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 = 517)	Enoxaparin 30 mg b.i.d. (N = 517)	Total (N =1034)
Non-evaluable VTE assessment up to day 11	**70 (13.5%)**	**70 (13.5%)**	**140 (13.5%)**
Both legs assessed-both inadequate	13 (2.5 %)	8 (1.5 %)	21 (2.0 %)
Both legs assessed-operated leg inadequate	22 (4.3 %)	17 (3.3 %)	39 (3.8 %)
Both legs assessed-non-operated leg inadequate	7 (1.4 %)	12 (2.3 %)	19 (1.8 %)
Operated leg assessed only- negative	16 (3.1 %)	22 (4.3 %)	38 (3.7 %)
Operated leg assessed only- inadequate	3 (0.6 %)	7 (1.4 %)	10 (1.0 %)
Non-operated leg assessed only-negative	7 (1.4 %)	3 (0.6 %)	10 (1.0 %)
Non-operated leg assessed only-inadequate	0 (0.0 %)	1 (0.2 %)	1 (0.1 %)
Examination performed before day 5	2 (0.4%)	0 (0.0%)	2 (0.2%)
No VTE assessment up to day 11	**86 (16.6%)**	**84 (16.2%)**	**170 (16.4%)**
VTE assessment after day 11	2 (0.4%)	2 (0.4%)	4 (0.4%)
Reasons for no VTE assessment			
Failed venous access	33 (6.4%)	28 (5.4%)	61 (5.9%)
Subject refuse/withdrew consent	21 (4.1%)	25 (4.8%)	46 (4.4%)
AE/SAE/deaths	5 (1.0%)	6 (1.2%)	11 (1.1%)
Premature treatment discontinuation	8 (1.5%)	10 (1.9%)	18 (1.7%)
Uncooperative/over-weighted for the test	4 (0.8%)	1 (0.2%)	5 (0.5%)
Technical problems	2 (0.4%)	0 (0.0%)	2 (0.2%)
Suspicion of iodine allergy	1 (0.2%)	3 (0.6%)	4 (0.4%)
Increased creatinine	1 (0.2%)	1 (0.2%)	2 (0.2%)
Discharged	0 (0.0%)	2 (0.4%)	2 (0.2%)
Normal US	0 (0.0%)	2 (0.4%)	2 (0.2%)
Symptom assessment only	7 (1.4%)	2 (0.4%)	9 (0.9%)
No reason mentioned	2 (0.4%)	0 (0.0%)	2 (0.2%)
Local but not central	2 (0.4%)	4 (0.8%)	6 (0.6%)
Total	**156 (30.2%)**	**154 (29.8%)**	**310 (30.0%)**

Reviewer's table based on NDA Study 95002, Appendix 14.2.1.3.3.

The main reasons for non-evaluable venogram were both legs assessed with operated leg inadequately assessed and operated leg assessed only with negative finding for both two treatment groups.

The main reasons for no VTE assessment up to day 11 were failed venous access and subject refusal/withdrew consent in both treatment groups. There were no major differences between the two treatment groups.

Other protocol deviations

Randomization irregularities mainly consisted of patients randomized out of order. This occurred in 10 patients overall.

The following table summarizes selected protocol deviations other than those leading to exclusion from the primary efficacy analysis. The most common deviation in both treatment groups was administration of less than 8 post-operative injections of active

drug or placebo, which was recorded for 3% of patients in the Org31540/SR90107A group and 4% of patients in the enoxaparin group.

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 = 517)	Enoxaparin 30 mg b.i.d. (N = 517)	Total (N = 1034)
	n (%)	n (%)	n (%)
Meeting exclusion criteria based on current labeling for LMWH[a]	7 (1.4)	3 (0.6)	10 (1.0)
Less than 8 post-operative injections of active drug or placebo[b]	14 (2.7)	20 (3.9)	34 (3.3)
Not allowed concomitant therapy[a,c,d]	7 (1.4)	13 (2.5)	20 (1.9)
Qualifying VTE examination for primary efficacy analysis more than 2 calendar days after last injection	3 (0.6)	2 (0.4)	5 (0.5)

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 flushes up to 200 IU/day
Sponsor's table in NDA Vol. 209, pp. 64

Demographic and baseline characteristics

All treated patients population

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

Of the 1034 randomized and treated patients, 607 (59%) were female, 914 (88.4%) were Caucasian, and 691 (67%) were 65 years of age or older. The mean age of patients was 68±10 years for both groups. The two treatment groups were similar with respect to demographic characteristics.
The two treatment groups were also similar with respect to surgical characteristics including duration of surgery, type of surgery, type of anesthesia, or use of cement.

Summary of demographic and surgical characteristics - All treated patients

Parameter		Org31540/SR90107A 2.5 mg o.d. (N = 517)	Enoxaparin 30 mg b.i.d. (N = 517)	Total (N = 1034)
Age	n	517	517	1034
(years)	Median	69	69	69
	Mean	67.5	67.5	67.5
	SD	10.7	10.2	10.4
	Min - Max	19 - 94	26 - 91	19 - 94
Age	< 65 years	168 (32.5%)	175 (33.8%)	343 (33.2%)
[n (%)]	[65 - 75[years	208 (40.2%)	207 (40.0%)	415 (40.1%)
	>75 years	141 (27.3%)	135 (26.1%)	276 (26.7%)
Height	n	515	516	1031
(cm)	Median	168	168	168
	Mean	168.1	169.0	168.6
	SD	10.7	10.8	10.8
	Min - Max	135 - 196	130 - 208	130 - 208
Weight	n	516	517	1033
(kg)	Median	87	86	87
	Mean	89.0	88.4	88.7
	SD	20.0	19.6	19.8
	Min - Max	45 - 166	43 - 163	43 - 166
BMI (kg/m^2)	<30	240 (46.7%)	241 (46.7%)	481 (46.7%)
[n (%)]	≥30	274 (53.3%)	275 (53.3%)	549 (53.3%)
	Missing	3	1	4
Gender	Male	204 (39.5%)	223 (43.1%)	427 (41.3%)
[n (%)]	Female	313 (60.5%)	294 (56.9%)	607 (58.7%)
Race	Caucasian	465 (89.9%)	449 (86.8%)	914 (88.4%)
[n (%)]	Black	34 (6.6%)	47 (9.1%)	81 (7.8%)
	Asian	2 (0.4%)	2 (0.4%)	4 (0.4%)
	Other race	16 (3.1%)	19 (3.7%)	35 (3.4%)
Type of surgery[a]	Primary	478 (92.5%)	479 (92.6%)	957 (92.6%)
[n (%)]	Revision	39 (7.5%)	38 (7.4%)	77 (7.4%)
Use of cement[a]	Yes	482 (93.2%)	484 (93.6%)	966 (93.4%)
[n (%)]	No	35 (6.8%)	33 (6.4%)	68 (6.6%)
Type of anesthesia[a]	General only	386 (74.7%)	369 (71.4%)	755 (73.0%)
[n (%)]	Regional only	126 (24.4%)	142 (27.5%)	268 (25.9%)
	Combination	5 (1.0%)	6 (1.2%)	11 (1.1%)
Duration of surgery[a]	n	517	517	1034
(hh:mm)	Median	2:00	2:00	2:00
	Mean	2:07	2:08	2:07
	SD	0:39	0:42	0:41
	Min - Max			

[a] For all treated and operated patients (Org31540/SR90107A, N = 517; enoxaparin, N = 517)
Sponsor's table in NDA Vol. 209, pp. 67

The following table presents the number (%) of patients with specific medical and surgical history for the all treated patients population. Enoxaparin group had slightly more patients with history of VTE, stroke and MI than Org31540/SR90107A group. However, the differences were not statistically significant ($p>0.05$).

There was no apparent difference between the treatment groups regarding history of orthopedic surgery within previous 12 months.

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 = 517)	Enoxaparin 30 mg b.i.d. (N = 517)	Total (N = 1034)
Specific medical history			
VTE	23 (4.4)	28 (5.4)	51 (4.9)
Stroke	11 (2.1)	18 (3.5)	29 (2.8)
Myocardial infarction	38 (7.4)	49 (9.5)	87 (8.4)
Cancer	86 (16.6)	78 (15.1)	164 (15.9)
Orthopedic surgery within the previous 12 months			
Any surgery	87 (16.8)	77 (14.9)	164 (15.9)
Hip replacement	3 (0.6)	1 (0.2)	4 (0.4)
Knee replacement	38 (7.4)	37 (7.2)	75 (7.3)
Other	51 (9.9)	44 (8.5)	95 (9.2)

Sponsor's table in NDA Vol. 209, pp. 68

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 drug 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 similar with respect to demographic and surgical characteristics.

Summary of demographic and surgical characteristics - Primary efficacy population

Parameter		Org31540/SR90107A 2.5 mg o.d. (N = 361)	Enoxaparin 30 mg b.i.d. (N = 363)	Total (N = 724)
Age	n	361	363	724
(years)	Median	70	70	70
	Mean	68.4	68.4	68.4
	SD	9.7	10.0	9.9
	Min - Max	38 - 94	30 - 90	30 - 94
Age	<65 years	111 (30.7%)	109 (30.0%)	220 (30.4%)
[n (%)]	[65 - 75[years	145 (40.2%)	150 (41.3%)	295 (40.7%)
	≥75 years	105 (29.1%)	104 (28.7%)	209 (28.9%)
Height	n	361	362	723
(cm)	Median	168	168	168
	Mean	167.8	168.7	168.3
	SD	10.7	10.3	10.5
	Min - Max	135 - 196	140 - 198	135 - 198
Weight	n	360	363	723
(kg)	Median	86	85	86
	Mean	87.2	86.6	86.9
	SD	18.7	18.9	18.8
	Min - Max	45 - 150	43 - 163	43 - 163
BMI (kg/m^2)	<30	176 (48.9%)	179 (49.4%)	355 (49.2%)
[n (%)]	≥30	184 (51.1%)	183 (50.6%)	367 (50.8%)
	Missing	1	1	2
Gender	Male	144 (39.9%)	154 (42.4%)	298 (41.2%)
[n (%)]	Female	217 (60.1%)	209 (57.6%)	426 (58.8%)
Race	Caucasian	327 (90.6%)	326 (89.8%)	653 (90.2%)
[n (%)]	Black	20 (5.5%)	25 (6.9%)	45 (6.2%)
	Asian	2 (0.6%)	1 (0.3%)	3 (0.4%)
	Other race	12 (3.3%)	11 (3.0%)	23 (3.2%)
Type of surgery	Primary	330 (91.4%)	332 (91.5%)	662 (91.4%)
[n (%)]	Revision	31 (8.6%)	31 (8.5%)	62 (8.6%)
Use of cement	Yes	336 (93.1%)	338 (93.1%)	674 (93.1%)
[n (%)]	No	25 (6.9%)	25 (6.9%)	50 (6.9%)
Type of anesthesia	General only	268 (74.2%)	256 (70.5%)	524 (72.4%)
[n (%)]	Regional only	90 (24.9%)	103 (28.4%)	193 (26.7%)
	Combination	3 (0.8%)	4 (1.1%)	7 (1.0%)
Duration of	n	361	363	724
surgery (hh:mm)	Median	2:00	1:57	2:00
	Mean	2:07	2:04	2:05
	SD	0:39	0:39	0:39
	Min - Max			

Sponsor's table in NDA Vol. 209, pp. 69

As seen in the all treated patient population, the enoxaparin group had slightly more patients with previous VTE, stroke and MI than did the Org31540/SR90107A group. Again, the differences were not statistically significant ($p>0.05$).

For the primary efficacy population, the two treatment groups were similar with respect to surgical history.

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 = 361)	Enoxaparin 30 mg b.i.d. (N = 363)	Total (N = 724)
	n (%)	n (%)	n (%)
Specific medical history			
VTE	15 (4.2)	21 (5.8)	36 (5.0)
Stroke	6 (1.7)	14 (3.9)	20 (2.8)
Myocardial infarction	25 (6.9)	36 (9.9)	61 (8.4)
Cancer	61 (16.9)	53 (14.6)	114 (15.7)
Orthopedic surgery within the previous 12 months			
Any surgery	58 (16.1)	50 (13.8)	108 (14.9)
Hip replacement	1 (0.3)	0 (0.0)	1 (0.1)
Knee replacement	29 (8.0)	25 (6.9)	54 (7.5)
Other	30 (8.3)	27 (7.4)	57 (7.9)

Sponsor's table in NDA Vol. 209, pp. 70

Extent of exposure

All treated patients population

The following table presents a summary of active treatment. Most patients in both treatment groups received active study drug at least up to Day 7±2, as required by the protocol. In accordance with the difference between the two study drugs in dosing regimens, the number of active injections differed between the two groups.

