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	49/624 7.9%	117/623 18.8%	-10.9%	$1x10^{-8}$
Any proximal DVT	6/650 0.9%	28/646 4.3%	-3.4	0.0001
Distal DVT only	42/627 6.7%	94/626 15.0%	-8.3	$2x10^{-6}$

p-value for distal DVT only was obtained by FDA Statistical Reviewer Dr. Mushfiqur Rashid, Ph.D.
Reviewer's table based on NDA Vol. 81, pp. 88-9

The DVT rates by side of examination (operative/non-operative leg) between two treatments are presented in the following table. A slightly higher incidence of DVT was observed in operated leg in the Org31540/SR90107A group and a nearly doubled incidence rate of DVT was observed in operated leg in the enoxaparin group as compared to non-operated leg.

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 40 mg o.d.
Any DVT		
Either side	49/624 (7.9) [5.9; 10.2]	117/623 (18.8) [15.8; 22.1]
Operative leg	30/652 (4.6) [3.1; 6.5]	89/660 (13.5) [11.0; 16.3]
Non-operative leg	23/642 (3.6) [2.3; 5.3]	52/645 (8.1) [6.1; 10.4]
Both sides	4/670 (0.6) [0.2; 1.5]	24/682 (3.5) [2.3; 5.2]
Any proximal DVT		
Either side	6/650 (0.9) [0.3; 2.0]	28/646 (4.3) [2.9; 6.2]
Operative leg	4/672 (0.6) [0.2; 1.5]	19/684 (2.8) [1.7; 4.3]
Non-operative leg	2/670 (0.3) [0.0; 1.1]	10/660 (1.5) [0.7; 2.8]
Both sides	0/692 (0.0) [0.0; 0.5]	1/698 (0.1) [0.0; 0.8]
Distal DVT only		
Either side	42/627 (6.7) [4.9; 8.9]	94/626 (15.0) [12.3; 18.1]
Operative leg	25/658 (3.8) [2.5; 5.6]	70/665 (10.5) [8.3; 13.1]
Non-operative leg	21/644 (3.3) [2.0; 4.9]	40/649 (6.2) [4.4; 8.3]
Both sides	4/675 (0.6) [0.2; 1.5]	16/688 (2.3) [1.3; 3.7]

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. 81, pp. 88

Curative treatment initiated after VTE assessment and prolonged prophylaxis of VTE

The number (%) of patients who had antithrombotic curative treatment initiated based on Investigator assessment of VTE up to Day 11 was higher (p=0.0003) in the enoxaparin group (Table below).

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

Curative Treatment[a]	Org31540/SR90107A 2.5 mg o.d. (N[b]= 702)	enoxaparin 40 mg o.d. (N[b]= 716)
All patients with curative treatment	43 (6.1%)	84 (11.7%)
Heparin (UFH, LMWH)/heparinoids	40 (5.7%)	80 (11.2%)
Vitamin K antagonist without heparin (UFH, LMWH)/heparinoids	1 (0.1%)	2 (0.3%)
Other than heparin or vitamin K antagonist	2 (0.3%)	2 (0.3%)

a Patients were only counted once b Number of patients with any VTE assessment up to Day 11
Sponsor's table in NDA Vol. 81, pp. 89

During the follow-up period, prolonged prophylaxis of VTE (mainly LMWH and vitamin K antagonist) was administered to 58.5% (461/788) of patients in the Org31540/SR90107A group and 55.8% (423/758) of patients in the enoxaparin group for the all treated patients population who did not receive curative treatment.

The number (%) of patients who had antithrombotic curative treatment initiated following the qualifying VTE examination used in the primary efficacy analysis was higher ($p=4.2x10^{-5}$) in the enoxaparin group (See Table below).

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

Curative Treatment[a]	Org31540/SR90107A 2.5 mg o.d. (N = 626)	Enoxaparin 40 mg o.d. (N= 624)
All patients with curative treatment	37 (5.9%)	80 (12.8%)
Heparin (UHF, LMWH)/heparinoids	34 (5.4%)	76 (12.2%)
Vitamin K antagonist without heparin (UHF, LMWH)/heparinoids	1 (0.2%)	2 (0.3%)
Other than heparin or vitamin K antagonist	2 (0.3%)	2 (0.3%)

[a] Patients were only counted once
Sponsor's table in NDA Vol. 81, pp. 90

During the follow-up period, prolonged prophylaxis of VTE (mainly LMWH and vitamin K antagonist) was administered to 57.9% (341/589) of patients in the Org31540/SR90107A group and 55.3% (301/544) 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.

A similarly low rate of symptomatic VTE was observed in both treatment groups up to Day 11. During this time period, 4 symptomatic VTEs (2 fatal PEs, 1 non-fatal PE and 1 symptomatic DVT) were recorded in each treatment group. Similarly, the rate of symptomatic VTE up to Day 49 was low and did not significantly differ between the 2 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 = 831)	Enoxaparin 40 mg o.d. (N = 840)	Fisher's Exact Test Result (p)
Up to Day 11	VTE	n (%) 95% CI	4 (0.5%) [0.1; 1.2]	4 (0.5%) [0.1; 1.2]	1.00
	DVT	n (%)	1 (0.1%)	1 (0.1%)	
	Non-fatal PE	n (%)	0 (0.0%)	1 (0.1%)	
	Fatal PE	n (%)	3 (0.4%)	2 (0.2 %)	
Up to Day 49	VTE	n (%) 95% CI	17 (2.0%) [1.2; 3.3]	13 (1.5%) [0.8; 2.6]	0.47
	DVT	n (%)	8 (1.0%)	3 (0.4%)	
	Non-fatal PE	n (%)	3 (0.4%)	4 (0.5%)	
	Fatal PE	n (%)	8 (1.0%)	7 (0.8%)	

Reviewer's table based on sponsor's tables in NDA Vol 81, pp. 91

Symptomatic VTEs recorded up to Day 49 were also summarized in the form of cumulative event rate curve, using Kaplan-Meier method; the comparison of the 2 groups revealed no statistically significantly difference in terms of time to the first event.

Exploratory analysis for primary efficacy endpoint

Subgroup analysis and adjustment for covariates

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

The treatment effect in favor of Org31540/SR90107A was shown numerically in 18 of 21 countries and statistically significantly in 3 countries (Czech Republic: $p=1 \times 10^{-5}$, Australia: p=0.013, The Netherlands: p=0.003, and Poland: p=0.024). The between-group difference in favor of Org31540/SR90107A was significantly more pronounced for the Czech Republic than for the other countries (covariate x treatment interaction significant with p=0.02). After removing Czech Republic from efficacy analysis, the incidence of VTE up to day 11 remained significantly lower in Org31540/SR90107A group than in enoxaparin group (8.4% vs. 16.6%, $p=5 \times 10^{-5}$).

When efficacy result was analyzed by study center, 50 centers were in favor of Org31540/SR90107A numerically, 34 centers were the same, and 15 centers were in favor of enoxaparin.

The treatment effect in favor of Org31540/SR90107A was shown numerically across all subgroups including gender, age, BMI, type of anesthesia, type of fracture, type of prosthesis, use of cement, duration of surgery, previous history of VTE, baseline creatinine level and previous use of antithrombotic medication. For race, more than 99% of patients were Caucasian who showed in favor of Org31540/SR90107A and only 9 patients were other races in primary efficacy population.

Number (%) of Patients With Adjudicated VTE up to Day 11 by Baseline Covariates - Primary Efficacy Population

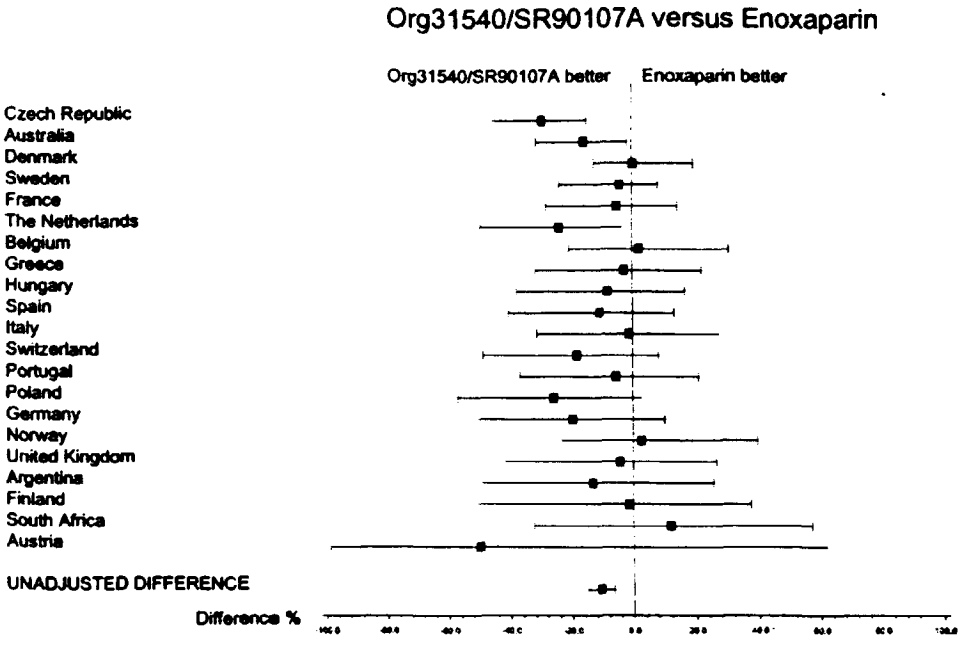
Covariate[a]	Org31540/SR90107A 2.5 mg o.d. (N = 626)				Enoxaparin 40 mg o.d. (N = 624)			
		VTE				VTE		
	N	n	%	95% CI	N	n	%	95% CI
Country								
Czech Republic	78	6	7.7	[2.9; 16.0]	75	28	37.3	[26.4; 49.3]
Australia	76	6	7.9	[3.0; 16.4]	76	18	23.7	[14.7; 34.8]
Denmark	52	2	3.8	[0.5; 13.2]	56	2	3.6	[0.4; 12.3]
Sweden	43	0	0.0	[0.0; 8.2]	45	2	4.4	[0.5; 15.1]
France	38	2	5.3	[0.6; 17.7]	38	4	10.5	[2.9; 24.8]
The Netherlands	35	0	0.0	[0.0; 10.0]	29	7	24.1	[10.3; 43.5]
Belgium	32	3	9.4	[2.0; 25.0]	27	2	7.4	[0.9; 24.3]
Greece	31	6	19.4	[7.5; 37.5]	27	6	22.2	[8.6; 42.3]
Hungary	29	3	10.3	[2.2; 27.4]	27	5	18.5	[6.3; 38.1]
Spain	26	2	7.7	[0.9; 25.1]	27	5	18.5	[6.3; 38.1]
Italy	26	9	34.6	[17.2; 55.7]	25	9	36.0	[18.0; 57.5]
Switzerland	26	2	7.7	[0.9; 25.1]	23	6	26.1	[10.2; 48.4]
Portugal	20	1	5.0	[0.1; 24.9]	28	3	10.7	[2.3; 28.2]
Poland	19	0	0.0	[0.0; 17.6]	23	6	26.1	[10.2; 48.4]
Germany	20	0	0.0	[0.0; 16.8]	20	4	20.0	[5.7; 43.7]
Norway	15	1	6.7	[0.2; 31.9]	24	1	4.2	[0.1; 21.1]
United Kingdom	21	3	14.3	[3.0; 36.3]	16	3	18.8	[4.0; 45.6]
Argentina	15	2	13.3	[1.7; 40.5]	15	4	26.7	[7.8; 55.1]
Finland	12	1	8.3	[0.2; 38.5]	10	1	10.0	[0.3; 44.5]
South Africa	10	3	30.0	[6.7; 65.2]	11	2	18.2	[2.3; 51.8]
Austria	2	0	0.0	[0.0; 84.2]	2	1	50.0	[1.3; 98.7]
Gender								
Male	144	6	4.2	[1.5; 8.8]	174	22	12.6	[8.1; 18.5]
Female	482	46	9.5	[7.1; 12.5]	450	97	21.6	[17.8; 25.6]
Race								
Caucasian	622	51	8.2	[6.2; 10.6]	619	118	19.1	[16.0; 22.4]
Black	1	0	0.0	[0.0; 97.5]	1	0	0.0	[0.0; 97.5]
Asian	3	1	33.3	[0.8; 90.6]	2	0	0.0	[0.0; 84.2]
Other races	0	0	NA	NA	2	1	50.0	[1.3; 98.7]
Age								
<65 years	90	3	3.3	[0.7; 9.4]	80	13	16.3	[8.9; 26.2]

