of patients who presented with protocol deviations which lead to exclusion from primary efficacy analysis are summarized in the following table and were similar for both treatment groups (30.2% in the Org31540/SR90107A group vs. 29.8% in the enoxaparin group). No VTE assessment up to day 11 (16%) and no evaluable venogram (13%) were reasons for exclusion for both treatment groups.

Number (%) of patients by reason for exclusion from primary efficacy analysis - All treated patients

Deviation[a]	Org31540/SR90107A 2.5 mg o.d. (N = 517)	Enoxaparin 30 mg b.i.d. (N = 517)	Total (N = 1034)
	n (%)	N (%)	n (%)
Non-evaluable venogram up to Day 11	70 (13.5%)	70 (13.5%)	140 (13.5%)
No VTE Assessment up to Day 11	86 (16.6%)	84 (16.2%)	170 (16.4%)
Total	156 (30.2)	154 (29.8)	310 (30.0)

[a] Patients were counted only once.
Sponsor's table in NDA Vol. 209, pp. 63

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