Summary of active treatment - All treated patients

	Org31540/SR90107A 2.5 mg o.d. (N = 517)	Enoxaparin 30 mg b.i.d. (N = 517)[a]
Number of active injections		
N	517	515
Median	6	9
Mean (SD)	6.2 (1.5)	9.9 (3.2)
Min - Max	—	—
Last day of active treatment[b] [n (%)]		
< Day 5	29 (5.6%)	24 (4.6%)
Day 5 to Day 9	484 (93.6%)	488 (94.4%)
> Day 9	4 (0.8%)	3 (0.6%)

[a] Two patients in the enoxaparin group received only placebo.
[b] 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. 209, pp. 71

The mean time (± SD) between the end of the surgery and the first active post-operative injection was 6±1 hours in the Org31540/SR90107A group and 21±2 hours in the enoxaparin group.

Primary efficacy population

Overall, the extent of exposure to active study drug for the primary efficacy population was similar to that observed for the all treated patients population (See Table below).

Summary of active treatment up to the qualifying VTE examination -Primary efficacy population

	Org31540/SR90107A 2.5 mg o.d. (N = 361)	Enoxaparin 30 mg b.i.d. (N = 363)
Number of active injections		
N	361	363
Median	5	8
Mean (SD)	5.5 (1.5)	9.2 (3.0)
Min - Max	—	—
Last day of active treatment[a] [n (%)]		
< Day 5	8 (2.2%)	2 (0.6%)
Day 5 to Day 9	351 (97.2%)	360 (99.2%)
> Day 9	2 (0.6%)	1 (0.3%)

[a]Day 1=Day of surgery
Sponsor's table in NDA Vol. 209, pp. 72

The mean time (± SD) between the end of the surgery and the first active post-operative injection was 6±1 hours in the Org31540/SR90107A group and 21±2 hours in the enoxaparin group.

Measurements of treatment compliance

As previously shown, the percentage of patients with less than 8 postoperative injections was similar in both groups (2.7% in the Org31540/SR90107A group and 3.9% in the enoxaparin group) for the all treated patients population. The number (%) of patients who received less than 8 postoperative injections up to the qualifying VTE examination in primary efficacy population was 5 (1.4%) in the Org31540/SR90107A group vs. 4 (1.1%) in the enoxaparin group.

One patient in the Org31540/SR90107A group received an injection of study drug from the wrong treatment kit on 2 study days. One patient in the enoxaparin group received an injection of study drug from the wrong treatment kit on 1 study day. Neither patient had a VTE. No bleeding event occurred in the patient in the Org31540/SR90107A group; the enoxaparin-treated patient had a minor bleeding event.

Concomitant medication

All treated patients population

The percentage of patients receiving not allowed or discouraged concomitant medications from the day of the first injection up to the day before the qualifying VTE examination or the day before the last injection, whichever came last, is presented in the table below.

The use of not allowed or discouraged concomitant medications during the treatment period was similar for both treatment groups.

Number (%) of patients who received not allowed or discouraged concomitant medication - All treated patients

Medication	Org31540/SR90107A 2.5 mg o.d. (N = 517)	Enoxaparin 30 mg b.i.d. (N = 517)
	n (%)	n (%)
Not allowed medication[a]		
Heparin (UFH, LMWH) or heparinoids[b]	5 (1.0)	6 (1.2)
Anti-platelet drugs other than ASA	1 (0.2)	3 (0.6)
Vitamin K antagonists	2 (0.4)	4 (0.8)
Discouraged medication[a]		
NSAID	53 (10.3)	62 (12.0)
ASA	12 (2.3)	16 (3.1)

Note: Patients were counted more than once if they took more than 1 disallowed concomitant medication.
[a] From the day of the first injection up to the day before the qualifying VTE examination or the day before the last injection, whichever came last
[b] As per protocol, did not take into account heparin flushes up to 200 IU/day
Sponsor's table in NDA Vol. 209, pp. 74

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

Number (%) of patients with physical prophylactic antithrombotic therapy during the treatment period - All treated patients

Physical therapy	Org31540/SR90107A 2.5 mg o.d. (N = 517)	Enoxaparin 30 mg b.i.d. (N = 517)
	n (%)	n (%)
Elastic stockings only	2 (0.4)	2 (0.4)
Physical therapy only	93 (18.0)	89 (17.2)
Both methods	421 (81.4)	424 (82.0)

Sponsor's table in NDA Vol. 209, pp. 74

Primary efficacy population

For the primary efficacy population, the use of not allowed or discouraged medication and physical prophylactic antithrombotic therapy during the treatment period were similar in both treatment groups (See Tables below).

Number (%) of patients who received not allowed or discouraged concomitant medication - Primary efficacy population

Medication	Org31540/SR90107A 2.5 mg o.d. (N = 361)	Enoxaparin 30 mg b.i.d. (N =363)
	n (%)	n (%)
Not allowed medication[a]		
Heparin (UFH, LMWH) or heparinoids[b]	2 (0.6)	4 (1.1)
Anti-platelet drugs other than ASA	0 (0.0)	3 (0.8)
Vitamin K antagonists	2 (0.6)	4 (1.1)
Discouraged medication[a]		
NSAID	40 (11.1)	47 (12.9)
ASA	7 (1.9)	14 (3.9)

Note: Patients were counted more than once if they took more than 1 disallowed concomitant medication.
[a] From the day of the first injection up to the day before the qualifying VTE examination
[b] As per protocol, did not take into account heparin flushes up to 200 IU/day
Sponsor's table in NDA Vol. 209, pp. 75

Number (%) of patients with physical prophylactic antithrombotic therapy during the treatment period - Primary efficacy population

Physical therapy	Org31540/SR90107A 2.5 mg o.d. (N = 361)	Enoxaparin 30 mg b.i.d. (N = 363)
	n (%)	n (%)
Elastic stockings only	0 (0.0)	0 (0.0)
Physical therapy only	62 (17.2)	69 (19.0)
Both methods	298 (82.5)	294 (81.0)

Sponsor's table in NDA Vol. 209, pp. 75

Duration of participation in the study

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

Summary of duration of participation in the study - All treated patients

Duration of study participation[a] (days)	Org31540/SR90107A 2.5 mg o.d. (N = 517)	Enoxaparin 30 mg b.i.d. (N = 517)
Median	44	43
Mean	45.3	43.4
SD	13.9	11.3
Min – Max		

[a] From first injection (active drug or placebo) to the last visit
Sponsor's table in NDA Vol. 209, pp. 76

The mean duration of participation was also similar in the two treatment groups for primary efficacy population. Additionally, the mean duration between surgery and the qualifying VTE examination was similar in the two treatment groups.

Summary of duration of participation in the study and duration between surgery and the qualifying VTE examination - Primary efficacy population

Parameter		Org31540/SR90107A 2.5 mg o.d. (N = 361)	Enoxaparin 30 mg b.i.d. (N = 363)
Duration of participation in the study [a] (days)	Median	44	43
	Mean	45.2	42.9
	SD	13.3	9.2
	Min - Max	[redacted]	[redacted]
Duration between surgery and qualifying VTE examination (days)	Median	7	7
	Mean	6.6	6.7
	SD	1.5	1.6
	Min - Max	[redacted]	[redacted]

[a] From first injection (active drug or placebo) to the last visit
Sponsor's table in NDA Vol. 209, pp. 76

Most patients underwent the qualifying VTE examination between Day 5 and Day 11. Only 4 patients (2 in Org31540/SR90107A group and 2 in the enoxaparin group) had a qualifying VTE examination before Day 5.

Patient follow-up

The following table summarizes location at discharge and living situation at the time of the follow-up assessment for the all treated patients population. The 2 treatment groups were similar with respect to these parameters.

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 = 517)	Enoxaparin 30 mg b.i.d. (N = 517)
Location at discharge[a]		
Home	247 (47.9)	245 (47.4)
Location other than home	269 (52.1)	272 (52.6)
Rehabilitation unit	261 (50.6)	261 (50.5)
Other	8 (1.6)	11 (2.1)
Missing	1	0
Living situation at follow-up assessment[b]		
Home	467 (91.2)	472 (92.9)
Home with professional assistance	19 (3.7)	20 (3.9)
Rest home	5 (1.0)	4 (0.8)
Nursing home	4 (0.8)	1 (0.2)
Rehabilitation unit	7 (1.4)	6 (1.2)
Other	8 (1.6)	5 (1.0)

[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. 209, pp. 77

Similar data were seen for the primary efficacy population (See table below).

Number (%) of patients by location at discharge and living situation at follow-up assessment - Primary efficacy population

Parameter	Org31540/SR90107A 2.5 mg o.d. (N = 361)	Enoxaparin 30 mg b.i.d. (N = 363)
Location at discharge[a]		
Home	173 (47.9)	166 (45.7)
Location other than home	188 (52.1)	197 (54.3)
Rehabilitation unit	184 (51.0)	194 (53.4)
Other	4 (1.1)	3 (0.8)
Living situation at follow-up assessment[b]		
Home	331 (91.9)	335 (92.8)
Home with professional assistance	14 (3.9)	16 (4.4)
Rest home	3 (0.8)	3 (0.8)
Nursing home	3 (0.8)	1 (0.3)
Rehabilitation unit	2 (0.6)	4 (1.1)
Other	6 (1.7)	2 (0.6)

[a] Percentages were based on non-missing information.
[b] Percentages were based on patients with a follow-up form available, excluding death up to Day 49 and missing data.
Sponsor's table in NDA Vol. 209, pp. 78

Efficacy Evaluation

Analysis of efficacy

Primary efficacy analysis

The primary efficacy endpoint 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 following table. The VTE rate up to Day 11 was statistically highly significantly lower in the Org31540/SR90107A group than in the enoxaparin group (12.5% versus 27.8%, respectively, $p=2.7 \times 10^{-7}$). This highly significant difference in VTE rate was mainly due to difference in DVT event rate between the two groups (12.5% vs. 27.0%, $p=9.6 \times 10^{-7}$). There was no difference in terms of PE up to day 11 between the two treatment groups.

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 = 361)	Enoxaparin 30 mg b.i.d. (N = 363)	Difference Org31540/SR90107A minus Enoxaparin (%)	Fisher's Exact Test (p)
VTE	45 12.5%	101 27.8%	-15.4%	2.7×10^{-7}
DVT	45 (12.5%)	98 (27.0%)	-14.5	1×10^{-6}
PE	1 (0.3%)	4 (1.1%)	-0.8	0.37
Fatal PE	0 (0.0%)	1 (0.3%)	-0.3	
Non-Fatal PE	1 (0.3%)	3 (0.8%)	-0.5	

Note: One patient had both DVT and non-fatal PE in each treatment group.
p-value for PE was obtained by FDA Statistical Reviewer Dr. Mushfiqur Rashid, Ph.D.
Reviewer's table based on NDA Vol. 3.81, pp. 145-153 and efficacy datasets

This reviewer further analyzed mortality data from this study. There were a total of 5 deaths (2 in Org31540/SR90107A group and 3 in enoxaparin group) in the study including 3 deaths occurred up to Day 11 (See table below).

Deaths from all causes and PE in the study

	Org31540/SR90107A 2.5 mg o.d. (N = 849)	Enoxaparin 40 mg o.d. (N = 862)
Death up to day 11		
All causes	1 (0.1%)	2 (0.2%)
Fatal PE	0 (0.0%)	1 (0.1%)
Death up to day 49		
All causes	2 (0.2%)	3 (0.3%)
Fatal PE	1 (0.1%)	1 (0.1%)

Reviewer's table based on NDA study 95-002 Appendix 14.2.4.2.1-2 and submitted datasets

Of 5 deaths, two fatal PE were identified with one in each of the two treatment groups. There were 2 autopsies (enoxaparin group) done among 5 deaths including the case with fatal PE in this group. In the Org31540/SR90107A group, another death was due to encephalopathy and respiratory aspiration. In the enoxaparin group, the SAEs other than PE leading to deaths were cardiac arrhythmia (rule out PE by autopsy) and ventricular tachycardia.

Secondary efficacy analyses

Adjudicated DVT

The number (%) of patients with adjudicated DVT, an adjudicated proximal DVT, and an adjudicated distal only DVT, up to Day 11 are summarized by treatment group in the following table. There was a statistically significantly lower incidence rate of any DVT and distal DVT (9.4% vs. 21.3%, $p = 9 \times 10^{-6}$) in the Org31540/SR90107A group than in the enoxaparin group. The rate of proximal DVT in the Org31540/SR90107A group was

numerically lower than that in the enoxaparin group but the difference did not reach statistical significance (2.4% vs. 5.4%, p=0.057).

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	45/ 361 12.5%	98/ 361 27.1%	-14.7%	9.6×10^{-7}
Any proximal DVT	9/ 368 2.4%	20/ 372 5.4%	-2.9%	0.057
Distal DVT only	35/ 372 9.4%	78/ 366 21.3%	-11.9%	9×10^{-6}

p-value for distal DVT only was obtained by FDA Statistical Reviewer Dr. Mushfiqur Rashid, Ph.D.
Reviewer's table based on sponsor's table in NDA Vol. 209, pp. 80.