65 - 75 years	123	14	11.4	[6.4; 18.4]	115	20	17.4	[11.0; 25.6]
≥75 years	409	35	8.6	[6.0; 11.7]	427	86	20.1	[16.4; 24.3]
Obesity								
BMI <30 kg/m^2	554	41	7.4	[5.4; 9.9]	544	102	18.8	[15.6; 22.3]
BMI ≥30 kg/m^2	31	6	19.4	[7.5; 37.5]	40	12	30.0	[16.6; 46.5]
Type of anesthesia								
Regional only	410	38	9.3	[6.6; 12.5]	406	75	18.5	[14.8; 22.6]
Other	216	14	6.5	[3.6; 10.6]	218	44	20.2	[15.1; 26.1]
Type of hip fracture								
Cervical only	305	15	4.9	[2.8; 8.0]	289	50	17.3	[13.1; 22.2]
Trochanteric[b]	278	28	10.1	[6.8; 14.2]	274	54	19.7	[15.2; 24.9]
Subtrochanteric	43	9	20.9	[10.0; 36.0]	59	15	25.4	[15.0; 38.4]
Type of surgery								
Half prosthesis	142	11	7.7	[3.9; 13.4]	127	27	21.3	[14.5; 29.4]
Total prosthesis	47	2	4.3	[0.5; 14.5]	45	10	22.2	[11.2; 37.1]
Other	437	39	8.9	[6.4; 12.0]	452	82	18.1	[14.7; 22.0]
Use of cement								
Yes	133	10	7.5	[3.7; 13.4]	130	29	22.3	[15.5; 30.4]
No	493	42	8.5	[6.2; 11.3]	494	90	18.2	[14.9; 21.9]
Duration of surgery[c]								
<median	308	26	8.4	[5.6; 12.1]	302	57	18.9	[14.6; 23.8]
≥median	318	26	8.2	[5.4; 11.8]	322	62	19.3	[15.1; 24.0]
Previous VTE								
Yes	21	1	4.8	[0.1; 23.8]	21	9	42.9	[21.8; 66.0]
No	605	51	8.4	[6.3; 10.9]	603	110	18.2	[15.2; 21.6]
Baseline creatinine[c]								
<median	298	24	8.1	[5.2; 11.7]	301	47	15.6	[11.7; 20.2]
≥median	313	25	8.0	[5.2; 11.6]	312	69	22.1	[17.6; 27.1]
Previous antithrombotic medication[d]								
Yes	22	3	13.6	[2.9; 34.9]	18	3	16.7	[3.6; 41.4]
No	604	49	8.1	[6.1; 10.6]	606	116	19.1	[16.1; 22.5]

a Per covariate, only non-missing observations were taken into account
b Not associated with any subtrochanteric fracture
c Median for duration of surgery was 1:35 h. Median for baseline creatinine was 0.904 mg/dL
d Not allowed per amendment
Sponsor's table in NDA Vol. 81, pp. 93-4

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

Country



Gender, race, age, obesity

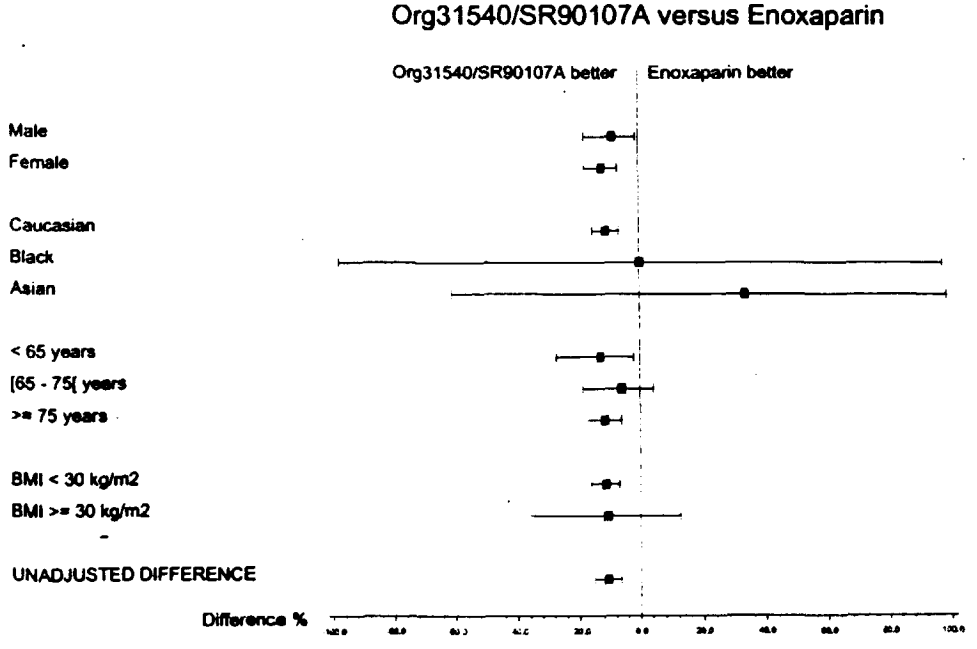
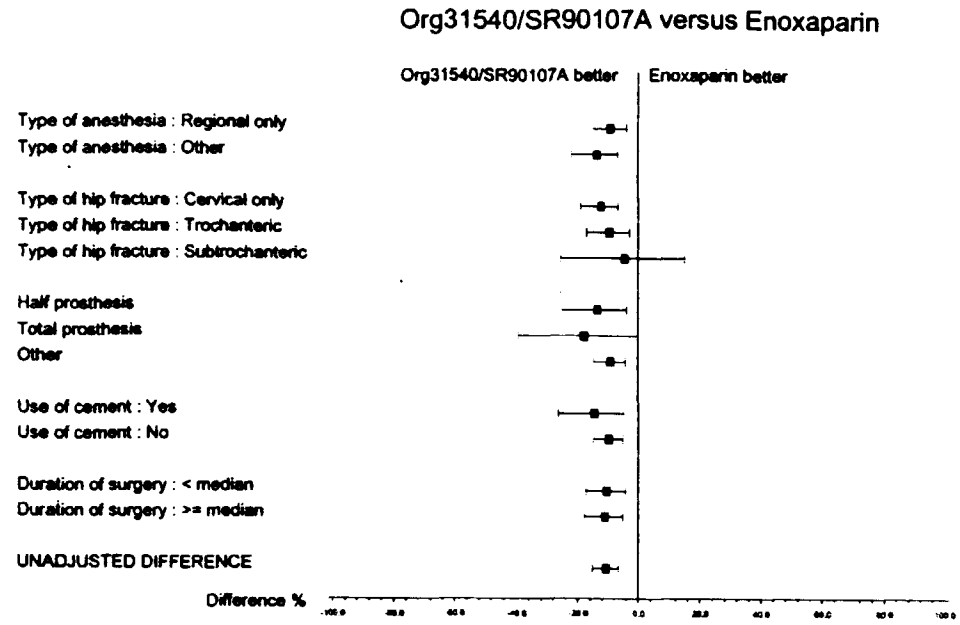


Figure (7.2.1) 1 - Differences (%) and 95% CIs Between Org31540/SR90107A and Enoxaparin Groups for Patients With Adjudicated VTE up to Day 11 According to Baseline Covariates - Primary Efficacy Population

Characteristics of surgery



Previous VTE, baseline creatinine, previous antithrombotic medication

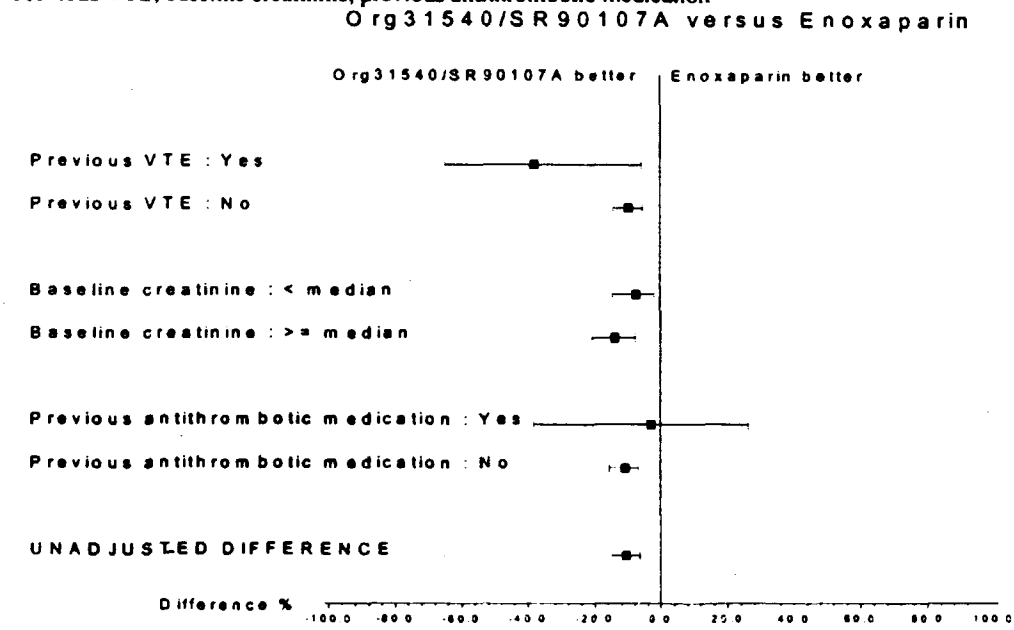


Figure (7.2.1) 1 - *continued* - Differences and 95% CIs Between Org31540/SR90107A and Enoxaparin Groups for Patients With Adjudicated VTE According to Baseline Covariates - Primary Efficacy Population

Sponsor's table in NDA Vol. 81, pp. 95-6

Sensitivity analysis

There were 205 (24.7%) patients in Org31540/SR90107A group and 216 (25.9%) 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 using all treated patients who underwent the appropriate surgery population by the sponsor.

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

Scenario	Org31540/SR9010A 2.5 mg o.d. (N= 831)	Enoxaparin 40 mg o.d. (N = 840)	Difference and exact 95%CI	Fisher's Exact p-value*
Best case scenario	52 (6.3 %)	119 (14.2 %)	-7.9% [-11.46; -4.82]	7.7×10^{-8}
Realistic scenario	92 (11.1 %)	160 (19.0 %)	-8.0% [-11.99; -4.36]	5.8×10^{-6}
Worst case scenario	257 (30.9 %)	335 (39.9 %)	-9.0% [-13.80; -4.28]	1.5×10^{-4}

*p-values were obtained by FDA Statistical Reviewer Dr. Mushfiqur Rashid, Ph.D.
Sponsor's table in NDA Vol. 81, pp. 97

The following table shows sensitivity analysis on all randomized patients.

Sensitivity analysis on all randomized population

Scenario	Org31540/SR9010A 2.5 mg o.d. (N= 849)	Enoxaparin 40 mg o.d. (N = 862)	Difference and exact 95%CI
Best case scenario	52 (6.1 %)	119 (13.8 %)	-7.7%[-11.14; -4.65]
Realistic scenario	95 (11.2 %)	164 (19.0 %)	-7.8% [-11.78; -4.25]
Worst case scenario	275 (32.4 %)	357 (41.4 %)	-9.0% [-13.86, -4.36]

Sponsor's table in NDA Amendment No. 4, Attachment No. 2, submitted on 5/1/2001

These results were consistent with efficacy results obtained from the primary efficacy population.

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 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 (see differences [and 95% CI] between the Org31540/SR90107A group and the enoxaparin group). Noted patients with concomitant use of ASA in Org31540/SR90107A Group had a higher incidence of VTE (5/47, 10.6%) than those without use of ASA (47/525, 8.1%).

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 = 626)				Enoxaparin 40 mg o.d. (N = 624)			
		VTE				VTE		
	N	n	%	95% CI	N	n	%	95% CI
Heparin (UFH, LMWH)/heparinoids								
With	17	1	5.9	[0.1; 28.7]	19	2	10.5	[1.3; 33.1]
Without	609	51	8.4	[6.3; 10.9]	605	117	19.3	[16.3; 22.7]
Antiplatelet drugs other than ASA								
With	5	0	0.0	[0.0; 52.2]	2	0	0.0	[0.0; 84.2]
Without	621	52	8.4	[6.3; 10.8]	622	119	19.1	[16.1; 22.4]
Vitamin K antagonists								
With	2	0	0.0	[0.0; 84.2]	1	0	0.0	[0.0; 97.5]
Without	624	52	8.3	[6.3; 10.8]	623	119	19.1	[16.1; 22.4]
Dextran								
With	1	1	100.0	[2.5; 0.0]	0	0	NA	NA
Without	625	51	8.2	[6.1; 10.6]	624	119	19.1	[16.1; 22.4]
NSAID								
With	101	2	2.0	[0.2; 7.0]	92	23	25.0	[16.6; 35.1]
Without	525	50	9.5	[7.2; 12.4]	532	96	18.0	[14.9; 21.6]
ASA								
With	47	5	10.6	[3.5; 23.1]	43	1	2.3	[0.1; 12.3]
Without	579	47	8.1	[6.0; 10.6]	581	118	20.3	[17.1; 23.8]
Penicillins								
With	94	5	5.3	[1.7; 12.0]	88	14	15.9	[9.0; 25.2]
Without	532	47	8.8	[6.6; 11.6]	536	105	19.6	[16.3; 23.2]
Cephalosporins								
With	282	26	9.2	[6.1; 13.2]	285	48	16.8	[12.7; 21.7]
Without	344	26	7.6	[5.0; 10.9]	339	71	20.9	[16.7; 25.7]
Antihistamines & phenothiazines								
With	39	3	7.7	[1.6; 20.9]	40	6	15.0	[5.7; 29.8]
Without	587	49	8.3	[6.2; 10.9]	584	113	19.3	[16.2; 22.8]
Cardiac glycosides								
With	39	3	7.7	[1.6; 20.9]	40	8	20.0	[9.1; 35.6]
Without	587	49	8.3	[6.2; 10.9]	584	111	19.0	[15.9; 22.4]
Macrolide antibiotics								
With	2	0	0.0	[0.0; 84.2]	3	2	66.7	[9.4; 99.2]
Without	624	52	8.3	[6.3; 10.8]	621	117	18.8	[15.8; 22.1]
Tetracyclines								
With	0	0	NA	NA	1	0	0.0	[0.0; 97.5]
Without	626	52	8.3	[6.3; 10.8]	623	119	19.1	[16.1; 22.4]
Other antibiotics								
With	25	2	8.0	[1.0; 26.0]	25	9	36.0	[18.0; 57.5]
Without	601	50	8.3	[6.2; 10.8]	599	110	18.4	[15.3; 21.7]
Vitamin C								
With	21	2	9.5	[1.2; 30.4]	24	3	12.5	[2.7; 32.4]
Without	605	50	8.3	[6.2; 10.8]	600	116	19.3	[16.2; 22.7]

NA = not applicable
Sponsor's table in NDA Vol. 81, pp. 98-9

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 EFC2698 was a multicenter, randomized, double-blind, double-dummy, parallel-groups study comparing Org31540/SR90107A 2.5 mg once daily SC (n=849) to enoxaparin 40 mg once daily SC (n=862) in 1711 patients undergoing hip fracture surgery.

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 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 1711 randomized patients in the study, 421 (25.2%) patients had missing primary efficacy endpoint due to non-evaluable venography/no VTE assessment up to day 11. They were similar in two treatment groups (205, 24.7% in the Org31540/SR90107A group and 216, 25.7% in the enoxaparin group). The missing rate associated with venography procedure in this study was comparable to that in studies in patients undergoing elective hip replacement surgery (21-29% in studies in NDA 20-164/000, Lovenox, FDA Medical Officer's Review, page 63 and 102; 31% in studies in NDA 20-287/S-008, Fragmin, FDA Medical Officer's Review, page 15).

Overall, EFC2698 was an adequate and well-controlled study. There were minor protocol deviations including use of not allowed concomitant medications (5.7% in the Org31540/SR90107A group vs. 4.8% in the enoxaparin group). The difference between the two groups was not statistically significant (p=0.4). The primary efficacy result was further analyzed by concomitant medication by the sponsor.

Study EFC2698 demonstrated that Org31540/SR90107A 2.5 mg once daily SC is superior to enoxaparin 40 mg once daily SC with a highly statistically significant difference for the primary efficacy endpoint of VTE up to day 11 (8.3% vs. 19.1%, p=2.6 x 10^{-8}). The difference between the two groups was mainly contributed by the component of DVT (7.8% vs. 18.1%, p=1 x 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 x 10^{-6}) in the Org31540/SR90107A 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 the treatment groups (0.5 % in each treatment group). 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 primary efficacy endpoint in favor of Org31540/SR901 treatment was seen in the majority of countries (18/21). The efficacy results were consistent across all subgroups including gender, age, BMI, type of anesthesia, type of fracture, type of prosthesis, use of

cement, duration of surgery, previous history of VTE, baseline creatinine level, previous use of antithrombotic medication, and concomitant antithrombotic medications.

2. For Prophylaxis of DVT in Patients Undergoing Hip Replacement Surgery

Trial 63118 – EPHESUS

Title of the Study

A multicenter, randomized, double-blind comparison of once daily subcutaneous Org31540/SR90107A with enoxaparin for the prevention of deep vein thrombosis or symptomatic pulmonary embolism in subjects undergoing elective hip replacement surgery.

Study Period

December 4, 1998 to January 28, 2000

Investigators and Study Centers

The study was carried out by investigators at 74 active centers in 16 European countries. There were 2 centers (1 in Austria and 1 in Italy) which did not recruit any patients.

Study Objectives

The objective of this study was to demonstrate superior efficacy of once-daily SC injections of 2.5 mg Org31540/SR90107A to once-daily SC injections of 40 mg enoxaparin, for the prevention of venous thromboembolic events (VTE), i.e. deep vein thrombosis (DVT) or symptomatic pulmonary embolism (PE), in patients undergoing primary elective total hip replacement (THR) surgery or a revision of component(s) of a THR.

Overall Study Design

The study design of 63118 was very similar to EFC2698 except for a different study population and use of a slightly different dose schedule. The efficacy and safety assessments in 63118 were the same as study EFC2698 and were adjudicated by the same CIAC.

This was a multinational, multicenter, randomized, double-blind, double-dummy, parallel-group study comparing 2.5 mg once daily subcutaneous Org31540/SR90107A to 40 mg once daily SC enoxaparin in patients undergoing elective, primary, total hip replacement (THR) or a revision of component(s) of a THR. The primary efficacy endpoint was VTE up to Day 11 including adjudicated venogram positive DVT (symptomatic or asymptomatic DVT) and adjudicated non-fatal or fatal PE.

Randomization was performed pre-operatively. The administration of Org31540/SR90107A was to be started post-operatively (at 6±2 hours after surgery closure) and that of enoxaparin was to be started pre-operatively (at 12±2 hours before surgery start). In case of planned spinal/epidural anesthesia or catheterization, the preoperative administration of study treatment was strongly discouraged. Treatment duration was 7±2 days. A mandatory venogram had to be performed between Day 5 and Day 11, but not more than 2 calendar days after the last study treatment administration. The follow-up period was up to Day 42±7.

Study Population

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

- undergoing either an elective, primary, total hip replacement (THR) surgery, or a revision of at least one component of a THR
- signed written informed consent
- men or women of non-childbearing potential (post-menopausal or with hysterectomy or bilateral tubal ligation) or women of childbearing potential with a negative pregnancy test within 48 hours prior to surgery or first study drug administration, whichever came first (protocol modification request no.1 dated 13 April 1999).
- 18 years of age or older.

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

Study Treatments

Patients were randomly assigned to one of two treatment groups:
- Org31540/SR90107A group: each patient received Org31540/SR90107A 2.5 mg (0.25 mL) once daily and placebo-enoxaparin (0.4 mL solution placebo matching enoxaparin) once daily.

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

Org31540/SR90107A was supplied by NV Organon (Oss, The Netherlands) and was provided as an isotonic 10 mg/mL solution for subcutaneous injection in 0.25 mL prefilled syringes (2.5 mg).

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

Placebo was supplied by NV Organon and was provided in 0.25 mL and 0.4 mL disposable prefilled syringes and contained isotonic sodium chloride for injection.

Randomization process

Treatments were allocated according to a pre-specified central randomization list produced by the Department of Clinical Supplies Management, NV Organon, Oss, The Netherlands (Sponsor). Randomization was balanced with a block size of four, with a 2:2 ratio of Org31540/SR90107A and enoxaparin treatments. Within the list of consecutive patient numbers, in each block of four, the treatments were coded as A and B. The central randomization was not stratified by center (or other factors), but whole blocks were required to be allocated to each center. A treatment box consisted of an active treatment (Org31540/SR90107A or enoxaparin) and a placebo of the other treatment. The centers were instructed to randomize an eligible patient by taking a study treatment box with the lowest patient number as labeled on the box. Each block had to be completed before starting a new one. A patient was considered as randomized as soon as a study treatment box was assigned and the investigator had reported the patient number on the front page of the CRF booklet. Randomized patients who did not start or complete treatment were not to be replaced.

Blinding procedures

This was a double-blind, double-dummy study. The placebo was administered in syringes identical to the Org31540/SR90107A and enoxaparin syringes. The blinding code was to be broken by the Investigators only in exceptional circumstances, when knowledge of the treatment group was essential for treating the patients.

Dosing schedule

The first injection of Org31540/SR90107A or placebo-Org31540/SR90107A was administered 6±2 hours after end of surgery, i.e. closure of surgical incision. Two dosing schemes were used due to different enoxaparin schedules. The recommended dosing scheme was as shown in the table below.

Recommended Dosing Schedule

Group	Subcutaneous Dosing Regimens ('Double-Dummy')			
	12±2 hours Pre-Op.[a]	Day 1 6±2 hours Post-Op.[b]	Day 2[c]	Day 3-9[d] at 8.00 A.M. (±2 hours)
Org31540/SR90107A	0.4 mL placebo	2.5 mg (0.25 mL)	2.5 mg (0.25 mL) + 0.4 mL placebo	2.5 mg (0.25 mL) + 0.4 mL placebo
Enoxaparin	40 mg (0.4 mL)	0.25 mL placebo	40 mg (0.4 mL) + 0.25 mL placebo	40 mg (0.4 mL) + 0.25 mL placebo

a Should be omitted in patients requiring spinal/epidural anesthesia or catheterization if there was a precaution/warning in the local datasheet of enoxaparin.
b Was to be administered on the (calendar) day of surgery (Day 1).
c >12 hours after dose of Day 1, but <24 hours after end of surgery.
d At least until Day 5.
Sponsor's table in NDA Vol. 117, pp. 31

An alternative dosing scheme (Table below) could be used in subjects for whom the end of surgery allowed for an evening dose of 0.4 mL on Day 1 according to the local datasheet of enoxaparin:

Alternative Dosing Schedule

Group	Subcutaneous Dosing Regimens ('Double-Dummy')						
		Day 1[b]		Day 2		Day 3-9.	
	12±2 hours Pre-Op.[a]	6±2 hours Post-Op.	Evening	morning[c]	evening[d]	morning (at 8.00 am ±2 hours)	evening
Org31540/ SR90107A	0.4 mL placebo	2.5 mg (0.25 mL)	0.4 mL placebo	2.5 mg (0.25 mL)	0.4 mL placebo	2.5 mg (0.25 mL)	0.4 mL placebo
Enoxaparin	40 mg (0.4 mL)	0.25 mL placebo	40 mg (0.4 mL)	0.25 mL Placebo	40 mg (0.4 mL)	0.25 mL placebo	40 mg (0.4 mL)

a Should be omitted in patients requiring spinal/epidural anesthesia or catheterization if there was a precaution/warning in the local datasheet of enoxaparin.
b Was to be administered on the (calendar) day of surgery (Day 1); an indwelling intrathecal or epidural catheter should no longer be present. The 0.4 mL dose was recommended to be administered 24±2 hours after the pre-operative dose (if given)
c >12 hours after the 0.25 mL dose of Day 1
d 24±2 hours after 0.4 mL dose of Day 1 e At least until Day 5.
Sponsor's table in NDA Vol. 117, pp. 32

Prior and concomitant therapy

The same disallowed medications listed in study EFC2698 could not be used in this study within two days prior to the day of first study medication, during the drug administration period and until the mandatory venogram had been obtained. Patients screened for the study were discouraged from using these medications within seven to three days prior to the day of first study medication.

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

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

Statistical methods

Determination of sample size

A VTE rate of 9.3% with enoxaparin 30mg b.i.d., and VTE rates of 2.0% with 3mg Org31540/SR90107A and 5.9% with 1.5mg Org31540/SR90107A were obtained in this indication from a dose ranging study (DRI2643) with 150 per-protocol evaluable patients in the enoxaparin group and approximately 100 patients in each Org31540/SR90107A group. In the current study, a dose of 2.5mg Org31540/SR90107A was to be used. A VTE event rate of 5% was assumed for the Org31540/SR90107A group. With 800 evaluable (non-missing efficacy assessment) patients per group, the power to detect a significant difference (with a 2-sided significance level α of 0.05) between the enoxaparin group (9%) and the Org31540/SR90107A group (5%) was greater than 85%.

About 2200 patients were to be randomized, assuming that approximately 30% of patients were expected to have a missing evaluation for the primary efficacy analysis.

Efficacy and safety analyses were same as study EFC2698.

Interim Analyses

No interim analysis was performed in this study.

Protocol Amendments

There were 2 protocol amendments during the study.

Protocol amendment #1 was dated April 13, 1999. The main changes are listed below:

- Inclusion criterion related to women of childbearing potential
- Exclusion criterion related to metformin intake
- Exclusion criterion related to prior treatment restrictions
- In statistical methods:
  - Clarification of primary endpoint
  - Additional exploratory sensitivity analyses
  - Methods for the secondary/exploratory analyses
  - Clarification of the safety analysis population
- Administrative changes/textual clarifications following discrepancies between table footnotes and text/other textual clarifications
- Study population included patients from Italy.