The DVT rates by side of examination (operative/non-operative leg) between two treatments are presented in the following table. There was a much higher incidence of DVT observed in operated leg than in non-operated leg for both treatment groups.

Number (%) and [95% confidence intervals] of Patients with Adjudicated Examination for Assessment of DVT up to Day 11 by 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	n/N (%)	45/ 361 (12.5)	98/ 361 (27.1)
	95% CI	[9.2; 16.3]	[22.6; 32.0]
Operative leg	n/N (%)	40/ 382 (10.5)	92/ 396 (23.2)
	95% CI	[7.6; 14.0]	[19.2; 27.7]
Non-operative leg	n/N (%)	7/ 386 (1.8)	12/ 373 (3. 2)
	95% CI	[0.7; 3.7]	[1.7; 5.6]
Both sides	n/N (%)	2/ 407 (0.5)	6/ 409 (1.5)
	95% CI	[0.1; 1.8]	[0.5; 3.2]
Any proximal DVT			
Either side	n/N (%)	9/ 368 (2.4)	20/ 372 (5.4)
	95% CI	[1.1; 4.6]	[3.3; 8.2]
Operative leg	n/N (%)	6/ 395 (1.5)	18/ 411 (4.4)
	95% CI	[0.6; 3.3]	[2.6; 6.8]
Non-operative leg	n/N (%)	3/ 395 (0.8)	2/ 385 (0.5)
	95% CI	[0.2; 2.2]	[0.1; 1.9]
Distal DVT only			
Either side	n/N (%)	35/ 372 (9.4)	78/ 366 (21.3)
	95% CI	[6.6; 12.8]	[17.2; 25.9]
Operative leg	n/N (%)	33/ 393 (8.4)	73/ 399 (18.3)
	95% CI	[5.9; 11.6]	[14.6; 22.4]
Non-operative leg	n/N (%)	4/ 392 (1.0)	10/ 381 (2.6)
	95% CI	[0.3; 2.6]	[1.3; 4.8]
Both sides	n/N (%)	2/ 413 (0.5)	5/ 414 (1.2)
	95% CI	[0.1; 1.7]	[0.4; 2.8]

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. 209, pp. 80

Curative treatment initiated after VTE assessment and prolonged prophylaxis of VTE
The percentage of patients who initiated curative antithrombotic treatment based on any Investigator assessment of VTE was higher in the enoxaparin group than in the Org31540/SR90107A group ($p=3x10^{-4}$) for the all treated patients population (See table below).

Number (%) of treated patients who initiated curative antithrombotic treatment based on any Investigator assessment of VTE - All treated patients who underwent the appropriate surgery with VTE assessment up to Day 11

	Org31540/SR90107A (N^b= 443)		Enoxaparin (N^b= 442)	
Curative treatment[a]	n	%	n	%
All patients with curative treatment	67	15.1	111	25.1
Heparin (UFH, LMWH)/heparinoids[c]	50	11.3	76	17.2
Vitamin K antagonist without	7	1.6	25	5.7
heparin (UFH, LMWH)/heparinoids				
Other than heparin or Vitamin K	5	1.1	4	0.9
antagonist				
No medication reported	5	1.1	6	1.4

[a] Patients were counted only once.
[b] Number of patients with any VTE assessment up to Day 11
[c] Did not take into account heparin flushes up to 200 IU/day
Sponsor's table in NDA Vol. 209, pp. 81

During the follow-up period, prolonged prophylaxis of VTE (mainly LMWH and vitamin K antagonists) was administered to 19.1% (86/450) of patients in the Org31540/SR90107A group and 20.2% (82/406) of patients in the enoxaparin group for the all treated patients population who did not receive curative treatment.

As shown in the all treated patients population, the percentage of patients in the primary efficacy population who initiated curative antithrombotic treatment following the qualifying VTE examination was higher in the enoxaparin group than in the Org31540/SR90107A group ($p=1x10^{-4}$) (See Table below).

Number (%) of patients who initiated curative antithrombotic treatment based on the qualifying VTE assessment - Primary efficacy population

Curative treatment[a]	Org31540/SR90107A (N = 361)		Enoxaparin (N = 363)	
	n	%	n	%
All patients with curative treatment	54	15.0	100	27.5
Heparin (UFH, LMWH)/heparinoids[b]	40	11.1	67	18.5
Vitamin K antagonist without	7	1.9	23	6.3
heparin (UFH, LMWH)/heparinoids[b]				
Other than heparin or vitamin K	4	1.1	4	1.1
antagonist				
No medication reported	3	0.8	6	1.7

[a] Patients were counted only once. [b] Did not take into account heparin flushes up to 200 IU/day
Sponsor's table in NDA Vol. 209, pp. 82

During the follow-up period, prolonged prophylaxis of VTE (mainly LMWH and vitamin K antagonists) was administered to 18.2% (56/307) of patients in the Org31540/SR90107A group and 17.9% (47/263) 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.

Up to Day 11, a total of 3 patients had symptomatic VTEs (2 patients with symptomatic DVT and 1 patient with both symptomatic DVT and non-fatal PE) in the Org31540/SR90107A group and 7 patients had symptomatic VTEs (3 patients with symptomatic DVT, 3 with non-fatal PE, and 1 with both symptomatic DVT and non-fatal PE) in the enoxaparin group. The difference in rate between the two treatment groups was not statistically significant. Similarly, the rate of symptomatic VTE up to Day 49 was low and did not statistically significantly differ between the two treatment groups.

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 = 517)	Enoxaparin 30 mg b.i.d. (N = 517)	Fisher's Exact Test result
Up to Day 11	VTE	n (%)	3 (0.6 %)	7 (1.4 %)	0.34
		95% CI	[0.1; 1.7]	[0.5; 2.8]	
	DVT	n (%)	3 (0.6%)	4 (0.8 %)	
	Non-fatal PE	n (%)	1 (0.2%)	4 (0.8 %)	
	Fatal PE	n (%)	0 (0%)	0 (0%)	
Up to Day 49	VTE	n (%)	5 (1.0 %)	10 (1.9 %)	0.30
		95% CI	[0.3; 2.2]	[0.9; 3.5]	
	DVT	n (%)	4 (1.1 %)	6 (1.7 %)	
	Non-fatal PE	n (%)	2 (0.4 %)	4 (0.8 %)	
	Fatal PE	n (%)	1 (0.2 %)	1 (0.2 %)	

Reviewer's table based on sponsor's tables in NDA Vol. 209, pp.83

Symptomatic VTEs recorded up to Day 49 were also summarized in the form of cumulative event rate curves, using Kaplan-Meier method; the comparison of the two groups revealed no statistically significant difference in terms of time to the first event.

Exploratory analysis for primary efficacy endpoint

Adjustment for covariates

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

No statistically significant heterogeneity of treatment effect was demonstrated for any covariate analyzed except for country and the use of cement. For these covariates, the between-group differences in favor of Org31540/SR90107A were significantly more pronounced for the US (11.1% vs. 29.7%, $p=2.6 \times 10^{-8}$) for Canada (18.1% vs. 20.8%, $p=0.69$) and for the use of cement (10.7% vs. 27.5%, $p<0.05$) compared to the non-use of

cement (36.0% vs. 32.0%, p>0.05) (covariate x treatment interaction significant with p=0.025 and p=0.033, respectively).

When the efficacy result was analyzed by study center, among the 64 centers, 32 were in favor of Org31540/SR90107A numerically, 25 centers were the same, and 7 centers were in favor of enoxaparin numerically.

The treatment effect in favor of Org31540/SR90107A was shown numerically across all subgroups including gender, age, BMI, type of anesthesia, type of surgery (primary or revision), duration of surgery, previous history of VTE, and baseline creatinine level. For race, more than 90% of patients were Caucasian in the primary efficacy population.

Number (%) of patients with adjudicated VTE up to Day 11 according to various baseline covariates - Primary efficacy population

Covariate[a] (subgroup)	Org31540/SR90107A 2.5 mg o.d. (N = 361)				Enoxaparin 30 mg b.i.d. (N = 363)			
		VTE				VTE		
	N	n	%	95 % CI	N	n	%	95 % CI
Country								
Canada	72	13	18.1	[10.0 ; 28.9]	77	16	20.8	[12.4; 31.5]
USA	289	32	11.1	[7.7 ; 15.3]	286	85	29.7	[24.5; 35.4]
Gender								
Male	144	19	13.2	[8.1; 19.8]	154	38	24.7	[18.1; 32.3]
Female	217	26	12.0	[8.0; 17.1]	209	63	30.1	[24.0; 36.9]
Race								
Caucasian	327	36	11.0	[7.8; 14.9]	326	93	28.5	[23.7; 33.8]
Black	20	5	25 0	[8.7; 49.1]	25	6	24.0	[9.4; 45.1]
Asian	2	1	50.0	[1.3; 98.7]	1	0	0.0	[0.0; 97.5]
Other races	12	3	25.0	[5.5; 57.2]	11	2	18.2	[2.3; 51.8]
Age								
<65 years	111	19	17.1	[10.6; 25.4]	109	29	26.6	[18.6; 35.9]
[65 - 75 [years	145	18	12.4	[7.5; 18.9]	150	43	28.7	[21.6; 36.6]
≥75 years	105	8	7.6	[3.3; 14.5]	104	29	27.9	[19.5; 37.5]
Obesity								
BMI <30 kg/m^2	174	24	13.8	[9.0; 19.8]	178	50	28.1	[21.6; 35.3]
BMI ≥30 kg/m^2	186	20	10.8	[6.7; 16.1]	184	51	27.7	[21.4; 34.8]
Type of anesthesia								
Regional only	90	12	13.3	[7.1; 22.1]	103	28	27.2	[18.9; 36.8]
Other	271	33	12.2	[8.5; 16.7]	260	73	28.1	[22.7; 34.0]
Type of surgery								
Primary	330	41	12.4	[9.1; 16.5]	332	97	29.2	[24.4; 34.4]
Revision	31	4	12.9	[3.6; 29.8]	31	4	12.9	[3.6; 29.8]
Use of cement								
Yes	336	36	10.7	[7.6; 14.5]	338	93	27.5	[22.8; 32.6]
No	25	9	36.0	[18.0; 57.5]	25	8	32.0	[14.9; 53.5]
Duration of surgery[b]								
< median	168	23	13.7	[8.9; 19.8]	180	59	32. 8	[26.0; 40.2]
≥ median	193	22	11.4	[7.3; 16.7]	183	42	23.0	[17.1; 29.7]

Previous VTE								
Yes	15	3	20.0	[4.3; 48.1]	21	9	42.9	[21.8; 66.0]
No	346	42	12.1	[8.9; 16.1]	342	92	26.9	[22.3 ;31.9]
Creatinine before surgery[c]								
<median	135	19	14.1	[8.7; 21.2]	153	48	31.4	[24.1; 39.4]
≥median	216	24	11.1	[7.3; 16.1]	203	50	24.6	[18.9; 31.2]

[a] For each covariate, only non-missing observations were taken into account.
[b] Median (hh;mm) for duration of surgery was 2:00 hours across the 2 treatment groups.
[c] Median for serum creatinine before surgery was 0.9 mg/dL across the 2 treatment groups.
Sponsor's table in NDA Vol. 209, pp. 85

Differences (and 95% CIs) between the Org31540/SR90107A group and the enoxaparin group are displayed in the following figure for each covariate analyzed.