Protocol amendment #2 was dated September 23, 1999. The main change was to extend the study to include patients from 7 Eastern and South European countries. This amendment also allowed baseline assessment performed less than 12 hours prior to surgery if no pre-operative dose was planned and recommended that randomization done 10-14 hours prior to surgery.

Study Results

Disposition of patients

A total of 2324 patients were enrolled at 74 active centers in 16 European countries with 1162 patients randomized to each treatment group. Among the 74 centers, the number of patients enrolled at each center ranged from 3 to 108 patients.

During the blind review of data before database lock, 15 patients were identified to be excluded from all analyses by the sponsor. Among them, 3 patients were 'randomized' to study medication already assigned to previously randomized but not treated patients. These patients received pseudo subject numbers not used in the randomization scheme and were considered not randomized by the sponsor. One SAE was reported among the three patients. No VTE or bleeding event was reported for these subjects.

Furthermore, all 12 patients of center 0454 (in Belgium) were excluded from all analyses by the sponsor due to lost CRFs in 7 patients and limited credibility of the remaining data. Among the 5 patients with CRF available, one proximal DVT was reported. No other VTE, bleeding or SAEs were reported.

Two patients were randomized twice in this trial. One patient was randomized the first time to enoxaparin without being operated and treated due to technical problem, and a second time to Org31540/SR90107A and completed the study. Another patient was randomized the first time to enoxaparin, had a surgery on the left side and completed the study. This patient was randomized a second time to Org31540/SR90107A at 10 month later, had a surgery on the right side and completed the study again. No adjudicated VTE or major/minor bleed was reported for these patients. These 2 cases were considered as 2 different patients in the statistical analysis by the sponsor.

Of the remaining 2309 patients randomized, 1155 were assigned to receive Org31540/SR90107A and 1154 were assigned to receive enoxaparin. The following chart presents the disposition of patients for each treatment group.

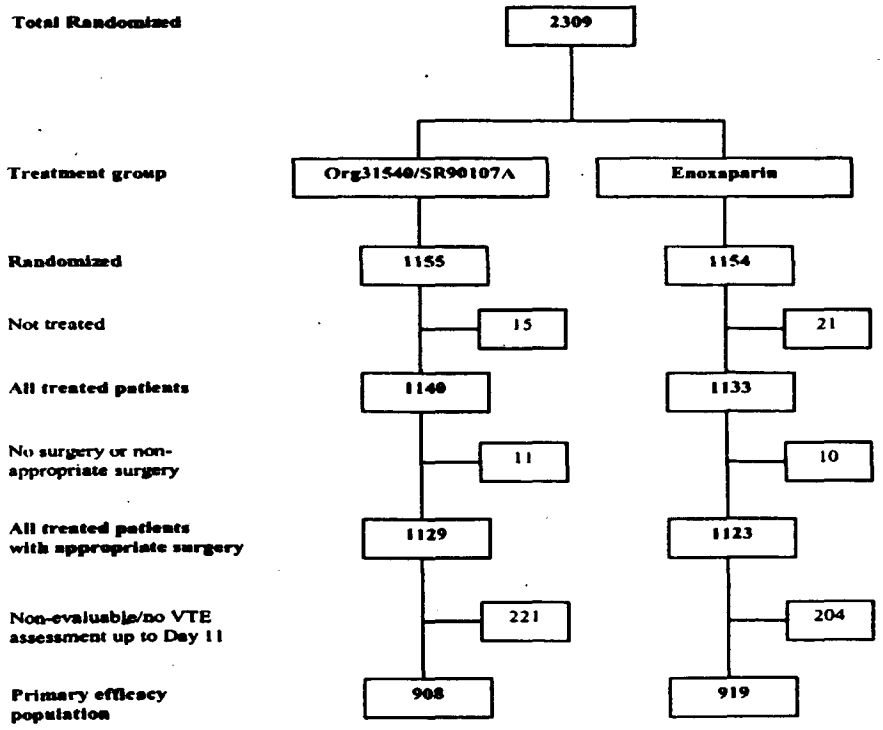


Figure (6.3) 1 - Number of Patients by Treatment Group and Population

Sponsor's figure in NDA Vol. 117, pp. 68

Of the 2309 patients randomized, 36 did not receive any study drug (See table below). The number of patients who were not treated was similar between the two groups. The main reason for not being treated was informed consent withdrawn.

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

Reason for Not Being Treated	Org31540/SR90107A 2.5 mg o.d. (N=1155)	Enoxaparin 40 mg o.d. (N=1154)	Total (N=2309)
Informed consent withdrawn	7 (0.6 %)	11 (1.0 %)	18 (0.8 %)
Inclusion/exclusion criteria not met	2 (0.2 %)	5 (0.4 %)	7 (0.3 %)
Technical problem	3 (0.3 %)	2 (0.2 %)	5 (0.2 %)
Adverse event[a]	3 (0.3 %)	2 (0.2 %)	5 (0.2 %)
Other	0 (0.0 %)	1 (0.1 %)	1 (0.0 %)
Total	15 (1.3 %)	21 (1.8 %)	36 (1.6 %)

[a] No serious adverse events were among these events.
Sponsor's table in NDA Vol. 117, pp. 63

The adverse events were allergic reaction to morphine, surgery postponed due to urinary tract infection, " not done total hip replacement" in Org31540/SR90107A group, and bleeding postoperatively and anemia in enoxaparin group. "Other" reasons for not being treated included a patient with postoperative corticoids required due to the patient's rheumatoid arthritis.

A total of 2273 patients (1140 in the Org31540/SR90107A group and 1133 in the enoxaparin group) were randomized and treated ('all treated patients' population). The number (%) of randomized and treated patients is presented by country in the table below.

Number (%) of Randomized and Treated Patients by Country

Country[a] (Number of Centers)	Org31540/SR90107A 2.5 mg o.d.	Enoxaparin 40 mg o.d.	Total
Denmark (15)	279	278	557 (24.5%)
Finland (6)	118	119	237 (10.4%)
Germany (4)	107	106	213 (9.4%)
Austria (3)	88	88	176 (7.7%)
Sweden (6)	89	87	176 (7.7%)
The Netherlands (5)	90	83	173 (7.6%)
Norway (5)	86	84	170 (7.5%)
Czech Republic (5)	69	69	138 (6.1%)
Belgium (4)	59	60	119 (5.2%)
United Kingdom (3)	56	58	114 (5.0%)
France (7)	40	40	80 (3.5%)
Hungary (3)	18	18	36 (1.6%)
Poland (2)	17	18	35 (1.5%)
Spain (3)	10	12	22 (1.0%)
Greece (1)	8	7	15 (0.7%)
Italy (1)	6	6	12 (0.5%)
TOTAL (73)	1140	1133	2273 (100.0%)

NOTE: A patient was considered to be treated when he/she received at least one injection of either placebo or active drug

a Sorted in decreasing order of randomized and treated patients
Sponsor's table in NDA Vol. 117, pp. 64

A total of 128 (5.6%) of the 2273 randomized and treated patients prematurely stopped study drug (See table below).

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

Premature Treatment Discontinuation / Reason for Stopping	Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)	Total (N=2273)
Patients who discontinued study drug Prematurely	70 (6.1 %)	58 (5.1 %)	128 (5.6 %)
Reason for discontinuation[a]:			
Lack of efficacy	7 (0.6 %)	5 (0.4 %)	12 (0.5 %)
Reached endpoint - DVT	4 (0.4 %)	4 (0.4 %)	8 (0.4 %)
Reached endpoint - PE	3 (0.3 %)	1 (0.1 %)	4 (0.2 %)
AE/SAE[b]	18 (1.6 %)	15 (1.3 %)	33 (1.5 %)
Bleeding AE/SAE	7 (0.6 %)	3 (0.3 %)	10 (0.4 %)
Suspicion of drug induced decrease of platelet count [c]	1 (0.1 %)	0 (0.0 %)	1 (0.0 %)
Other AE/SAE	11 (1.0 %)	13 (1.5 %)	24 (1.0 %)
Withdrawn	24 (2.1%)	22 (1.9%)	46 (2.0%)
Subject withdrew consent	23 (2.0 %)	20 (1.8 %)	43 (1.8 %)
Physician withdrew patients	1 (0.1 %)	2 (0.2%)	3 (0.1%)
Protocol violations	20 (1.8%)	15 (1.3%)	35 (1.5%)
No THR surgery	7 (0.6 %)	2 (0.2%)	9 (0.4%)
Epidural catheter for >6 hours	5 (0.4%)	2 (0.2%)	7 (0.3%)
Dosing mistakes	3 (0.3 %)	5 (0.4 %)	8 (0.4 %)
Received other anticoagulants	3 (0.3 %)	5 (0.4 %)	8 (0.4 %)
"Protocol violation"	1 (0.1 %)	1 (0.1 %)	2 (0.1%)
"Lost blood test"	1 (0.1 %)	0 (0.0 %)	1 (0.0%)

a According to the Investigators' judgment
b Including AEs recorded before the first study drug injection (based on data collected in the End Of Treatment Form)
c This reason for stopping was only recorded on the End Of Treatment Form (patient 08581218). The drop of platelet count occurred at Day 2 and was therefore not reported as an AE; for this patient, a coagulation disorder (preferred term) was recorded as AE leading to discontinuation
NOTE: No patients permanently discontinued study drug due to AEs starting before first study drug administration
Reviewer's table based on NDA study 63118 Appendix 14.2.1.1.16

The majority of premature discontinuations of study drug were due to subject withdrawal of informed consent followed by protocol violations and adverse events. There were slightly more patients who discontinued treatment permanently in the Org31540/SR90107A group as compared to the enoxaparin group for all reasons including those due to bleeding AE/SAEs but there was no statistically significant difference.

Most cases of premature treatment discontinuation occurred before Day 5 in both treatment groups (48 in the Org31540/SR90107A group and 44 in the enoxaparin group).

No patients were lost to follow-up during the treatment period. A total of 54 patients (28 in the Org31540/SR90107A group and 26 in the enoxaparin group) had no information on the final Follow-up Assessment Form.

The randomization code was broken for 1 enoxaparin-treated patient in an emergency situation due to an SAE (pneumonia) observed during the treatment period.

Protocol deviations

Protocol deviations leading to exclusion from primary efficacy analysis

All randomized and treated patients who presented with any of the following deviations were excluded from the primary efficacy analysis:
- No or non-appropriate surgery;
- Missing VTE evaluation up to Day 11, i.e. non-evaluable or no VTE assessment up to Day 11.

The number (%) of patients who presented with such protocol deviations is summarized by treatment group in the following table. The percentage of patients who were excluded from the primary efficacy analysis was similar for both treatment groups (20.4% in Org31540/SR90107A group vs. 18.9% in enoxaparin group). No VTE assessment up to day 11 was the main reason for exclusion in both treatment groups (12.8 in Org31540/SR90107A group and 11.7% in enoxaparin group) followed by non-evaluable venogram.

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

Deviation[a]	Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)	Total (N=2273)
No surgery / Non-appropriate surgery	11 (1.0 %)	10 (0.9 %)	21 (0.9 %)
Non-evaluable venogram up to Day 11	75 (6.6 %)	71 (6.3 %)	146 (6.4 %)
No VTE assessment up to day 11	146 (12.8%)	133 (11.7%)	279 (12.3%)
Total for exclusion from primary efficacy analysis	232 (20.4 %)	214 (18.9 %)	446 (19.6 %)

[a] patients were counted only once
Sponsor's table in NDA Vol. 117, pp. 66

The detailed reasons for non-evaluable/no VTE assessment between two treatment groups are presented in the following table.