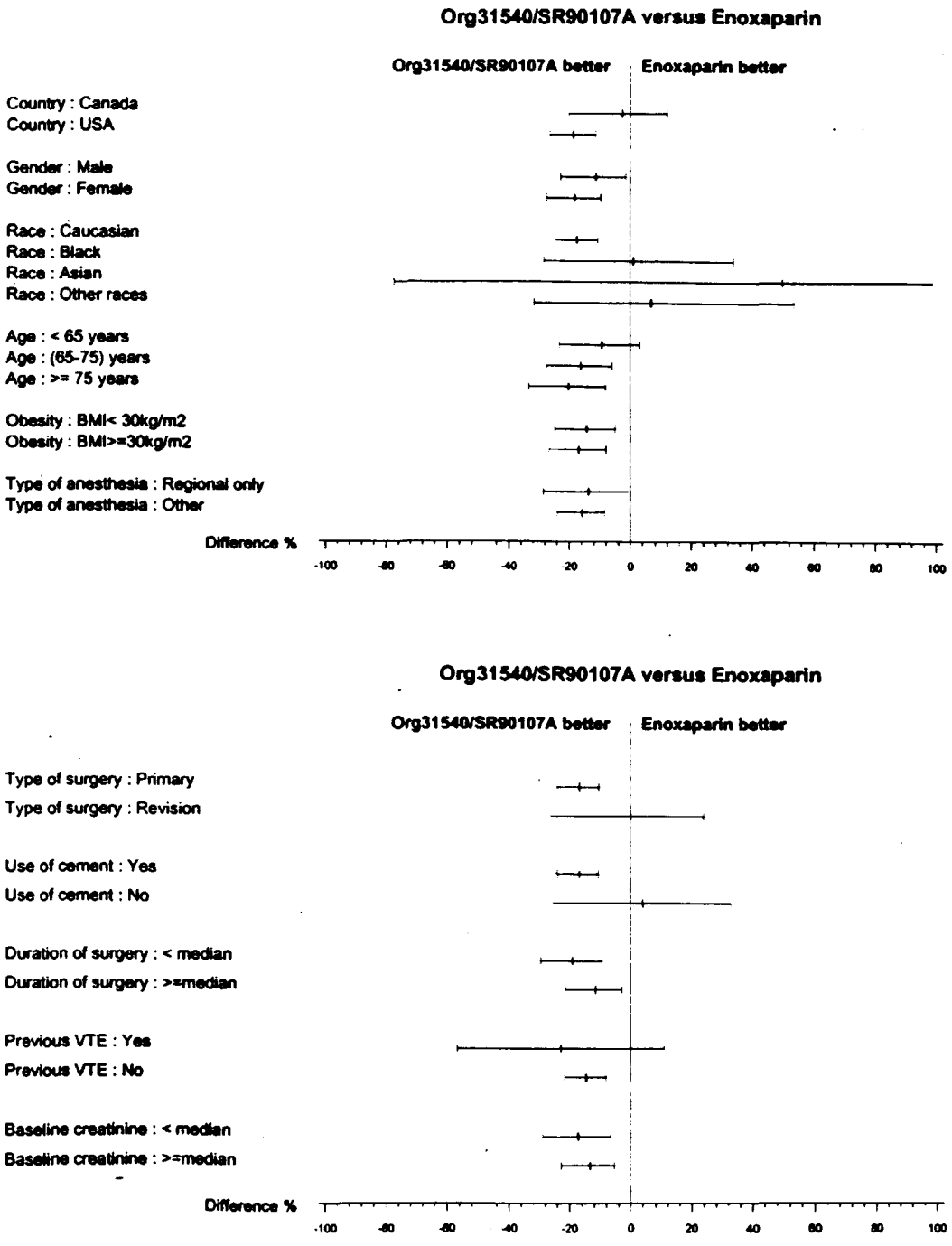


Figure (7.2.1) 1 - Differences (%) and 95% CIs between Org31540/SR90107A and enoxaparin groups for the percentage of patients with adjudicated VTE up to Day 11 according to baseline covariates - Primary efficacy population

Sponsor's table in NDA Vol. 209, pp. 86

Sensitivity Analysis

There were 156 (30.2%) patients in the Org31540/SR90107A group and 154 (29.8%) 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 table presents 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 of the primary efficacy endpoint- All treated patients who underwent the appropriate surgery

Scenario	Org31540/SR90107A 2.5 mg o.d. (N = 517)	Enoxaparin 30 mg b.i.d. (N = 517)	Difference and exact 95% CI	Fisher's Exact Test p-value*
	n (%)	n (%)		
Best case scenario	45 (8.7%)	101 (19.5%)	-10.8% [-15.9; -6.2]	2.7×10^{-7}
Realistic case scenario	89 (17.2%)	143 (27.7%)	-10.4% [-16.2; -5 0]	7.4×10^{-5}
Worst case scenario	201 (38.9%)	255 (49.3%)	-10.4% [-16.6; -4.2]	8.9×10^{-5}

*p-values were obtained by FDA Statistical Reviewer Dr. Mushfiqur Rashid, Ph.D.
Sponsor's table in NDA Vol. 209, pp. 87

The following table shows sensitivity analysis on all randomized patients. The results were consistent with those observed for the primary efficacy analysis.

Sensitivity analysis in ITT population

Scenario	Org31540/SR90107A 2.5 mg o.d. (N = 526)	Enoxaparin 30 mg b.i.d. (N = 523)	Difference and exact 95% CI
	n (%)	n (%)	
Best case scenario	45 (8.6%)	101 (19.3%)	-10.8% [-15.8; -6.2]
Realistic case scenario	91 (17.3%)	145 (27.7%)	-10.4% [-16.2; -5 0]
Worst case scenario	210 (39.9%)	261 (49.9%)	-10.0% [-16.2; -3.8]

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 a potential interaction with heparin, according to the 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. However, the data were limited by small number of patients with concomitant medications.

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 = 361)				Enoxaparin 30 mg b.i.d. (N = 363)			
		VTE				VTE		
	N	n	%	95% CI	N	n	%	95% CI
Heparin (UFH, LMWH) or heparinoids								
With	2	0	0.0	[0.0; 84.2]	4	1	25.0	[0.6; 80.6]
Without	359	45	12.5	[9.3; 16.4]	359	100	27.9	[23.3; 32.8]
Anti-platelet drugs other than ASA								
With	0	0	NA	NA	3	0	0.0	[0.0; 70.8]
Without	361	45	12.5	[9.2; 16.3]	360	101	28.1	[23.5; 33.0]
Vitamin K antagonists								
With	2	1	50.0	[1.3; 98.7]	4	1	25.0	[0.6; 80.6]
Without	359	44	12.3	[9.0; 16.1]	359	100	27.9	[23.3; 32.8]
NSAID								
With	40	4	10.0	[2.8; 23.7]	48	13	27.1	[15.3; 41.8]
Without	321	41	12.8	[9.3; 16.9]	315	88	27.9	[23.1; 33.2]
ASA								
With	7	0	0.0	[0.0; 41.0]	14	1	7.1	[0.2; 33.9]
Without	354	45	12.7	[9.4; 16.6]	349	100	28.7	[24.0; 33.7]
Penicillins								
With	3	0	0.0	[0.0; 70.8]	3	1	33.3	[0.8; 90.6]
Without	358	45	12.6	[9.3; 16.5]	360	100	27.8	[23.2; 32.7]
Cephalosporins								
With	311	43	13.8	[10.2; 18.2]	314	87	27.7	[22.8; 33.0]
Without	50	2	4.0	[0.5; 13.7]	49	14	28.6	[16.6; 43.3]
Anti-histamines & phenothiazines								
With	172	21	12.2	[7.7; 18.1]	177	50	28.2	[21.7; 35.5]
Without	189	24	12.7	[8.3; 18.3]	186	51	27.4	[21.1; 34.4]
Cardiac glycosides								
With	20	3	15.0	[3.2; 37.9]	16	5	31.3	[11.0; 58.7]
Without	341	42	12.3	[9.0; 16.3]	347	96	27.7	[23.0; 32.7]
Macrolide antibiotics								
With	1	0	0.0	[0.0; 97.5]	3	1	33.3	[0.8; 90.6]
Without	360	45	12.5	[9.3; 16.4]	360	100	27.8	[23.2; 32.7]
Tetracyclines								
With	2	1	50.0	[1.3; 98.7]	1	0	0.0	[0.0; 97.5]
Without	359	44	12.3	[9.0; 16.1]	362	101	27.9	[23.3; 32.8]
Other antibiotics								
With	7	2	28.6	[3.7; 71.0]	7	1	14.3	[0.4; 57.9]
Without	354	43	12.1	[8.9; 16.0]	356	100	28.1	[23.5; 33.1]
Vitamin C								
With	165	21	12.7	[8.1; 18.8]	159	50	31.4	[24.3; 39.3]
Without	196	24	12.2	[8.0; 17.7]	204	51	25.0	[19.2; 31.5]

NOTE: As per protocol, forbidden medications did not include heparin flushes up to 200 IU/day. NA = Not applicable
Sponsor's table in NDA Vol. 209, pp. 88-9

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 95-002 was a multicenter, randomized, double-blind, parallel-groups study comparing Org31540/SR90107A 2.5 mg once daily SC (n=526) to enoxaparin 30 mg twice daily SC (n=523) in 1049 patients undergoing elective major knee surgery or a revision of major knee surgery.

Administration of drugs was started post-operatively in all patients. Org31540/SR90107A was started 6±1 hours as compared to 21±2 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 1049 randomized patients in the study, 310 (30.0%) patients had missing primary efficacy endpoint due to non-evaluable venography/no VTE assessment up to day 11. Percentages of patients missing efficacy data were similar in the two treatment groups [156 (30.0%) in the Org31540/SR90107A group and 154 (29.8% in the enoxaparin group]. The missing rate associated with venography procedure in this study was compatible to other studies in patients undergoing elective knee replacement surgery (32% in overall 2 studies in NDA 20-164/002, Lovenox, FDA Medical Officer's Review, Page 8).

Overall, 95-002 was an adequate and well-controlled study. There were minor protocol deviations including use of not allowed concomitant medications (2.7% in Org31540/SR90107A group vs. 3.9% in enoxaparin group).

Study 95-002 demonstrated that Org31540/SR90107A 2.5 mg once daily SC is statistically significantly superior to enoxaparin 30 mg twice daily SC for the primary efficacy endpoint of VTE up to day 11 (12.5% vs. 27.8%, $p=2.7 \times 10^{-7}$). The difference between the two groups was mainly contributed by the component of DVT (12.5% vs. 27.0%, $p=9.6 \times 10^{-7}$). There was a significantly lower incidence of distal DVT only (9.4% vs. 21.3%, $p=9 \times 10^{-6}$) in the Org31540/SR901 treatment group as compared to the enoxaparin treatment group. There was no difference in the incidence of PE (0.3% vs. 1.1%, p=0.37) and proximal DVT (2.4% vs. 5.4%, p=0.057) up to day 11 between the two treatment groups. For symptomatic VTE, there was no difference between the two treatment groups up to day 11 (p=0.34) and up to day 49 (p=0.30).

The primary efficacy endpoint in favor of Org31540/SR901 treatment was seen significantly in United States alone (11.1% vs. 29.7%, $p=2.6 \times 10^{-8}$) but the difference between the two treatment groups was not observed in Canada (18.1% vs. 20.8%, p=0.69). The efficacy results in favor of Org31540/SR901 treatment were consistent across almost all subgroups including gender, age, BMI, type of anesthesia, type of surgery (primary or revision), duration of surgery, previous history of VTE, and baseline

creatinine level. The result was significantly in favor of Org31540/SR901 in the subgroup of patients with use of cement ($p<0.05$) but not in those without use of cement.

It appears that most patients enrolled in this study underwent knee replacement surgery although a major knee surgery, a more broad term, was required in the inclusion criteria. In response to FDA request to identify the specific type of major knee surgery the sponsor stated "it is not possible on the basis of the recorded information to identify the subset of patients undergoing 'knee replacement' versus 'other' surgery". However, in the NDA submission, all narratives submitted (45 patients who experienced death, SAEs, and/or discontinuation due to AE) indicated that knee replacement surgeries were performed in all these patients. Therefore, patients undergoing knee replacement surgery instead of major knee surgery should be used in the labeling. The Division has asked the FDA Division of Scientific Investigation to inspect the largest center (n=93) in the study, USA-0221, for the type of surgery in study patients. The result is pending at the time of review.

Trial 095001 ———

Title of the Study

A Multicenter, Concurrent Control, Randomized, Open-Label, Assessor-Blind, Dose-Ranging Study of Org 31540/SR90107A in the Prophylaxis of Deep Vein Thrombosis in Subjects Undergoing Total Knee Replacement Surgery

Study Period

November 1996 to March 1998

Investigators and Study Centers

The study was carried by investigators at 19 centers in the United States.

Study Objectives

The primary objective of this study was to establish the optimal dose of a once daily, subcutaneous (SC) injection of Org31540/SR90107A starting post-operatively and continuing for a minimum of 5 days for venous thrombosis prophylaxis following total knee replacement surgery.

Overall Study Design

This study was a Phase II, multicenter, randomized, open-label with assessor-blind, parallel, dose-ranging study of Org31540/SR90107A (0.75 mg, 1.5 mg, 3.0 mg, 6.0 mg, or 8.0 mg) once daily SC in patients undergoing elective total knee replacement surgery. Subjects were to be treated for a minimum of 5 days up to a maximum of 10 days.

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 4 to 6 weeks following the end of the treatment period.

Study Population

Inclusion Criteria

- 18 years of age
- Undergoing total knee replacement surgery
- Male, or a non-childbearing female (post-menopausal for more than 1 year or with hysterectomy or bilateral tubal ligation for at least 6 months prior to enrollment)
- Written informed consent given by the subject (or legal authorized representative).