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

Non-evaluable /No VTE assessment up to day 11	Org31540/SR90107A 2.5 mg o.d. (N = 1140)	Enoxaparin 40 mg o.d. (N = 1133)	Total (N =2273)
Non-evaluable VTE assessment up to day 11	**75 (6.6%)**	**71 (6.3%)**	**146 (6.4%)**
Both legs assessed-both inadequate	7 (0.6%)	9 (0.8%)	16 (0.7%)
Both legs assessed-operated leg inadequate	9 (0.8%)	6 (0.5%)	15 (0.7%)
Both legs assessed-non-operated leg inadequate	11 (1.0%)	6 (0.5%)	17 (0.7%)
Operated leg assessed only- negative	37 (3.2%)	37 (3.3%)	74 (3.3%)
Operated leg assessed only- inadequate	2 (0.2%)	3 (0.3%)	5 (0.2%)
Non-operated leg assessed only-negative	8 (0.7%)	9 (0.8%)	17 (0.7%)
Non-operated leg assessed only-inadequate	0 (0.0%)	0 (0.0%)	0 (0.0%)
Examination performed before day 5	1 (0.1%)	1 (0.1%)	2 (0.1%)
No VTE assessment up to day 11	**146 (12.8%)**	**133 (11.7%)**	**279 (12.3%)**
VTE assessment after day 11	8 (0.7%)	6 (0.5%)	14 (0.6%)
Reasons for no VTE assessment			
Failed venous access	36 (3.2%)	35 (3.1%)	71 (3.1%)
Subject refuse/withdrew consent	50 (4.4%)	49 (4.3%)	99 (4.4%)
AE/SAE	15 (1.3%)	10 (0.9%)	25 (1.1%)
Premature treatment discontinuation	16 (1.4%)	9 (0.8%)	25 (1.1%)
Uncooperative/"too ill" for the test	6 (0.5%)	4 (0.4%)	10 (0.4%)
Technical problems	4 (0.4%)	7 (0.6%)	11 (0.5%)
Allergy to contrast media	0 (0.0%)	3 (0.3%)	3 (0.1%)
Re-operation	1 (0.1%)	1(0.1%)	2 (0.1%)
Increased creatinine	1 (0.1%)	1 (0.1%)	2 (0.1%)
Normal US	0 (0.0%)	1 (0.1%)	1 (0.0%)
Symptom assessment for DVT	2 (0.2%)	2 (0.2%)	4 (0.2%)
No reason mentioned	5 (0.4%)	4 (0.4%)	9 (0.4%)
Local but not central	2 (0.2%)	0 (0.0%)	2 (0.1%)
Total	**221 (19.4%)**	**204 (18.0%)**	**421 (25.2%)**

Reviewer's table based on NDA Study 63118 Appendix 14.2.1.3

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

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

Other protocol deviations

As previously mentioned, 3 patients were 'randomized' to study medication already assigned to previously randomized but not treated patients and were excluded from all analyses by the sponsor. Two patients were randomized twice in this trial. Some other randomization errors included: in total nine partial blocks were sent out with each block used by two centers; further, one center had an incomplete block with a gap in-between (i.e. one treatment of the block was skipped and study drug was returned); occasionally, a center started a new treatment block before completion of the previous one.

All 12 patients of center 0454 (in Belgium) were excluded from all analyses by the sponsor due to lost CRFs in 7 patients and limited credibility of the remaining data.

The following table summarizes the main protocol deviations other than those leading to exclusion from the primary efficacy analysis. The most common deviation, which was observed with a similar frequency (4%) in both treatment groups, was the intake of not allowed concomitant therapy.

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

Deviation	Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)	Total (N=2273)
Meeting exclusion criteria based on current labeling for LMWH [a]	5 (0.4%)	3 (0.3%)	8 (0.4%)
Less than 8 post-operative injections (of placebo or active drug) [b]	28 (2.5%)	25 (2.2%)	53 (2.3%)
Not allowed concomitant therapy [c,d]	39 (3.4%)	36 (3.2%)	75 (3.3%)
Qualifying VTE examination for primary efficacy analysis more than 2 calendar days after last injection	3 (0.3%)	3 (0.3%)	6 (0.3%)

[a] Patients with more than one protocol deviation were counted once
[b] Unless discontinuation due to AE or lack of efficacy
[c] From 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, heparin flushes and heparin in cell saver equipment on Day 1 were not taken into account
Sponsor's table in NDA Vol. 117, pp. 67

According to the dosing schedule, the pre-operative injection was scheduled as placebo in the Org31540/SR90107A group and as active in the enoxaparin group. However, nine patients in the Org31540/SR90107A group received one active pre-operative injection, whereas 4 patients in the enoxaparin group received two active pre-operative injections, for various reasons including postponed surgery.

Demographic and baseline characteristics

All treated patients

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

Of the 2273 randomized and treated patients, 1307 (57.5%) were female and 2253 (99.2%) were Caucasian. The mean age of patients was 65±11 years for both groups. The two treatment groups were similar with regard to demographic and surgical characteristics.

Summary of Demographic and Surgery Characteristics - All Treated Patients

Parameter		Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)	Total (N=2273)
Age (years)	n	1140	1133	2273
	Median	66	67	67
	Mean	65.1	65.5	65.3
	S.D.	11.3	11.1	11.2
	Min - Max	29 - 92	24 - 97	24 - 97
Age (years)	< 65	493 (43.2 %)	465 (41.0 %)	958 (42.1 %)
[n (%)]	[65 - 75[	402 (35.3 %)	438 (38.7 %)	840 (37.0 %)
	≥ 75	245 (21.5 %)	230 (20.3 %)	475 (20.9 %)
Height (cm)	n	1117	1098	2215
	Median	168	168	168
	Mean	168.4	167.7	168.1
	S.D.	9.0	9.0	9.0
	Min - Max	141 - 198	132 - 197	132 - 198
Weight (kg)	n	1136	1126	2262
	Median	75	75	75
	Mean	76.2	76.3	76.3
	S.D.	14.6	14.7	14.7
	Min - Max	40 - 135	40 - 145	40 - 145
BMI (kg/m^2)	< 30	899 (80.5 %)	838 (76.5 %)	1737 (78.5 %)
[n (%)]	≥ 30	218 (19.5 %)	258 (23.5 %)	476 (21.5 %)
	Missing	23	37	60
Gender	Male	493 (43.2 %)	473 (41.7 %)	966 (42.5 %)
[n (%)]	Female	647 (56.8 %)	660 (58.3 %)	1307 (57.5 %)
Race	Caucasian	1128 (99.0 %)	1125 (99.4 %)	2253 (99.2 %)
[n (%)]	Black	6 (0.5 %)	6 (0.5 %)	12 (0.5 %)
	Asian/Oriental	2 (0.2 %)	1 (0.1 %)	3 (0.1 %)
	Other	3 (0.3 %)	0 (0.0 %)	3 (0.1 %)
	Missing	1	1	2
Type of surgery [a]	Primary	1002 (88.8 %)	978 (87.0 %)	1980 (87.9 %)
[n (%)]	Revision	127 (11.2 %)	146 (13.0 %)	273 (12.1 %)
	Missing	2	0	2
Use of cement [a]	Yes	674 (59.8 %)	673 (60.0 %)	1347 (59.9 %)
[n (%)]	No	453 (40.2 %)	448 (40.0 %)	901 (40.1 %)
	Missing	4	3	7
Type of anesthesia [a]	General only	394 (34.8 %)	430 (38.3 %)	824 (36.5 %)
[n (%)]	Regional only	685 (60.6 %)	646 (57.5 %)	1331 (59.0 %)
	Combination	52 (4.6 %)	48 (4.3 %)	100 (4.4 %)
Duration of surgery [a]	n	1123	1120	2243
(hh:mm)	Median	2:15	2:15	2:15
	Mean	2:20	2:24	2:22
	S.D.	0:48	0:52	0:50
	Min - Max			

Note: Age range [65, 75[denotes age from 65 years (included) up to <75 years
[a] For all treated and operated patients (Org31540/SR90107A, N=1131; enoxaparin, N=1124)
Sponsor's table in NDA Vol. 117, pp. 70

The following table shows the number (%) of patients with specific medical and surgical history at the time of inclusion.

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=1140)	Enoxaparin 40 mg o.d. (N=1133)	Total (N=2273)
Specific medical history			
VTE	45 (3.9 %)	56 (4.9 %)	101 (4.4 %)
Stroke	16 (1.4 %)	26 (2.3 %)	42 (1.8 %)
Myocardial infarction	40 (3.5 %)	44 (3.9 %)	84 (3.7 %)
Cancer	56 (4.9 %)	81 (7.1 %)	137 (6.0 %)
Orthopedic surgery within the previous 12 months			
Any surgery	113 (9.9 %)	105 (9.3 %)	218 (9.6 %)
Hip replacement	62 (5.4 %)	60 (5.3 %)	122 (5.4 %)
Knee replacement	7 (0.6 %)	4 (0.4 %)	11 (0.5 %)
Hip fracture	20 (1.8 %)	10 (0.9 %)	30 (1.3 %)
Other surgery	31 (2.7 %)	33 (2.9 %)	64 (2.8 %)

Sponsor's table in NDA Vol. 117, pp. 71

Enoxaparin group had more patients with specific medical history especially cancer (7.1% vs. 4.9%, p=0.025) than those in Org31540/SR90107A group.

There was no apparent difference between the treatment groups regarding history of orthopedic surgery within previous 12 months except for slightly more patients with history of hip fracture (1.8% vs. 0.9%, p=0.069) in Org31540/SR90107A group vs. enoxaparin group.

The number (%) of patients who received medications with potential impact on hemostasis within 2 days prior to the day of first study drug injection (placebo or active) was similar for both treatment groups (8.2% in Org31540/SR90107A group vs. 8.7% in enoxaparin group).

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 two treatment groups were also similar.

Summary of Demographic and Surgery Characteristics -Primary efficacy Population

Parameter		Org31540/SR90107A 2.5 mg o.d. (N=908)	Enoxaparin 40 mg o.d. (N=919)	Total (N=1827)
Age (years)	n	908	919	1827
	Median	67	67	67
	Mean	65.1	65.6	65.4
	S.D.	11.0	10.7	10.8
	Min - Max	30 - 90	24 - 97	24 - 97
Age (years)	< 65	385 (42.4 %)	377 (41.0 %)	762 (41.7 %)
[n (%)]	[65 - 75[	336 (37.0 %)	358 (39.0 %)	694 (38.0 %)
	≥ 75	187 (20.6 %)	184 (20.0 %)	371 (20.3 %)
Height (cm)	n	894	897	1791
	Median	168	168	168
	Mean	168.5	168.0	168.2
	S.D.	9.0	9.0	9.0
	Min - Max	141 - 198	132 - 197	132 - 198
Weight (kg)	n	907	914	1821
	Median	75	75	75
	Mean	75.9	75.9	75.9
	S.D.	14.5	14.7	14.6
	Min - Max	40 - 130	40 - 145	40 - 145
BMI (kg/m^2)	< 30	721 (80.6 %)	702 (78.4 %)	1423 (79.5 %)
[n (%)]	≥ 30	173 (19.4 %)	193 (21.6 %)	366 (20.5 %)
	Missing	14	24	38
Gender	Male	396 (43.6 %)	402 (43.7 %)	798 (43.7 %)
[n (%)]	Female	512 (56.4 %)	517 (56.3 %)	1029 (56.3 %)
Race	Caucasian	899 (99.0 %)	913 (99.3 %)	1812 (99.2 %)
[n (%)]	Black	3 (0.3 %)	4 (0.4 %)	7 (0.4 %)
	Asian/Oriental	2 (0.2 %)	1 (0.1 %)	3 (0.2 %)
	Other	3 (0.3 %)	0 (0.0 %)	3 (0.2 %)
	Missing	1	1	2
Type of surgery	Primary	802 (88.3 %)	800 (87.1 %)	1602 (87.7 %)
[n (%)]	Revision	106 (11.7 %)	119 (12.9 %)	225 (12.3 %)
Use of cement	Yes	542 (59.8 %)	558 (60.8 %)	1100 (60.3 %)
[n (%)]	No	365 (40.2 %)	360 (39.2 %)	725 (39.7 %)
	Missing	1	1	2
Type of anesthesia	General only	309 (34.0 %)	345 (37.5 %)	654 (35.8 %)
[n (%)]	Regional only	555 (61.1 %)	529 (57.6 %)	1084 (59.3 %)
	Combination	44 (4.8 %)	45 (4.9 %)	89 (4.9 %)
Duration of surgery	n	905	917	1822
(hh:mm)	Median	2:15	2:15	2:15
	Mean	2:20	2:23	2:21
	S.D.	0:49	0:50	0:49
	Min - Max			

Note: Age range [65, 75] denotes age from 65 years (included) up to <75 years
Sponsor's table in NDA Vol. 117, pp. 72

As seen in all treated patient population, enoxaparin group had more patients with specific medical history especially cancer (7.3% vs. 4.8%, p=0.025) and stroke (2.3% vs. 1.2%, p=0.08) than those in Org31540/SR90107A group. In patients with history of cancer, 3 (6.8%) patients in the Org31540/SR90107A group and 6 (9.0%) patients in the enoxaparin group experienced an adjudicated VTE up to Day 11.

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=908)	Enoxaparin 40 mg o.d. (N=919)	Total (N=1827)
Specific medical history			
VTE	35 (3.9 %)	40 (4.4 %)	75 (4.1 %)
Stroke	11 (1.2 %)	21 (2.3 %)	32 (1.8 %)
Myocardial infarction	29 (3.2 %)	39 (4.2 %)	68 (3.7 %)
Cancer	44 (4.8 %)	67 (7.3 %)	111 (6.1 %)
Orthopedic surgery within the previous 12 months			
Any surgery	85 (9.4 %)	84 (9.1 %)	169 (9.3 %)
Hip replacement	45 (5.0 %)	48 (5.2 %)	93 (5.1 %)
Knee replacement	4 (0.4 %)	1 (0.1 %)	5 (0.3 %)
Hip fracture	16 (1.8 %)	8 (0.9 %)	24 (1.3 %)
Other surgery	24 (2.6 %)	29 (3.2 %)	53 (2.9 %)

Sponsor's table in NDA Vol. 117, pp. 73

More patients had history of hip fracture (p=0.09) in Org31540/SR90107A group as compared to enoxaparin group.