Exclusion Criteria

- Any major orthopedic surgery less than 12 months prior to enrollment. Amendment 3 (effective September 15, 1997) changed this criterion to read as "Any major orthopedic surgery less than 3 months prior to enrollment."
- Body weight <45 kg or >135 kg
- Subject with known congenital or acquired bleeding tendency, or bleeding tendency revealed by one or more of the following pre-operative tests: platelet count <125 x 10^9/L, prothrombin time (PT) <65% of control or with an International Normalized Ratio (INR) >1.3, ratio activated partial thromboplastin time (aPTT)/control >1.2
- Serum creatinine >200 µmol/L (>2.3 mg/dL) in a well hydrated subject. Amendment 1 (effective September 25, 1996) changed this exclusion criterion to read as "Serum creatinine >141 µmol/L (>1.6 mg/dL) in a well hydrated subject."
- Systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg. Amendment 3 (effective September 15, 1997) changed this criterion to read as "systolic blood pressure >180 mm Hg or diastolic blood pressure >90 mm Hg."
- Previous (i.e., within last 3 months) ischemic or hemorrhagic cerebral stroke or myocardial infarction
- Participation in another clinical investigational drug study within the last 90 days
- Any contraindication to heparin (standard or low molecular weight heparin [LMWH]) or heparinoids
- Subject who had received one of the following forbidden drug(s) within one week prior to the start of the study: heparin (standard or LMWH) or heparinoid, anti-platelet drugs (e.g., ticlopidine, aspirin), oral anti-coagulant drugs (Vitamin K antagonists), fibrinolytic agents, and dextrans
- Known progressive malignant disease
- Known drug-addictive disorder or history of alcoholism
- Clinical signs or symptoms of PE or DVT within the last 12 months with confirmatory test results. Amendment 2 (effective December 6, 1996) changed this criterion to include clinical signs "and/or" symptoms of PE or DVT.
- Subject 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 and/or administering epidural or spinal anesthesia (e.g., more than two attempts or a bloody tap). Amendment 2 (effective December 6, 1996) added this exclusion criteria to the protocol.

Study Treatment

Treatment was to be initiated on Day 1 (day of surgery) and was to continue for a minimum of 5 days up to a maximum of 10 days. The first injection was to be administered within 6 ± 2 hours after closure of the surgical incision; on Day 2 to Day 10, the study drug was to be administered at 8:00 a.m. ± 2 hours. Protocol Amendment 3 added that if the first dose of study drug was administered after 8:00 p.m. but before 11:59 p.m. on Day 1, the Day 2 dose was not to be administered less than 12 hours later. All doses given thereafter (for Days 3-10) were to be administered every 24 hours starting from the time of the Day 2 dose.

Efficacy Endpoints

The primary endpoint was the incidence of adjudicated, confirmed deep vein thrombosis (DVT) occurring during the treatment period.

The secondary endpoints were the incidence of adjudicated, confirmed pulmonary embolism (PE) and the incidence of adjudicated, confirmed venous thromboembolic events (VTE), which included PE and DVT.

The efficacy outcomes were adjudicated by a central independent adjudication committee (CIAC). The criteria for DVT and PE used in this study were the same as Study 95001.

Safety Assessment

Bleeding assessments included the incidences of major and minor bleedings. Other safety variables included adverse events (AEs), laboratory parameters, and vital signs.

Major bleeding was defined as:

- Death due to bleeding
- Intra-cranial bleeding or bleeding within a critical organ (e.g., eye, or adrenal gland)
- Re-operation due to bleeding (hematoma) in the surgical area
- Clinically overt bleeding and/or quantitative blood loss which the CIAC deemed to be a major bleed.

Major bleeding also was adjudicated by an additional CIAC according to the Hamilton criteria as was done for the study 95001. All adjudication committees acted independently and were blinded to treatment allocation.

Statistical Methods

Sample size determination
Approximately 90 subjects were estimated to be randomized to each dose group with the expectation that 71 subjects per dose group would be included in the per-protocol Group. This sample size was expected to provide characterization of the dose-response curve based on simulations carried out under various assumptions by the sponsor. Additionally, with this sample size, if the incidence of DVT for the lowest dose group is assumed to be at least 30% versus an incidence of not more than 10% in a higher dose group, with a 2-tailed test at 5% level of significance, the power was at least 80%.

Stopping rule
A dose group was to be discontinued if either the lower limit of the two-sided 95% confidence interval (CI) for the incidence of DVT exceeded 15% for that dose group (based on the Per-Protocol Group) or the lower limit of the two-sided 95% CI for the incidence of major bleeding exceeded 3% for that dose group (based on the All-Subjects-Treated Group).. If a dose group was discontinued, subsequent subjects were to be randomized to one of the remaining dose groups.

Analyzed populations
All-Subjects-Treated: all randomized subjects who were treated with at least one dose.

Intent-to-Treat: subpopulation of All-Subjects-Treated Group who had total knee replacement surgery and, during the treatment period, an adjudicated evaluable bilateral (or positive unilateral) venogram, or a symptomatic adjudicated, confirmed PE or DVT.

Per-Protocol: subpopulation of the Intent-to-Treat Group excluding subjects with major protocol violations.

Efficacy analyses
The incidence (and the 95% CI) for DVT only (overall, proximal, and distal), PE only, and VTE (DVT and/or PE) were computed for each Org31540/SR90107A dose group. The relationship of dose and incidence of DVT was examined using a probit model.

Safety analyses
Analyses were performed for the All-Subjects-Treated Group. The incidences (and the 95% CIs) of major bleeds and minor bleeds only were computed for each Org31540/SR90107A dose group. The relationship of dose and incidence of major bleeding events was examined using a probit model. Descriptive statistics were calculated for the volume of blood loss and transfusions. All AEs, including those considered related to study drug (i.e., AEs with a relation to the study drug reported as definitely, probably, or possibly by the investigator,) were summarized by system-organ class and preferred term for the treatment period and the follow-up period. For laboratory parameters, descriptive statistics and the number (%) of subjects with postbaseline values outside of defined limits were presented.

Protocol Amendments

There were five amendments to the protocol for this study.

Amendment 1: September 25, 1996
Amendment 2: December 6, 1996
Amendment 3: September 15, 1997
Amendment 4: November 18, 1997
Amendment 5: April 21, 1998

The main changes included:

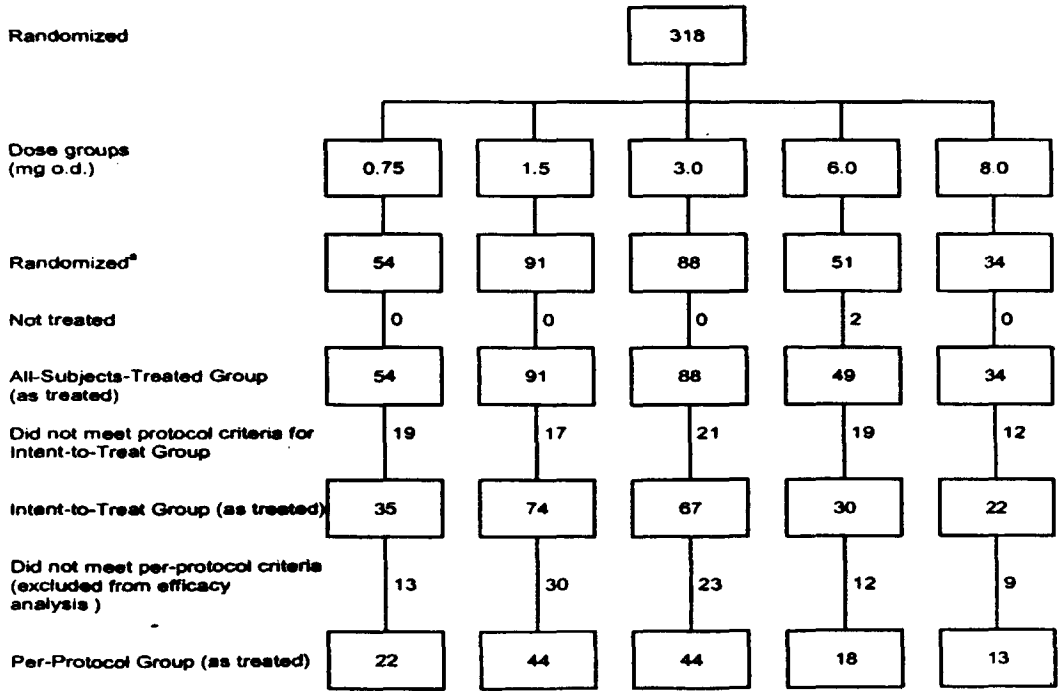
- Modifications of exclusion criterion (Amendment 1, 2, 3)
- Modification of dosing schedule (Amendment 3)
- Addition of criteria to determine the grade of bleeding and diagnostic criteria for assessing each subject's venogram (Amendment 4)
- Addition of criteria for major bleeding. (Amendment 5).

Study Results

Disposition of Patients

The sponsor's Figure 1 illustrates the disposition of subjects in this study.

Figure 1 Disposition of Subjects According to Dose Actually Received



* Four subjects received a different dose than the dose they were randomized to receive. In particular, 1 subject randomized to receive 1.5 mg received 8.0 mg, 1 subject randomized to receive 3.0 mg received 0.75 mg, and 2 subjects randomized to receive 3.0 mg received 1.5 mg. Subjects were counted in the All-Subjects Treated, Intent-to-Treat, and Per-Protocol Groups based on the dose they actually received (i.e., as treated). For all subject populations, this figure displays the information for the subjects based on the dose they actually received.
Data were taken from Appendices 13.7.1.3.1, 13.7.1.3.2, 13.7.1.4.1, and 13.7.1.4.2.

Sponsor's table in NDA Vol. 42, pp. 60

Of the 318 randomized subjects, two subjects (the 6.0mg group) did not receive study drug due to consent withdrawn or failure of vein access for confirmation of hemostasis after surgery. Of the 316 subjects received at least one dose of study drug, 88 did not meet Intent-to-Treat criteria due to no efficacy assessment or non-evaluable efficacy assessment. Therefore, the Intent-to-Treat Group consisted of 228 subjects. Of the 228 subjects in the Intent-to-Treat Group, 87 subjects did not meet the Per-Protocol criteria so the Per-Protocol Group consisted of 141 subjects.

Four subjects received a different dose than the dose they were randomized to receive. These four subjects were counted in their as-treated dose group (i.e., the actual dose received).

Randomization to the 0.75 mg, 6.0 mg, and 8.0 mg dose groups was terminated early during the study due to increased incidence of DVT that met the pre-specified stopping rule in the 0.75 mg dose group (11/17, 64.7%, 95% CI: 38.3-85.8%), and increased incidence of major bleeding that met the pre-specified stopping rule in 7.0mg dose group (5/45, 11.1%, 95% CI: 3.7-24.1%) and 8.0 mg dose group (4/32, 12.5%, 95% CI 3.5-29.0%).

Of the 316 treated subjects, 42 (13.3%) discontinued treatment prematurely (See Table below). The most common reason for premature discontinuation of study drug was other reasons and AEs/SAEs. The other reasons included subject's withdrawal of consent, refusal of venogram, and use of not allowed antithrombotic medication.

Number (%) of Subjects Discontinued Prematurely from Study Drug per Dose Group by Reason for Discontinuation - All-Subjects-Treated Group

Reason discontinued[a]	Dose group (mg o.d.)				
	0.75 (N = 54)	1.5 (N = 91)	3.0 (N = 88)	6.0 (N = 49)	8.0 (N = 34)
	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse event/serious adverse event	2(3.7)	1(1.1)	4(4.5)	4(8.2)	4(11.8)
Protocol violation	2(3.7)	5(5.5)	2(2.3)	1(2.0)	1(2.9)
Lack of efficacy	0(0.0)	0(0.0)	0(0.0)	1(2.0)	0(0.0)
Other reasons	4(7.4)	4(4.4)	4(4.5)	2(4.1)	1(2.9)

Sponsor's table in NDA Vol. 42, pp. 61

Protocol Violation/Deviations

A total of 163 (51.6%) of the 316 treated subjects had at least one major protocol violation. The most common violations were scheduled venography performed prior to the last dose of study drug or >12 hours after the last dose of study drug; improperly scheduled times of dosing (dose not taken within two hours of scheduled time); and no adjudicated venogram.

The number of patients with protocol deviations leading to their exclusion from All-Subject-Treated Group are summarized in the table below.

Number (%) of Subjects in the All-Subjects-Treated Group Not Included in the Intent-to-Treat Group by Dose Group and Reason for Exclusion

Reason for exclusion	Dose group (mg o.d.)				
	0.75	1.5	3.0	6.0	8.0
	(N = 54)	(N = 91)	(N = 88)	(N = 49)	(N = 34)
	n (%)	n (%)	n (%)	n (%)	n (%)
No efficacy assessment	12(22.2)	12(13.2)	14(15.9)	8(16.3)	6(17.6)
Non-evaluable assessment	7(13.0)	5(5.5)	7(8.0)	11(22.4)	6(17.6)
Total # of subjects excluded from Intent-to-Treat Group	19(35.2)	17(18.7)	21(23.9)	19(38.8)	12 (35.3)
Total # of subjects in the Intent-to-Treat Group	35(64.8)	74(81.3)	67(76.1)	30(61.2)	22(64.7)

Sponsor's table in NDA Vol. 42, pp. 63

The venograms of three subjects were lost and thus not adjudicated and were excluded from the efficacy analyses.