The number (%) of patients who received medications with potential impact on hemostasis within 2 days prior to the day of first study drug injection (placebo or active) was similar for both treatment groups (8.7% in Org31540/SR90107A group vs. 9.0% in enoxaparin group).

Extent of exposure

All treated patients

The following table summarizes the number (%) of patients who received active pre-operative injection(s) according to the type of anesthesia. Overall, 0.8% of the patients in the Org31540/SR90107A group and 78.0% in the enoxaparin group received at least one active pre-operative injection.

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

Patients with	Org31540/SR90107A 2.5 mg o.d.	Enoxaparin 40 mg o.d.
General anesthesia only	2 / 391 (0.5%)	350 / 430 (81.4%)
Regional anesthesia only or combination	7 / 729 (1.0%)	526 / 693 (75.9%)
Total with active pre-operative injection(s)	9 / 1120 (0.8%)	876 / 1123 (78.0%)

Note: Treated and operated patients (Org31540/SR90107A, N=1131; enoxaparin, N=1124)
Sponsor's table in NDA Vol. 117, pp. 74

Four patients in the enoxaparin group received 2 active pre-operative injection due to a delay of the surgery for more than 24 hours or due to unknown reasons.

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 following table presents a summary of active treatment. Most patients in both treatment groups received active study drug up to Day 5 to Day 9. In the protocol, patients in the enoxaparin group could receive their first active post-operative dose either as an evening dose on Day 1 or a morning dose on Day 2 as long as the timing of dosing was maintained consistently throughout the study. Enoxaparin patients undergoing the mandatory venogram on Day 5 could have had their last active daily dose on the evening of Day 4 and a placebo dose on the morning of Day 5. This may explain the apparent difference in the number of patients receiving their last active treatment dose before Day 5. There was no difference between the 2 treatment groups in the number of active injections.

Summary of Active Treatment - All Treated Patients

	Org31540/SR90107A 2.5 mg o.d. (N=1140)	**Enoxaparin 40 mg o.d. (N=1133)**
Number of active injections		
n	1121	1132
Median	8	8
Mean (SD)	7.5 (1.4)	7.4 (1.7)
Min - Max		
Last day of active treatment [n (%)] [a]		
< Day 5	30 (2.7 %)	76 (6.7 %)
Day 5 to Day 9	1060 (94.6 %)	1036 (91.5 %)
> Day 9	31 (2.8 %)	20 (1.8 %)

[a] Day 1=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. 117, pp. 75

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 populations, as shown below.

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

Patients With	**Org31540/SR90107A 2.5 mg o.d. (N=908)**	**Enoxaparin 40 mg o.d. (N=919)**
General anesthesia only	2 / 309 (0.6%)	278 / 345 (80.6%)
Regional anesthesia only or combination	6 / 599 (1.0%)	440 / 574 (76.7%)
Total with active pre-operative injection(s)	8 / 908 (0.9%)	718 / 919 (78.1%)

Sponsor's table in NDA Vol. 117, pp. 75

In the enoxaparin group, the mean time between the last active pre-operative injection and start of surgery was 12±2 hours. The mean time between the end of the surgery and the first active post-operative injection was 6±3 hours in the Org31540/SR90107A group and 13±6 hours in the enoxaparin group.

The following table presents a summary of active treatment up to the qualifying VTE examination. Most patients in both treatment groups received active study drug up to Day 5 to Day 9 (i.e. Day 7±2). No statistically significant difference between the 2 treatment groups was found in the number of active injections.

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

	Org31540/SR90107A 2.5 mg o.d. (N=908)	**Enoxaparin 40 mg o.d. (N=919)**
Number of active injections		
N	908	919
Median	8	8
Mean (S.D.)	7.6 (1.2)	7.6 (1.3)
Min – Max		
Last day of active treatment [n (%)] [a]		
< Day 5	4 (0.4 %)	28 (3.0%)
Day 5 to Day 9	885 (97.5%)	880 (95.8%)
> Day 9	19 (2.1%)	11 (1.2%)

[a]Day 1=surgery
Sponsor's table in NDA Vol. 117, pp. 76

Measurements of treatment compliance

In the all treated patient population, the percentage of patients with less than 8 postoperative injections was similar between the two treatment groups (2.5% in the Org31540/ SR90107A group and 2.2% in the enoxaparin group). In the primary efficacy population, there were 5 (0.6%) patients who received less than 8 postoperative injections up to the qualifying VTE examination in Org31540/SR90107A group as compared to 6 (0.7 %) patients in Exnoxaparin group besides temporary or permanent discontinuation due to AE or lack of efficacy. Overall, treatment compliance was similar between the treatment groups.

In total, 7 patients received temporarily study medication belonging to another patient which usually occurred only for single injections during the treatment period. No VTE or major bleeding was recorded in these patients, except for two patients (#13530919 in the enoxaparin group and #08551108 in the Org31540/SR90107A group) who both had a pre-operative dose and experienced a major bleed on Day 1. For both patients, the exact date/time of the administration of study medication belonging to another patient was not reported.

Concomitant medications

All treated patients

The percentage of patients receiving not allowed or discouraged concomitant medications from the day of first injection up to the day before the qualifying VTE examination or the day before the last injection, whichever came last, is presented in the following table. The use of not allowed or discouraged concomitant medications was similar for both treatment groups

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

Medication	Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)
Not allowed medications[a]	39 (3.4 %)	36 (3.2 %)
- Heparin (UFH, LMWH)/heparinoid [b]	24 (2.1 %)	21 (1.9 %)
- Antiplatelet drugs other than ASA	6 (0.5 %)	7 (0.6 %)
- Vitamin K antagonist	9 (0.8 %)	9 (0.8 %)
- Dextran	1 (0.1 %)	2 (0.2 %)
Discouraged medications[a]	583 (51.1 %)	588 (51.9 %)
- NSAID	550 (48.2 %)	551 (48.6 %)
- ASA	72 (6.3 %)	69 (6.1 %)

a From the day of first injection up to the day before qualifying VTE examination or the day before the last injection, whichever came last

b As per-protocol, heparin flushes and heparin in cell saver equipment on Day 1 were not taken into account

Sponsor's table in NDA Vol. 1 17, pp. 78

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

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

Physical Therapy	Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)
Elastic stockings only	28 (2.5 %)	25 (2.2 %)
Physiotherapy only	270 (23.7 %)	270 (24.0 %)
Both methods	779 (68.5 %)	768 (68.2 %)

Sponsor's table in NDA Vol. 1 17, pp. 79

Primary efficacy population

The same observations were made for the primary efficacy population as those made for the all treated patients population (See tables below).

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

Medication	Org31540/SR90107A 2.5 mg o.d. (N=908)	Enoxaparin 40 mg o.d. (N=919)
Not allowed medication [a]	29 (3.2 %)	30 (3.3 %)
- Heparin(UFH, LMWH)/heparinoids [b]	18 (2.0 %)	16 (1.7 %)
- Antiplatelet drugs other than ASA	5 (0.6 %)	6 (0.7 %)
- Vitamin K antagonist	6 (0.7 %)	8 (0.9 %)
- Dextran	1 (0.1 %)	2 (0.2 %)
Discouraged medication [a]	483 (53.2 %)	493 (53.6 %)
- NSAID	452 (49.8 %)	461 (50.2 %)
- ASA	60 (6.6 %)	59 (6.4 %)

a From the day of first injection up to the day before qualifying VTE examination
b As per-protocol, heparin flushes and heparin in cell saver equipment on Day 1 were not taken into account
Sponsor's table in NDA Vol. 117, pp. 80

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

Physical Therapy	Org31540/SR90107A 2.5 mg o.d. (N=908)	Enoxaparin 40 mg o.d. (N=919)
Elastic stockings only	19 (2.1 %)	19 (2.1 %)
Physiotherapy only	211 (23.3 %)	210 (22.9 %)
Both methods	630 (69.5 %)	635 (69.2 %)

Sponsor's table in NDA Vol. 117, pp. 80

Duration of participation in the study

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

Summary of Duration of Study Participation - All Treated Patients

Duration of Study Participation [a] (Days)	Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)
Median	45	45
Mean	46.9	46.2
S.D.	13.9	10.7
Min – Max		

a From the first injection (active drug or placebo) to the last visit
Sponsor's table in NDA Vol. 117, pp. 81

For the primary efficacy population, the mean duration of study participation was similar between the two treatment groups, and was similar to that observed for the all treated patients population (See table below). In addition, the mean time between surgery and the qualifying VTE examination between the two groups was similar.

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

Parameter		Org31540/SR90107A 2.5 mg o.d. (N=908)	Enoxaparin 40 mg o.d. (N=919)
Duration of study participation[a] (in days)	Median	45	45
	Mean	47.4	46.9
	S.D.	12.0	9.3
	Min - Max	[redacted]	[redacted]
Duration between surgery and the qualifying VTE examination (in days)	Median	8	8
	Mean	7.9	7.9
	S.D.	1.2	1.1
	Min - Max	[redacted]	[redacted]

[a] From first injection (active drug or placebo) to last visit
Sponsor's table in NDA Vol. 117, pp. 82

Most patients underwent the qualifying VTE examination between Day 5 and Day 11. Only 1 patient in the Org31540/SR90107A group had a qualifying VTE examination before Day 5 (this patient experienced a symptomatic DVT on Day 3).

Patients follow-up

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

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

Parameter	Org31540/SR90107A 2.5 mg o.d. (N=1140)	Enoxaparin 40 mg o.d. (N=1133)
Location at Discharge [a]		
Home	800 (70.4 %)	810 (71.8 %)
Other location than home	337 (29.6 %)	318 (28.2 %)
Rehabilitation Unit/facility	317 (27.9 %)	301 (26.7 %)
Other location	20 (1.8 %)	17 (1.5 %)
Missing	3	5
Living situation at follow-up assessment [b]		
Home	978 (88.6 %)	990 (90.2 %)
Home with professional assistance	49 (4.4 %)	37 (3.4 %)
Rest home	0 (0.0 %)	1 (0.1 %)
Nursing home	11 (1.0 %)	13 (1.2 %)
Rehabilitation Unit	48 (4.3 %)	38 (3.5 %)
Other	18 (1.6 %)	18 (1.6 %)

[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. 117, pp. 83

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=908)	Enoxaparin 40 mg o.d. (N=919)
Location at Discharge [a]		
Home	634 (69.8 %)	649 (70.7 %)
Other location than home	274 (30.2 %)	269 (29.3 %)
Rehabilitation Unit/facility	264 (29.1 %)	258 (28.1 %)
Other location	10 (1.1 %)	11 (1.2 %)
Missing	0	1
Living situation at follow-up assessment [b]		
Home	808 (89.7 %)	824 (91.2 %)
Home with professional assistance	36 (4.0 %)	29 (3.2 %)
Rest home	0 (0.0 %)	1 (0.1 %)
Nursing home	7 (0.8 %)	11 (1.2 %)
Rehabilitation Unit	39 (4.3 %)	26 (2.9 %)
Other	11 (1.2 %)	13 (1.4 %)

[a] Percentages were based on non missing information.
[b] Percentages were based on patients with a follow-up form available, excluding death up to day 49 and missing data
Sponsor's table in NDA Vol. 117, pp. 84

Efficacy Evaluation

Analysis of efficacy

Primary efficacy analysis

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

Results for the primary efficacy endpoint are presented in the table below. The VTE rate up to Day 11 was statistically significantly lower in the Org31540/SR90107A group than in the enoxaparin group (4.1% versus 9.2%; $p=9 \times 10^{-6}$). This highly significant difference in VTE rate was mainly due to difference in DVT component between the two groups (4.0% vs. 9.0%, $p=1.1 \times 10^{-5}$). There was no difference in the incidence of PE up to Day 11 between the two 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 = 908)	Enoxaparin 40 mg o.d. (N = 919)	Difference Org31540/SR90107A minus Enoxaparin (%)	Fisher's Exact Test (p)
VTE	37 4.1%	85 9.2%	-5.2%	9×10^{-6}
DVT	36 (4.0%)	83 (9.0%)	-10.8	1.1×10^{-5}
PE	2 (0.2%)	2 (0.2%)	0.0	1.0
Fatal PE	0 (0.0%)	0 (0.0%)	0.0	
Non-Fatal PE	2 (0.2%)	2 (0.2%)	0.0	

Note: one patient had both DVT and PE in Org31540/SR90107A group
p-value for PE was obtained by FDA Statistical Reviewer Dr. Milton C. Fan, Ph.D.
Reviewer's table based on NDA Vol. 117, pp. 84-89 and efficacy datasets

This reviewer further analyzed mortality data from this study. There were 7 deaths (2 in Org31540/SR90107A group and 5 in enoxaparin group) in the study including 2 deaths which occurred up to Day 11 (See table below). Of 7 deaths, one fatal PE was identified from autopsy in Org31540/SR90107A group at day 30. There were 4 autopsies (1 in Org31540/SR90107A group and 3 in enoxaparin group) done among 7 deaths including the case with fatal PE.

Deaths from all causes and PE in the study

Deaths	Org31540/SR90107A 2.5 mg o.d. (N = 1140)	Enoxaparin 40 mg o.d. (N = 1133)
Death up to day 11		
All causes	0 (0.0%)	2 (0.2%)
Fatal PE	0 (0.0%)	0 (0.0%)
Death up to day 49		
All causes	2 (0.2%)	4 (0.4%)
Fatal PE	1 (0.1%)	0 (0.0%)
Death after day 49 (up to day 60)		
All deaths	0 (0.0%)	1 (0.1%)
Fatal PE	0 (0.0%)	0 (0.0%)
Total		
All deaths	2 (0.2%)	5 (0.4%)
Fatal PE	1 (0.1%)	0 (0.0%)

Reviewer's table based on NDA study 63118, Appendix 14.2.4.2.2-4 and submitted datasets

In Org31540/SR90107A group, another death was due to pneumonia/sepsis. In the enoxaparin group, the SAEs leading to deaths were MI (2), suicide, sepsis, and bronchopneumonia.

A total of 14 mandatory venographies (8 in the Org31540/SR90107A group and 6 in the enoxaparin group) were performed after Day 11 and were consequently disqualified from all efficacy analyses. Adjudication of these examinations revealed only one

asymptomatic proximal DVT reported on Day 27 in the Org31540/SR90107A group and one asymptomatic distal only DVT reported on Day 12 in the enoxaparin group.

Secondary efficacy analyses

Adjudicated DVT

The numbers (%) of patients with adjudicated DVTs, adjudicated proximal DVTs and distal only DVTs up to Day 11 are summarized in the following table. There was a statistically significantly lower rate of any 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/SR90107A group than in the enoxaparin group.

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

Endpoints	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	36 / 908 4.0%	83 / 918 9.0%	-5.0%	$1.1x10^{-5}$
Any proximal DVT	6 / 922 0.7%	23 / 927 2.5%	-1.8%	0.0021
Distal DVT only	30 / 909 3.3%	67 / 917 7.3%	-4.0%	0.0001

Reviewer's table based on NDA Vol. 117, pp. 86-7. P-value for distal DVT only was calculated by FDA Statistical Reviewer Dr. Milton C. Fan, Ph.D.

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

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

Location of DVT		Org31540/SR90107A 2.5 mg o.d.	Enoxaparin 40 mg o.d.
Any DVT			
Either side	n / N (%)	36 / 908 (4.0)	83 / 918 (9.0)
	95% CI	[2.8;5.4]	[7.3;11.1]
Operative leg	n / N (%)	24 / 957 (2.5)	64 / 960 (6.7)
	95% CI	[1.6;3.7]	[5.2;8.4]
Non-operative leg	n / N (%)	15 / 920 (1.6)	34 / 926 (3.7)
	95% CI	[0.9;2.7]	[2.6;5.1]
Both sides	n / N (%)	3 / 969 (0.3)	15 / 968 (1.5)
	95% CI	[0.1;0.9]	[0.9;2.5]
Any proximal DVT			
Either side	n / N (%)	6 / 922 (0.7)	23 / 927 (2.5)
	95% CI	[0.2;1.4]	[1.6;3.7]
Operative leg	n / N (%)	5 / 967 (0.5)	16 / 972 (1.6)
	95% CI	[0.2;1.2]	[0.9;2.7]
Non-operative leg	n / N (%)	1 / 934 (0.1)	8 / 938 (0.9)
	95% CI	[0.0;0.6]	[0.4;1.7]
Both sides	n / N (%)	0 / 979 (0.0)	1 / 983 (0.1)
	95% CI	[0.0 ;0.4]	[0.0;0.6]
Distal only DVT			
Either side	n / N (%)	30 / 909 (3.3)	67 / 917 (7.3)
	95% CI	[2.2;4.7]	[5.7;9.2]
Operative leg	n / N (%)	19 / 959 (2.0)	48 / 961 (5.0)
	95% CI	[1.2;3.1]	[3.7;6.6]
Non-operative leg	n / N (%)	14 / 922 (1.5)	26 / 927 (2.8)
	95% CI	[0.8;2.5]	[1.8;4.1]
Both sides	n / N (%)	3 / 972 (0.3)	7 / 971 (0.7)
	95% CI	[0.1;0.9]	[0.3;1.5]

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. 117, pp. 86

Curative treatment initiated after VTE assessment and prolonged prophylaxis of VTE
As shown in the table below, the percentage of patients who initiated curative treatment based on the Investigator assessment of VTE was higher ($p=1.8 \times 10^{-6}$) in the enoxaparin group.

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

Curative treatment [a]	Org31540/SR90107A 2.5 mg o.d. (N[b] = 997)	Enoxaparin 40 mg o.d. (N [b] = 999)
All patients with curative treatment	40 (4.0 %)	88 (8.8 %)
- heparin (UFH, LMWH)/heparinoids	39 (3.9 %)	80 (8.0 %)
- vitamin K antagonist without heparin (UFH, LMWH)/heparinoids	0 (0.0 %)	5 (0.5 %)
- other than heparin or vitamin K antagonist	1 (0.1 %)	2 (0.2 %)
- no medication reported	0 (0.0 %)	1 (0.1 %)

a. Patients were counted only once. b. Number of patients with any VTE assessment up to Day 11.
Sponsor's table in NDA Vol. 117, pp. 87

The percentage of patients who initiated antithrombotic curative treatment following qualifying VTE assessment used in the primary efficacy analysis was higher ($p=3.6x10^{-6}$) in the enoxaparin group (See Table below).

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

Curative treatment[a]	Org31540/SR90107A 2.5 mg o.d. (N = 908)	Enoxaparin 40 mg o.d. (N = 919)
All patients with curative treatment	31 (3.4 %)	80 (8.7 %)
- heparin (UFH, LMWH)/heparinoids	30 (3.3 %)	72 (7.8 %)
- vitamin K antagonist without heparin (UFH, LMWH)/heparinoids	0 (0.0 %)	5 (0.5 %)
- other than heparin or vitamin K antagonist	1 (0.1 %)	2 (0.2 %)
- no medication reported	0 (0.0 %)	1 (0.1 %)

a. Patients were counted only once.
Sponsor's table in NDA Vol. 117, pp. 88

During the follow-up period, prolonged prophylaxis of VTE (mainly LMWH and vitamin K antagonists) was administered to 50.4% of the patients in the Org31540/SR90107A group and 46.5% of the 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.

A similarly low rate of patients with symptomatic VTE was observed in both treatment groups up to Day 11. During this period, 5 patients in the Org31540/SR90107A group experienced a symptomatic VTE (3 symptomatic DVT, 2 non-fatal PE), as compared to 3 patients in the enoxaparin group (1 symptomatic DVT, 2 non-fatal PE).

Similarly, the percentage of patients with 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=1129)	Enoxaparin 40 mg o.d. (N=1123)	Fisher's Exact p-value
Up to Day 11	VTE	n (%)	5 (0.4 %)	3 (0.3 %)	0.73
		95% CI	[0.1;1.0]	[0.1;0.8]	
	DVT	n (%)	3 (0.3 %)	1 (0.1 %)	
	Non-fatal PE	n (%)	2 (0.2 %)	2 (0.2 %)	
	Fatal PE	n (%)	0 (0.0 %)	0 (0.0 %)	
Up to Day 49	VTE	n (%)	12 [a] (1.1 %)	9 (0.8 %)	0.66
		95% CI	[0.6;1.8]	[0.4;1.5]	
	DVT	n (%)	9 (0.8 %)	6 (0.5 %)	
	Non-fatal PE	n (%)	3 (0.3 %)	3 (0.3 %)	
	Fatal PE	n (%)	1 (0.1 %)	0 (0.0 %)	

[a] One patient experienced after Day 11 a symptomatic DVT and a non-fatal PE.
Reviewer's table based on sponsor's tables in NDA Vol. 117, pp. 89

Symptomatic VTEs recorded up to Day 49 were also summarized in form of cumulative event rate curves, using Kaplan-Meier method; the comparison of the 2 treatment groups revealed no statistically significant difference in terms of time to the first event.

Exploratory analysis for primary efficacy endpoint

Subgroup Analysis

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

The treatment effect in favor of Org31540/SR90107A was shown numerically in all countries except Finland and Austria and the difference in the incidence of VTE up to day 11 was statistically significant in 3 countries [Norway (p=0.038), Netherlands (p=0.014) and Poland (p=0.018); p-values were obtained by FDA Statistical Reviewer Dr. Milton C. Fan using Fisher's Exact test].

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), use of cement, duration of surgery, previous history of VTE, baseline creatinine level and previous use of antithrombotic medication. For race, more than 99% of patients were Caucasians in the study.

There were significantly fewer VTE in Org31540/SR901 group as compared to enoxaparin group in patients with male gender, age ≥65 years, BMI <30 Kg/m^2, regional

anesthesia, creatinine ≥medium before surgery, and no previous antithrombotic treatment prior to surgery.

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

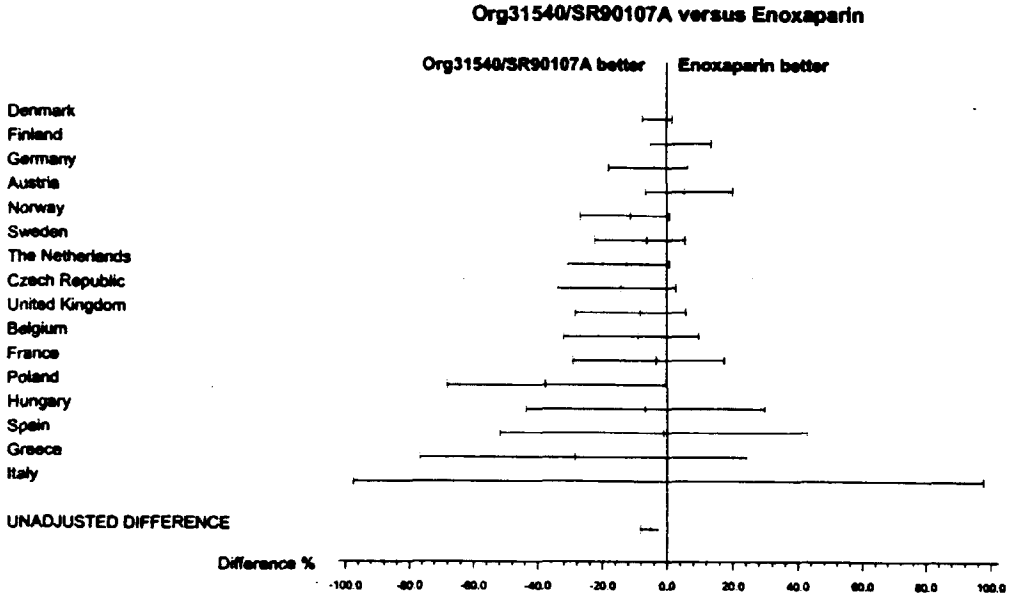
Covariate [a]	Org31540/SR90107A 2.5 gm o.d. (N=908)				Enoxaparin 40 mg o.d. (N=919)			
		VTE				VTE		
Subgroup	**N**	**n**	**%**	**95% CI**	**N**	**n**	**%**	**95% CI**
Country								
Denmark	217	1	0.5	[0.0;2.5]	211	5	2.4	[0.8;5.4]
Finland	97	4	4.1	[1.1;10.2]	110	2	1.8	[0.2;6.4]
Germany	90	4	4.4	[1.2;11.0]	86	7	8.1	[3.3;16.1]
Austria	78	8	10.3	[4.5;19.2]	79	4	5.1	[1.4;12.5]
Norway	75	4	5.3	[1.5;13.1]	78	13	16.7	[9.2;26.8]
Sweden	70	2	2.9	[0.3;9.9]	67	6	9.0	[3.4;18.5]
The Netherlands	60	1	1.7	[0.0;8.9]	56	8	14.3	[6.4;26.2]
Czech Republic	54	6	11.1	[4.2;22.6]	59	15	25.4	[15.0;38.4]
United Kingdom	43	0	0.0	[0.0;8.2]	49	4	8.2	[2.3;19.6]
Belgium	40	3	7.5	[1.6;20.4]	43	7	16.3	[6.8;30.7]
France	34	2	5.9	[0.7;19.7]	33	3	9.1	[1.9;24.3]
Poland	16	0	0.0	[0.0;20.6]	16	6	37.5	[15.2;64.6]
Hungary	15	1	6.7	[0.2;31.9]	15	2	13.3	[1.7;40.5]
Spain	10	1	10.0	[0.3;44.5]	9	1	11.1	[0.3;48.2]
Greece	8	0	0.0	[0.0;36.9]	7	2	28.6	[3.7;71.0]
Italy	1	0	0.0	[0.0;97.5]	1	0	0.0	[0.0;97.5]
Gender								
Male	396	9	2.3	[1.0;4.3]	402	37	9.2	[6.6;12.5]
Female	512	28	5.5	[3.7;7.8]	517	48	9.3	[6.9;12.1]
Race								
Caucasian	899	37	4.1	[2.9;5.6]	913	85	9.3	[7.5;11.4]
Black	3	0	0.0	[0.0;70.8]	4	0	0.0	[0.0;60.2]
Asian	2	0	0.0	[0.0;84.2]	1	0	0.0	[0.0;97.5]
Other races	3	0	0.0	[0.0;70.8]	0	0	NA	NA
Age								
< 65 years	385	12	3.1	[1.6;5.4]	377	25	6.6	[4.3;9.6]
[65 - 75[years	336	14	4.2	[2.3;6.9]	358	37	10.3	[7.4;14.0]
≥ 75 years	187	11	5.9	[3.0;10.3]	184	23	12.5	[8.1;18.2]
Obesity								
BMI < 30 kg/m^2	721	28	3.9	[2.6;5.6]	702	70	10.0	[7.9;12.4]
BMI ≥ 30 kg/m^2	173	9	5.2	[2.4;9.6]	193	14	7.3	[4.0;11.9]
Type of anesthesia								
Regional only	555	19	3.4	[2.1;5.3]	529	54	10.2	[7.8;13.1]
Other	353	18	5.1	[3.0;7.9]	390	31	7.9	[5.5;11.1]
Type of surgery								
Primary	802	35	4.4	[3.1;6.0]	800	79	9.9	[7.9;12.2]
Revision	106	2	1.9	[0.2;6.6]	119	6	5.0	[1.9;10.7]
Use of cement								
Yes	542	25	4.6	[3.0;6.7]	558	51	9.1	[6.9;11.8]
No	365	12	3.3	[1.7;5.7]	360	34	9.4	[6.6;12.9]