The number (%) of subjects excluded from the Per-Protocol Group by reason for exclusion and dose group is presented in the following table.

The most common reasons for excluding subjects from the Per-Protocol Group were improperly scheduled dosing from Day 2 - Day 10 (recorded for 18.9% - 27.3% of subjects across the dose groups) and venography performed either prior to or >12 hours after the last dose of study drug (recorded for 8.6% - 11.9% of subjects across the dose groups).

Number (%) of Subjects in the Intent-to-Treat Group Not Included in the Per-Protocol Group by Dose Group and Reason for Exclusion

Reason for exclusion	Dose group (mg o.d.)				
	0.75	1.5	3.0	6.0	8.0
	(N = 35)	(N = 74)	(N = 67)	(N = 30)	(N = 22)
	n (%)	n (%)	n (%)	n (%)	n (%)
Less then 5 days on drug unless positive venogram or PE prior to Day 5	0(0.0)	3(4.1)	0(0.0)	0(0.0)	0(0.0)
Venography prior to last dose or >12 hr after last dose	3(8.6)	7(9.5)	8(11.9)	3(10.0)	2(9.1)
Missed dose	0(0.0)	1(1.4)	0(0.0)	0(0.0)	0(0.0)
Use of prohibited prestudy/concomitant drugs	1(2.9)	6(8.1)	4(6.0)	1(3.3)	1(4.5)
First dose <4 hr or >8 hr from surgery	5(14.3)	7(9.5)	7(10.4)	0(0.0)	1(4.5)
Improperly scheduled dosing[a]	9(25.7)	14(18.9)	15(22.4)	7(23.3)	6(27.3)
Use of prohibited mechanical devices	0(0.0)	2(2.7)	2(3.0)	1(3.3)	0(0.0)
Previous surgery <3 months (after September 15, 1997) or <12 months (before September 15, 1997)	2(5.7)	1(1.4)	0(0.0)	1(3.3)	0(0.0)
Total # of subjects excluded from Per-Protocol Group	13(37.1)	30(40.5)	23(34.3)	12(40.0)	9(40.9)
Total # of subjects in Per-Protocol Group	22(62.9)	44(59.5)	44(65.7)	18(60.0)	13(59.1)

[a] Includes doses (other than the first dose) not taken within two hours of scheduled time
Note: Subjects were counted only once in the total # of subjects excluded from the PP Group.
Sponsor's table in NDA Vol. 42, pp. 65

Demographic and Other Characteristics

The following table presents the demographic and other subject characteristics for the All-Subjects-Treated Group.

The All-Subjects-Treated Group consisted of a population with a majority of females (64.2%), mainly of Caucasian (88.0%), with a mean age of 68.7 years. Nearly all of the subjects had primary surgery (95.3%) and use of cement (90.2%). The overall mean duration of the surgical procedure was 129.2 minutes, with similar mean durations across the five dose groups (122.1-131.6 minutes). For the type of anesthesia, 45.6% of subjects received only general anesthesia, 25.9% received only regional anesthesia, and 28.5% of the subjects received a combination of general, regional, or other anesthetics. No significant differences in demographic and baseline characteristics were observed among groups.

Demographic and Baseline Characteristics - All-Subjects-Treated Group

Parameter	Dose group (mg o.d.)									
	0.75 (N = 54)		1.5 (N = 91)		3.0 (N = 88)		6.0 (N = 49)		8.0 (N = 34)	
Age (yr)										
Mean	68.5		69.5		67.9		68.8		69.0	
SD	9.4		8.9		9.8		9.6		8.4	
Median	68.5		71.0		70.0		70.0		69.0	
MAX	90.0		87.0		84.0		88.0		84.0	
MIN	42.0		47.0		34.0		48.0		53.0	
<65: n(%)	14	(25.9)	25	(27.5)	27	(30.7)	12	(24.5)	8	(23.5)
65-75: n(%)	28	(51.9)	39	(42.9)	45	(51.1)	26	(53.1)	20	(58.8)
>75: n(%)	12	(22.2)	27	(29.7)	16	(18.2)	11	(22.4)	6	(17.6)
Weight (kg)										
Mean	82.6		84.4		84.6		82.0		81.7	
SD	19.8		14.5		18.6		17.5		19.2	
Median	86.0		84.8		83.9		81.2		79.4	
MAX	123.0		127.0		133.8		128.8		140.0	
MIN	47.6		54.9		52.2		52.3		49.9	
Height (cm)										
Mean	166.1		167.9		167.5		165.6		165.1	
SD	12.0		9.4		11.6		9.3		10.4	
Median	167.5		167.6		167.6		165.1		163.1	
MAX	189.0		200.0		195.5		191.0		190.0	
MIN	135.9		147.3		125.0		147.3		145.0	
Gender n (%)										
Male	20	(37.0)	37	(40.7)	34	(38.6)	14	(28.6)	8	(23.5)
Female	34	(63.0)	54	(59.3)	54	(61.4)	35	(71.4)	26	(76.5)

(Continued)

Parameter	Dose group (mg o.d.)									
	0.75 (N = 54)		1.5 (N = 91)		3.0 (N = 88)		6.0 (N = 49)		8.0 (N = 34)	
Race: n (%)										
Caucasian	46	(85.2)	83	(91.2)	81	(92.0)	42	(85.7)	26	(76.5)
Black	5	(9.3)	5	(5.5)	4	(4.5)	4	(8.2)	3	(8.8)
Other	3	(5.6)	3	(3.3)	3	(3.4)	3	(6.1)	5	(14.7)
Type of current surgery: n (%)										
Primary	53	(98.1)	83	(91.2)	83	(94.3)	48	(98.0)	34	(100)
Revision	1	(1.9)	8	(8.8)	5	(5.7)	1	(2.0)	0	(0)
Cemented n (%)										
Yes	49	(90.7)	83	(91.2)	78	(88.6)	44	(89.8)	31	(91.2)
No	4	(7.4)	7	(7.7)	8	(9.1)	5	(10.2)	3	(8.8)
Both[a]	1	(1.9)	0	0	2	(2.3)	0	0	0	0
Type of anesthesia n (%)										
General only	32	(59.3)	34	(37.4)	37	(42.0)	25	(51.0)	16	(47.1)
Spinal or epidural only	13	(24.1)	26	(28.6)	24	(27.3)	12	(24.5)	7	(20.6)
Combined[b]	9	(16.7)	31	(34.1)	27	(30.7)	12	(24.5)	11	(32.4)
Duration of surgical procedure[c] (minutes)										
Mean	130.9		131.6		130.3		122.1		127.1	
SD	52.2		43.5		40.4		44.4		36.7	
Median	117.5		115.0		119.0		110.0		115.0	
MAX	—		—		—		—		—	
MIN	—		—		—		—		—	

[a] Includes subjects who had both cemented and non-cemented technique.
[b] Includes a combination of general, regional and other types of anesthesia.
[c] Defined as the interval between the time of induction of anesthesia to the time of incision closure.
Data were taken from Appendix 13.7.1.5.1.

Sponsor's table in NDA Vol. 42, pp. 66-7

The following table presents a summary of the potential risk factors for DVT for the All-Subjects-Treated Group. The most common risk factors were the intake of estrogen and obesity (investigator's judgment), with 83 (26.3%) and 66 (20.9%) subjects having these factors, respectively. Other common risk factors were smoking history (46 subjects; 14.6%) and varicose veins (42 subjects; 13.3%).

Summary of Potential Risk Factors for DVT - All-Subjects-Treated Group

Potential risk factors	Dose group (mg o.d.)				
	0.75 (N = 54)	1.5 (N = 91)	3.0 (N = 88)	6.0 (N = 49)	8.0 (N = 34)
	n (%)	n (%)	n (%)	n (%)	n (%)
Obesity[a]	13(24.1)	19(20.9)	19(21.6)	9(18.4)	6(17.6)
Arterial or venous thromboembolic Problems	4(7.4)	7(7.7)	9(10.2)	4(8.2)	4(11.8)
Varicose veins	6(11.1)	16(17.6)	13(14.8)	4(8.2)	3(8.8)
Intake of estrogen	10(18.5)	21(23.1)	24(27.3)	17(34.7)	11(32.4)
Severe heart failure	0(0.0)	2(2.2)	0(0.0)	0(0.0)	0(0.0)
Rheumatoid arthritis	6(11.1)	9(9.9)	5(5.7)	3(6.1)	2(5.9)
Cancer	5(9.3)	13(14.3)	7(8.0)	3(6.1)	2(5.9)
Smoking history	10(18.5)	17(18.7)	11(12.5)	8(16.3)	0(0.0)
Other	2(3.7)	2(2.2)	4(4.5)	2(4.1)	5(14.7)

[a] Investigator's judgment
Note: Subjects may have none, one, or more than one potential risk factor.
Sponsor's table in NDA Vol. 42, pp. 68

The demographic and baseline characteristics for the Per-Protocol Group and Intent-to-treat group were comparable to those of the All-Subjects-Treated Group. The dose groups were comparable to each other for most demographic and baseline characteristics.

The findings for the potential risk factors for DVT for the Per-Protocol Group were comparable to those of the All-Subjects-Treated Group. The most common potential risk factors were the intake of estrogen and obesity (investigator's judgment), with 38 (27.0%) and 33 (23.4%) subjects having these factors, respectively. Other common potential risk factors were smoking history (21 subjects; 14.9%) and varicose veins (18 subjects; 12.8%).

Extent of Exposure

The following table presents a summary of the number of days on drug for the All-Subjects-Treated Group.

Summary Values for Number of Days on Study Drug by Dose Group
All-Subjects-Treated Group

Number of days on drug[a]	Dose group (mg o.d.)				
	0.75	1.5	3.0	6.0	8.0
	(N = 54)	(N = 91)	(N = 88)	(N = 49)	(N = 34)
Mean	6.0	5.8	5.7	5.8	6.1
SD	1.5	1.7	1.7	1.7	1.7
Median	6.0	5.0	5.0	5.0	6.0
MAX	[redacted]				
MIN					

[a] number of days on drug = number of injections, except for two subjects who missed a dose (1 in the 1.5 mg dose group and 1 in the 6.0 mg dose group).
Sponsor's table in NDA Vol. 42, pp. 75

The mean and median number of days on drug were comparable across all dose groups, ranging from 5.7 to 6.1 days.

Concomitant Medications

The percentage of subjects taking concomitant antithrombotic medications from first dose to the day before venography (ITT Group) or the day before last dose (for subjects excluded from the ITT Group) ranged from 1.9% to 4.1% across all dose groups.

The overall percentage of subjects in the All-Subjects-Treated Group using mobilization, elastic bandages/stockings, or elevation of the foot was 97.2%, 91.1%, and 89.6%, respectively. The use of these physical methods for prophylaxis of DVT was comparable across the dose groups.

Efficacy Evaluation

Primary efficacy endpoint

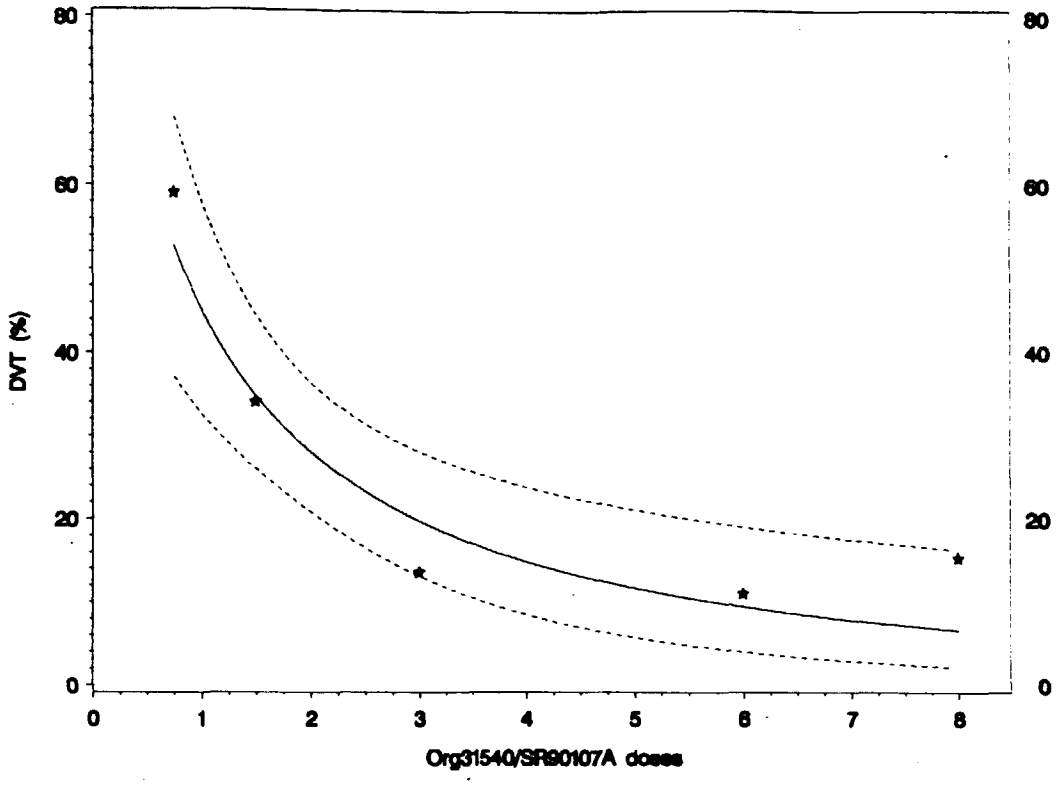
The following table presents the number and percentage of patients with adjudicated DVT, proximal DVT and distal only DVT in this study by treatment group.

Number (%) of Patients with any Adjudicated total DVT, Proximal DVT, and Distal only DVT During the Treatment Period (Per-Protocol Population)

DVT		Org31540/SR90107A				
		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 = 22)	(N = 44)	(N = 44)	(N = 18)	(N = 13)
Total DVT	n (%)	13 (59.1)	15 (34.1)	6 (13.6)	2 (11.1)	2 (15.4)
	95% CI	[36.4; 79.3]	[20.5; 49.9]	[5.2; 27.4]	[1.4; 34.7]	[1.9; 45.4]
Any proximal DVT	n (%)	1 (4.5)	2 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)
	95% CI	[0.1; 22.8]	[0.6; 15.5]	[NA; NA]	[NA; NA]	[NA; NA]
Distal only DVT	N	12 (54.5)	13 (29.5)	6 (13.6)	1 (5.6)	2 (15.4)
	95% CI	[32.2; 75.6]	[16.8; 45.2]	[5.2; 27.4]	[0.1; 27.3]	[1.9; 45.4]

Reviewer's table based on sponsor's table in NDA Vol. 42, pp. 84

The following Figure presents a plot of the percentages of patients with DVT per Org31540/SR90107A dose.



★:observed incidence for Org31540/SR90107A group, and probit estimation with 95% CI fiducial limit

Figure (4.2.4) 1 - Plot of the Percentage of Patients with Adjudicated DVT During the Treatment Period by Org31540/SR90107A Dose in 095-001 (PP Population)

Sponsor's table in NDA Vol. 42, pp. 85

The primary analysis demonstrated a statistically significant dose-dependent effect for Org31540/SR90107A (p=0.0001). The incidence of DVT decreased with increasing Org31540/SR90107A dose.

In the ITT Group, the incidence of DVT was 40.0% and 28.4% in the 0.75 mg and 1.5 mg groups, compared with 17.9%, 13.8%, and 18.2% in the 3.0 mg, 6.0 mg, and 8.0 mg dose groups, respectively. ITT analyses on the primary endpoint for dose-dependent effect were consistent with those of the primary analysis described above (p = 0.006 for protocol defined ITT)

Secondary efficacy endpoints

The following table presents the number and percentage of patients with adjudicated VTE and 95% CIs in this study by treatment group.

Number (%) of Subjects with a VTE During the Treatment Period by Dose Group Per-Protocol Group

Number (%) of subjects Positive for VTE	Dose group (mg o.d.)				
	0.75	1.5	3.0	6.0	8.0
	(N = 22)	(N = 44)	(N = 44)	(N = 18)	(N = 13)
n (%)	13 (59.1)	15 (34.1)	6 (13.6)	2 (11.1)	2 (15.4)
95% C.I.	36.4 - 79.3	20.5 - 49.9	5.2 - 27.4	1.4 - 34.7	1.9 - 45.4

Sponsor's table in NDA Vol. 42, pp. 90

The following table presents the result from Intent-to-Treat group.

Number (%) of Subjects with a VTE During the Treatment Period by Dose Group Intent-to-Treat Group

Number (%) of subjects Positive for VTE	Dose group (mg o.d.)				
	0.75	1.5	3.0	6.0	8.0
	(N = 35)	(N = 74)	(N = 67)	(N = 30)	(N = 22)
n (%)	14 (40.0)	21 (28.4)	12 (17.9)	5[a](16.7)	4 (18.2)
95% C.I.	23.9 - 57.9	18.5 - 40.1	9.6- 29.2	5.6 - 34.7	5.2 - 40.3

[a] One subject had a confirmed PE.
Sponsor's table in NDA Vol. 42, pp. 90

Only 1 subject in this study (6.0 mg group) had a confirmed PE. The subject received study drug for 5 days, and 3 days after the last dose of study drug a ventilation perfusion (V/Q) scan was done, which was adjudicated by the CIAC as "high" probability of PE. Although this diagnostic testing was done more than 48 hours after the last dose, suspicion of PE arose during the treatment period. This subject was not included in the PP population because of a major protocol violation.

Since there was 1 confirmed PE which was not included in the PP population, the results for adjudicated VTE were the same as for DVT with a statistically significant dose-dependent effect (p = 0.0001).

Reviewer's Summary

Study 095001 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 without comparative treatment group in 318 patients undergoing total knee replacement surgery. 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 study in patients undergoing elective total knee replacement surgery.

During the study, 3 dose groups (0.75mg, 6.0mg and 8.0 mg) were terminated early due to the pre-specified stopping rule for increased rate of DVT (0.75mg dose group) and increased rate of major bleeding (6.0 and 8.0 mg dose groups).

The study demonstrated a statistically significant dose response within the selected dose range for the per protocol population (p=0.0001) and for the intent-to-treat population (p=0.006). Between the two completed groups, the 3.0 mg Org31540/SR90107A dose group had a lower incidence of VTE as compared to the 1.5 mg Org31540/SR90107A dose group for the intent-to treated population (17.9% vs. 28.4%) and for per protocol population (13.6% vs. 34.1%).

Study 095001 provided the basis of dose selection for Phase III study (95-002) in patients undergoing knee replacement surgery. The finding of a significant dose response relationship in this study supported the efficacy of the drug in patients undergoing knee replacement surgery.

D. Efficacy Conclusions

For prophylaxis of VTE in patients undergoing hip fracture surgery

One pivotal trial (Study EFC2698) was submitted to support this proposed indication. Study EFC2698 was a multicenter (99 centers in 21 countries), randomized, double-blind, double-dummy, parallel groups controlled study of Org31540/SR90107A 2.5 mg SC once daily as compared to enoxaparin 40 mg SC once daily in patients undergoing hip fracture surgery. 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. A total of 1711 patients (849 in the Org31540/SR90107A group and 862 in the enoxaparin group) were randomized in the study, 1673 were treated, and 1250 (626 in the Org31540/SR90107A group and 624 in the enoxaparin group) were evaluable for the primary efficacy endpoint. Patients ranged in age from 17 to101 years (mean age 77.0 years) with 25% of men and 75% of women. Patients were 99.2% Caucasian, 0.8% other races. Administration of drugs was started post-operatively in majority of patients (88% in the Org31540/SR90107A group and 74% in the enoxaparin group). Org31540/SR90107A was started 6±2 hours after surgical closure as compared to 18±5 hours for enoxaparin for post-operatively administration. The average treatment duration was 7±2 days. The study was an adequate and well-controlled study.

Study EFC2698 demonstrated that Org31540/SR90107A 2.5 mg once daily SC is superior to enoxaparin 40 mg once daily SC with highly statistically significance for the primary efficacy endpoint of VTE up to day 11 (8.3% vs. 19.1%, $p=2.6 \times 10^{-8}$). The difference between the two groups was mainly contributed by the component of DVT (7.8% vs. 18.1%, $p=1 \times 10^{-8}$). There was a significantly lower incidence of proximal DVT (0.9% vs. 4.3%, p=0.0001) as well as distal DVT (6.7% vs. 15.0%, $p=2 \times 10^{-6}$) in the Org31540/SR901 treatment group as compared to the enoxaparin treatment group. There was no difference in the incidence of PE up to day 11 between the two treatment groups (0.5 % in each treatment group, p=1.0). For symptomatic VTE, there was no difference between the two treatment groups up to day 11 (0.5 % in each treatment group, p=1.0) and up to day 49 (2.0% vs. 1.5%, p=0.47).

The following characteristics of study EFC2698 make this single study adequate to support the effectiveness claim (See Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, Section II (C) 3 Evidence of Effectiveness from a Single Study).

1. Large multicenter study

In a large multicenter study in which
(1) no single study site provided an unusually large fraction of the patients and
(2) no single investigator or site was disproportionately responsible for the favorable effect seen, the study's internal consistency lessens concerns about lack of generalizability of the finding or an inexplicable result attributable only to the practice of a single investigator.

Study EFC2698 enrolled 1711 patients undergoing hip fracture surgery at 99 centers in 21 countries. The number of patients at each center ranged from a single patient to 74 patients. When the efficacy result was analyzed by center, there were 50 centers (51%) numerically in favor of Org31540/SR90107A while only 15 centers (16%) favored enoxaparin. When analyzed by country, the results showed 18 of 21 countries were numerically in favor of Org31540/SR90107A. The difference was statistically significant ($p<0.05$) in 4 countries (Czech Republic, Australia, The Netherlands, and Poland). Czech Republic had a more pronounced significant result in favor of Org31540/SR90107A than other countries; however, the overall efficacy results excluding this center remained significantly in favor of Org31540/SR90107A ($p=5 \times 10^{-5}$).

2. Consistency across study subsets

Study EFC2698 showed consistency of the efficacy results in favor of Org31540/SR90107A across most countries, gender, age, body mass index, creatinine level, previous history of VTE, previous history of antithrombotic medication, type of fracture, type of anesthesia, type of prosthesis, use of cement, and duration of surgery. In this study, 99% of study patients were Caucasian.

The positive results in favor of Org31540/SR90107A in study EFC2698 were also supported by Studies 63118 and 95002 where patients undergoing total hip and knee replacement surgery were studied, respectively.

3. Statistically very persuasive finding

The Study EFC2698 demonstrated superior efficacy of Org31540/SR90107A over enoxaparin with a very low p-value (3×10^{-8}). This indicates that the result is highly inconsistent with the null hypothesis of no difference between the two treatments. The study results by country showed 18 of 21 centers in favor of Org31540/SR90107A with a statistically significant result in 3 centers (Czech Republic: $p=1 \times 10^{-5}$, Australia: $p=0.013$, The Netherlands: $p=0.003$, and Poland: $p=0.024$).

Study EFC2698 did not enroll any US center. However, the results from study 95002 that was conducted mostly in US patients undergoing knee replacement surgery supported the antithrombotic effect of Org31540/SR90107A in the US population.

In the proposed indication, prophylaxis of VTE that includes DVT and PE was proposed. Although VTE was a primary efficacy endpoint in Study EFC2698, the difference in the incidence of VTE between the two treatment groups was mainly due to difference in the incidence of DVT. There were no differences between the incidence of PE between the two treatment groups. Therefore, DVT instead of VTE should be the event in the proposed indication.

Overall, the sponsor has provided substantial evidence to support the indication of prophylaxis of DVT, which may lead to PE, in patients undergoing hip fracture surgery.

For prophylaxis of VTE in patients undergoing total hip replacement surgery

Two pivotal studies (63118 and EFC2442) and one supportive dose-ranging study (DRI2643) were submitted for this indication.

Study 63118 was a multicenter (74 centers in 16 European countries), randomized, double-blind, double dummy, parallel groups study of Org31540/SR90107A 2.5 mg SC once daily as compared to enoxaparin 40 mg SC once daily in patients undergoing hip replacement surgery. 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. A total of 2324 patients (1162 in each treatment group) were randomized in the study, 2278 were treated, and 1827 (908 in the Org31540/SR90107A group and 919 in the enoxaparin group) were evaluable for the primary efficacy endpoint. Patients ranged in age from 24 to 97 years (mean age 65.3 years) with 43% of men and 57% of women. Patients were 99.2% Caucasian, 0.8% other races. Administration of drugs was started post-operatively in nearly all patients (99%) in the Org31540/SR90107A group and 22% in the enoxaparin group. In the enoxaparin group, the mean time between the last active pre-operative injection and start of surgery was 13±14 hours. The mean time between the end of the surgery and the first active post-operative injection was 6±4 hours in the Org31540/SR90107A group and 13±6 hours in the enoxaparin group. The average treatment duration was 7±2 days. This study was an adequate and well-controlled study.

Study 63118 demonstrated that Org31540/SR90107A 2.5 mg once daily SC is superior to enoxaparin 40 mg once daily SC with a highly statistically significant result for the primary efficacy endpoint of VTE up to day 11 (4.1% vs. 9.2%, $p=9 \times 10^{-6}$). The difference between two groups was mainly contributed by the component of DVT (4.0% vs. 9.0%, $p=1 \times 10^{-5}$). There was a significantly lower incidence of proximal DVT (0.7% vs. 2.5%, p=0.002) as well as distal DVT (3.3% vs. 7.3%, p=0.0001) in the Org31540/SR901 treatment group as compared to the enoxaparin treatment group. There was no difference in the incidence of PE up to day 11 between the two treatment groups

(0.2% in each treatment group, p=1.0). For symptomatic VTE, there was no difference between the two treatment groups up to day 11 (p=0.73) and up to day 49 (p=0.66).

Study EFC2442 was a multicenter (139 centers in 3 countries including 94 centers in US), randomized, double-blind, parallel group study of Org31540/SR90107A 2.5 mg SC post-operatively once daily as compared to enoxaparin 30 mg SC post-operatively twice daily in patients undergoing hip replacement surgery. 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. The main difference between EFC2442 and 63118 was the dose regimen for enoxaparin. A total of 2275 patients (1138 in the Org31540/SR90107A group and 1137 in the enoxaparin group) were randomized in the study, 2257 were treated, and 1584 (787 in the Org31540/SR90107A group and 797 in the enoxaparin group). Patients ranged in age from 18 to 92 years (mean age 64.6 years) with 48% of men and 52% of women. Patients were 93.8% Caucasian, 4.3% Black, <1% Oriental, and 1.7% others.

Study EFC2442 failed to demonstrate superiority of Org31540/SR90107A 2.5 mg post-operatively once daily SC over enoxaparin 30 mg SC post-operatively every 12 hours for the 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 SC post-operatively once daily had a numerically lower incidence of VTE up to day 11 than those treated with enoxaparin 30 mg SC post-operatively every 12 hours (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/SR90107A treatment group as compared to the enoxaparin treatment group. There was no difference in the incidence of PE (p=0.12) and proximal DVT (p=0.42) up to day 11 between the two treatment groups. For symptomatic VTE, there was a statistically significantly higher incidence in the Org31540/SR901 group as compared to that in the enoxaparin group up to day 11 (p=0.006) and up to day 49 (p=0.013).

There were inconsistent results among 3 countries for the primary efficacy endpoint in Study EFC2442. The incidence of VTE up to day 11 was numerically lower in the 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 the Org31540/SR90107A group as compared to the enoxaparin group. After adjusting for the interaction between treatment and country, the p-value for treatment (p=0.069) still failed to reach statistical significance, but was close to the 0.05 significance level.

Although Study EFC2442 failed to show superiority of Org31540/SR90107A over enoxaparin for VTE up to day 11, the overall results including the lower incidence of VTE and the significant reduction of DVT rate in patients who received Org31540/SR90107A treatment are consistent with results from Study 63118.

Study DRI 2643 was a multicenter, randomized, comparative controlled with enoxaparin, phase II dose-ranging study in 950 patients undergoing hip replacement surgery. This

study demonstrated a statistically significant dose response among 5 Org31540/SR90107A selected doses (p=0.0024). The 3.0 mg Org31540/SR90107A SC once daily dose group had a statistically significantly lower incidence of VTE as compared to 0.75 mg Org31540/SR90107A dose group (2.0% vs. 12.7%, p=0.005) and enoxaparin 30 mg SC twice daily group (2.0% vs. 9.3%, p=0.019). This study provided the basis for dose selection in Phase III trials and the results support the efficacy claim.

In the proposed indication, prophylaxis of VTE that includes DVT and PE was proposed. Although VTE was a primary efficacy endpoint in Study 63118, the difference in the incidence of VTE between the two treatment groups was mainly due to difference in the incidence of DVT. There were no differences in the incidence of PE between the two treatment groups in Study 63118 or in Study EFC2442. Therefore, DVT instead of VTE should be the event in the proposed indication.

Overall, the sponsor has provided substantial evidence to support the indication of prophylaxis of DVT, which may lead to PE, in patients undergoing total hip replacement surgery.

For prophylaxis of VTE in patients undergoing major knee surgery

One single pivotal study (95-002) and one supportive phase II dose-ranging study (95001) were submitted for this indication.

Study 95002 was a multicenter (64 centers in US and Canada), randomized, double-blind, parallel groups study of Org31540/SR90107A 2.5 mg SC post-operatively once daily as compared to enoxaparin 30 mg SC post-operatively twice daily in patients undergoing major knee surgery. 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. A total of 1049 patients (526 in the Org31540/SR90107A group and 523 in the enoxaparin group) were randomized in the study, 1034 were treated, and 724 (361 in the Org31540/SR90107A group and 363 in the enoxaparin group) were evaluable for the primary efficacy endpoint. Patients ranged in age from 19 to 94 years (mean age 67.5 years) with 41% of men and 59% of women. Patients were 88% Caucasian, 8% Black, <1% Oriental, and 3% others. This study was an adequate and well-controlled study.

Study 95-002 demonstrated that Org31540/SR90107A 2.5 mg post-operatively once daily SC is superior to enoxaparin 30 mg SC post-operatively twice daily with a highly statistically significant result for the primary efficacy endpoint of VTE up to day 11 (12.5% vs. 27.8%, $p=2.7 \times 10^{-7}$). The difference between two groups was mainly contributed by the component of DVT (12.5% vs. 27.0%, $p=9.6 \times 10^{-7}$). There was a significantly lower incidence of distal DVT only (9.4% vs. 21.3%, $p=9 \times 10^{-6}$) in the Org31540/SR901 treatment group as compared to the enoxaparin treatment group. There was no difference in the incidence of PE (0.3% vs. 1.1%, p=0.37) and proximal DVT (2.4% vs. 5.4%, p=0.057) up to day 11 between the two treatment groups. For

symptomatic VTE, there was no difference between the two treatment groups up to day 11 (p=0.34) and up to day 49 (p=0.30).

The following characteristics of study 95002 that make the study as adequate support for the effectiveness claim (See Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products II (C) 3 Evidence of Effectiveness from a Single Study).

1. Large multicenter study

In a large multicenter study in which
(3) no single study site provided an unusually large fraction of the patients and
(4) no single investigator or site was disproportionately responsible for the favorable effect seen, the study's internal consistency lessens concerns about lack of generalizability of the finding or an inexplicable result attributable only to the practice of a single investigator.

Study 95-002 enrolled 1049 patients undergoing knee replacement surgery at 64 centers in two countries. The number of patients at each center ranged from a single patient to 93 patients. When efficacy result analyzed by center, there were 32 centers (50%) in favor of Org31540/SR90107A while only 7 centers (11%) in favor of enoxaparin. When analyzed by country, the results in both countries were in favor of Org31540/SR90107A. The US itself had a significant result in favor of Org31540/SR90107A (11.1% vs. 29.7%, $p=2.6 \times 10^{-8}$).

2. Consistency across study subsets

Study 95002 showed a consistent efficacy result in favor of Org31540/SR90107A across country, gender, age, body mass index, creatinine level, previous history of VTE, type of surgery (primary or revision), type of anesthesia (regional only or other), use of cement, and duration of surgery. In this study, 88% of randomized patients were Caucasian and this population showed a result in favor of Org31540/SR90107A.

The positive results in favor of Org31540/SR90107A in study 95002 were also supported by Study EFC2698 and 63118 where patients undergoing hip fracture surgery and hip replacement surgery were studied, respectively.

3. Statistically very persuasive finding

Study 95002 demonstrated superior efficacy of Org31540/SR90107A over enoxaparin with a very low p-value (3×10^{-7}). This indicates that the result is highly inconsistent with the null hypothesis of no difference between the two treatments. The study results by center showed 32 of 64 centers numerically in favor of Org31540/SR90107A while only 7 of 64 centers were in favor of enoxaparin; the remaining centers were even.

It appears that most of the patients enrolled in this study underwent knee replacement surgery although a major knee surgery, a more broad term, was required in the inclusion

criteria. When requested to identify the specific type of major knee surgery, the sponsor responded that it was unable to identify the type of major knee surgeries in this study. However, in the NDA submission, the narratives for all 45 patients (deaths, SAEs, and discontinuation) indicated that knee replacement surgeries were performed in all these patients. Therefore, patients undergoing knee replacement surgery instead of major knee surgery should be used in the labeling.

Study 95001 was a multicenter, randomized, open-label, no-comparative group controlled, phase II dose-ranging study in 318 patients undergoing knee replacement surgery. This study demonstrated a statistically significant dose response among 5 selected doses of Org31540/SR90107A ($p=0.006$). This study provided supportive information for dose selection in Phase III trials and the results support the proposed claim.

In the proposed indication, prophylaxis of VTE that includes DVT and PE was proposed. Although VTE was a primary efficacy endpoint in Study 95-002, the difference in the incidence of VTE between the two treatment groups was mainly due to difference in the incidence of DVT. There were no differences in the incidence of PE between the two treatment groups in Study 95-002. Therefore, DVT instead of VTE should be the event in the proposed indication.

Overall, the sponsor has provided substantial evidence to support the indication of prophylaxis of DVT, which may lead to PE, in patients undergoing knee replacement surgery.

X. Conclusions and Recommendations

A. Overall Efficacy Conclusions

For prophylaxis of DVT in patients undergoing hip fracture surgery
There is no currently approved product for prophylaxis of DVT, which may lead to PE, in patients undergoing hip fracture surgery. Pulmonary embolism is one of the most common causes of death in this population. The current application has demonstrated the effectiveness of fondaparinux sodium 2.5mg SC post-operatively once daily by showing superior to enoxaparin 40 mg SC post-operatively once daily for prophylaxis of DVT in patients undergoing hip fracture surgery ($p<0.0001$). Fondaparinux sodium may provide significant benefit to this population.

For prophylaxis of DVT in patients undergoing hip replacement surgery
The current application has demonstrated that fondaparinux sodium 2.5 mg SC post-operatively once daily is superior to an established approved regimen, enoxaparin 40 mg SC pre-operatively once daily, with statistically significance ($p<0.0001$), but was not superior to enoxaparin 30 mg SC post-operatively every 12 hours, for prophylaxis of DVT in patients undergoing hip replacement surgery. Since there is a high risk of DVT, which may lead to a life-threatening complication PE, in patients undergoing hip replacement surgery, fondaparinux sodium, a product with better effectiveness than an

approved regimen (enoxaparin 40mg SC once daily), may provide more benefit to this population.

For prophylaxis of DVT in patients undergoing knee replacement surgery
The current application has demonstrated that fondaparinux sodium 2.5 mg SC post-operatively once daily is superior to an established approved product (enoxaparin 30 mg SC post-operatively every 12 hours) with highly statistically significant ($p<0.0001$) for prophylaxis of DVT in patients undergoing knee replacement surgery. Since there is a high risk of DVT, which may lead to a life-threatening complication PE, in patients undergoing knee replacement surgery, fondaparinux sodium, a product with better effectiveness than currently approved product (enoxaparin), may provide more benefit to this population.

The effectiveness of this product has not been studied adequately in other races other than Caucasian.

B. Recommendations
From a clinical perspective for efficacy review, fondaparinux sodium should be approved for prophylaxis of DVT, which may lead to PE, in patients undergoing hip fracture surgery, hip replacement surgery, or knee replacement surgery with the following labeling recommendations (See also Appendix 1).

1. The indications section of the labeling should be revised to read as follows:

   ARIXTRA™ is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism:
   - in patients undergoing hip fracture surgery
   - in patients undergoing hip replacement surgery
   - in patients undergoing knee replacement surgery.

   The proposed indication stated as "major orthopedic surgery of the lower limbs" is inappropriate. The specific populations as stated above should be used in the labeling.

   The proposed wording "prevention of venous thromboembolic events" is inappropriate. The "prophylaxis of DVT, which may lead to PE" should be used in the labeling to be consistent with labeling of other products.

2. In clinical studies section of the labeling, the following should be revised:

1) The first three paragraphs regarding "major orthopedic surgery of the lower limbs" and the [redacted] should be deleted.
2) The number of patients enrolled and treated and the demographic data of patients (age, gender and race) should be presented under each clinical trial section.
3) The category of PE for each clinical trial should be added in the table of efficacy results.

3. In dosage and administration section, the last sentence [redacted] should be deleted.

See Dr. Ann Farrell's Medical Review for safety conclusions and recommendations.

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Kathy Robie-Suh
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MEDICAL OFFICER

Lilia Talarico
7/20/01 02:24:47 PM
MEDICAL OFFICER

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