Duration of surgery [b]								
< median	448	17	3.8	[2.2;6.0]	441	40	9.1	[6.6;12.1]
≥ median	457	20	4.4	[2.7;6.7]	476	45	9.5	[7.0;12.4]
Previous VTE								
Yes	35	4	11.4	[3.2;26.7]	40	7	17.5	[7.3;32.8]
No	873	33	3.8	[2.6;5.3]	879	78	8.9	[7.1;11.0]
Baseline creatinine [b]								
< median	436	20	4.6	[2.8;7.0]	442	35	7.9	[5.6;10.8]
≥ median	452	15	3.3	[1.9;5.4]	465	50	10.8	[8.1;13.9]
Previous antithrombotic treatment [c]								
Yes	6	0	0.0	[0.0;45.9]	1	0	0.0	[0.0;97.5]
No	902	37	4.1	[2.9;5.6]	918	85	9.3	[7.5;11.3]

Note: Age range [65, 75[denotes age from 65 years (included) up to <75 years NA= not applicable
[a] Per covariate, only non-missing observations were taken into account
[b] Median for duration of surgery was 2:15 h across treatment groups; median for baseline creatinine was 0.938 mg/dL across treatment groups
[c] Use of antithrombotic treatment within 2 days prior to the day of first study drug injection (per amendment no. 1)
Sponsor's table in NDA Vol. 117, pp. 91-92

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

COUNTRY



GENDER; RACE; AGE; OBESITY

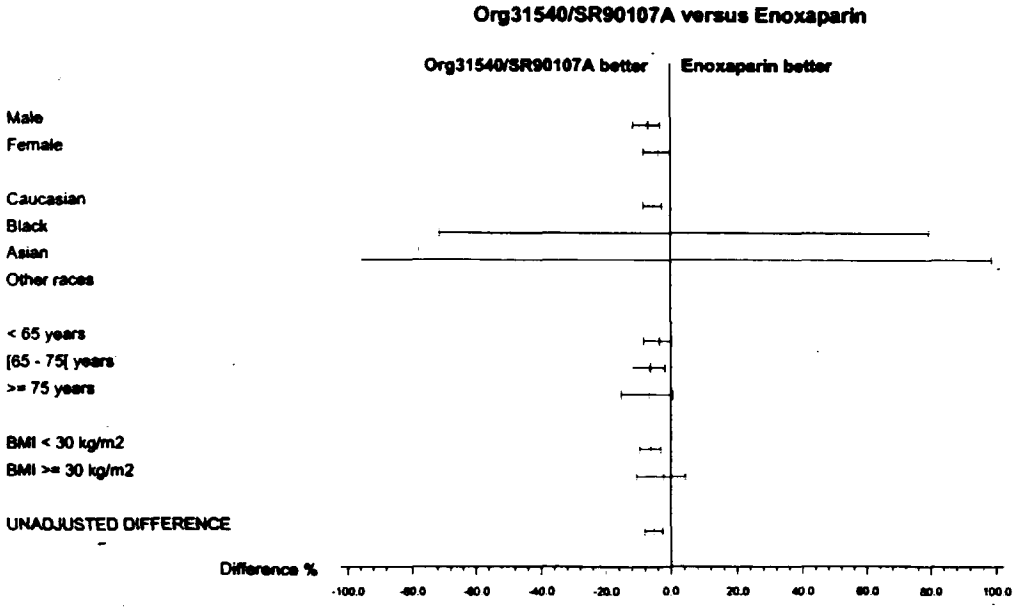
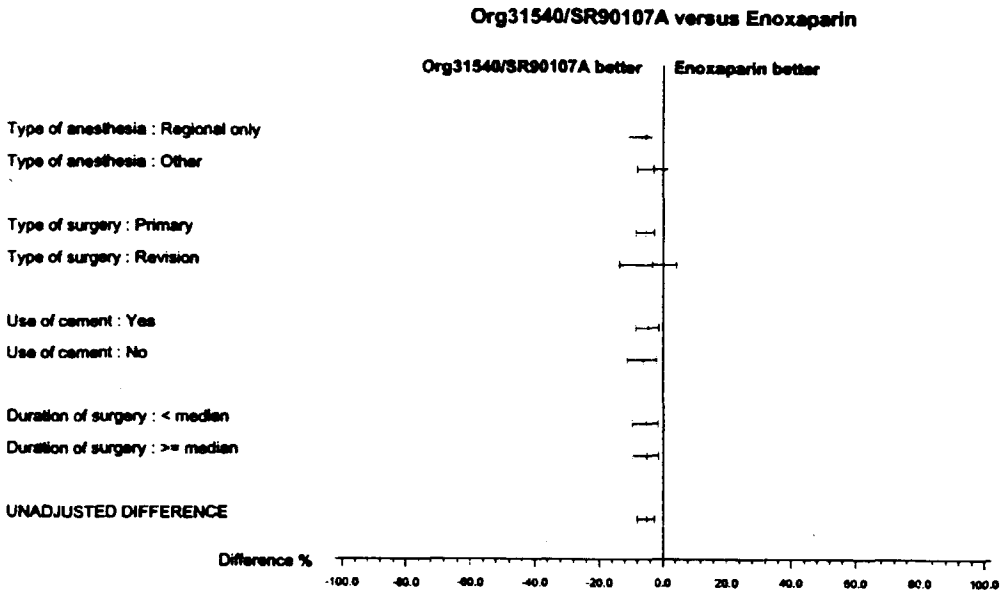


Figure (7.2.1) 1 - Differences (%) and 95% CIs Between Org31540/SR90107A and Enoxaparin Groups for Patients With Adjudicated VTE up to Day 11 According to Baseline Covariates - Primary Efficacy Population

Sponsor's figure in NDA Vol. 117, pp. 93

CHARACTERISTICS OF SURGERY



PREVIOUS VTE, BASELINE CREATININE, PREVIOUS ANTITHROMBOTIC MEDICATION

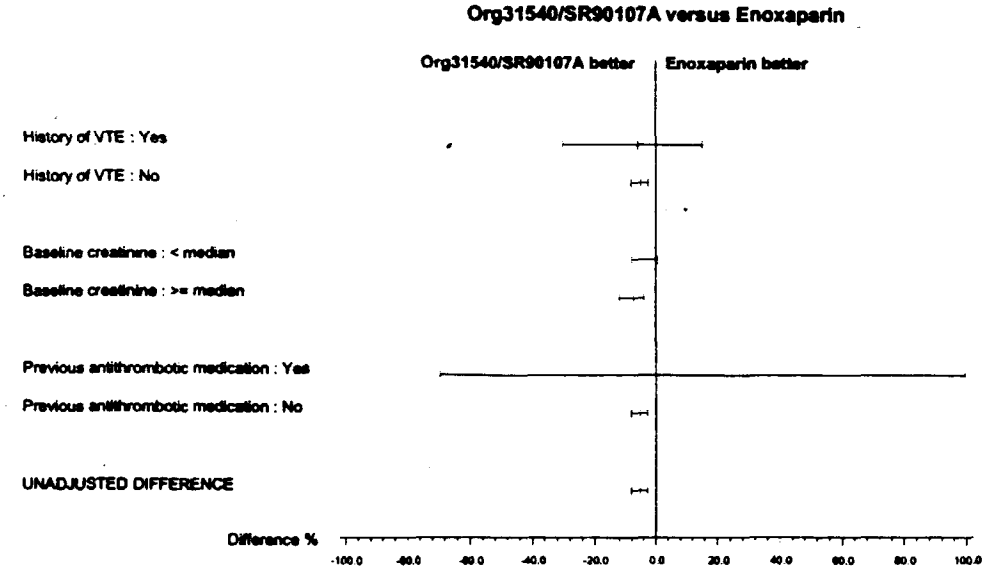


Figure (7.2.1) 1 - *continued* - Differences (%) and 95% CIs Between Org31540/SR90107A and Enoxaparin Groups for Patients With Adjudicated VTE up to Day 11 According to Baseline Covariates - Primary Efficacy Population

Note: Median for duration of surgery was 2:15 h across treatment groups; median for baseline creatinine was 0.938 mg/dL across treatment groups; Ref: Appendices 14.2.2.2.2.A, 14.2.2.2.2.B, 14.2.2.2.2.C, 14.2.2.2.2.D

Sponsor's table in NDA Vol. 117, pp. 94

Sensitivity Analysis

There were 232 (20.4%) patients in Org31540/SR90107A group and 214 (18.9%) 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 based on all treated patients who underwent the appropriate surgery. These results were consistent with those observed for the primary efficacy analysis.

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

Scenario	Org31540/SR90107A 2.5 mg o.d. (N=1129)	Enoxaparin 40 mg o.d. (N=1123)	Difference and Exact 95% CI	Fisher's Exact P-value*
Best case scenario	37 (3.3%)	85 (7.6%)	-4.3 [-6.7; -2.2]	<0.0001
Realistic case scenario	58 (5.1%)	103 (9.2%)	-4.0 [-6.7; -1.7]	0.0002
Worst case scenario	258 (22.9%)	289 (25.7%)	-2.9 [-6.8; +0.8]	0.116

*p-values were obtained by FDA Statistical Reviewer Dr. Milton C. Fan, Ph.D.
Sponsor's table in NDA Vol. 117, pp. 95

The following table shows sensitivity analysis on all randomized patients (excluding center 0454). The results were consistent with those observed for the primary efficacy analysis.

Sensitivity analysis in ITT population

Scenario	Org31540/SR9010A 2.5 mg o.d. (N= 1155)	Enoxaparin 40 mg o.d. (N = 1154)	Difference And exact 95%CI	Fisher's Exact P-value*
Best case scenario	37 (3.2 %)	85 (7.4 %)	-4.2% [-6.48; -2.11]	<0.001
Realistic scenario	60 (5.2 %)	106 (9.2 %)	-4.0% [-6.59; -1.65]	0.0002
Worst case scenario	284 (24.6 %)	319 (27.6 %)	-3.1% [-6.95; 0.71]	0.097

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

Handling of center 0454 (n=12) was further performed by the sponsor. At center 0454, 5 of 12 patients had DVT adjudications based on available venography (one had proximal DVT and four had no DVT); 11 of 12 patients could additionally be included in sensitivity analysis based on all treated patients who underwent the appropriate surgery; one patient was not treated. The following differences and exact 95% confidence intervals were found for the percentage of VTE: Primary efficacy analysis: -5.0% [-8.0%; -2.6%] with p-value 1×10^{-5}; best case scenario: -4.2% [-6.6%; -2.1%]; realistic case scenario: -3.9% [-6.6%; -1.6%]; worst case scenario: -2.9% [-6.8%; 0.8%]. The results from sensitivity analysis were consistent with those observed for the primary efficacy analysis after excluding center 0454.

Drug-drug and drug-disease interactions

The primary efficacy endpoint was further analyzed according to specific concomitant medication classes, i.e. not allowed or discouraged medication as well as medication which were reported to have a possible interaction with heparin, according to US PDR 1999 (See Table below).

No apparent interactions were found between treatment and concomitant medication classes examined.

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

	Org31540/SR90107A 2.5 mg o.d. (N=908)				Enoxaparin 40 mg o.d. (N=919)			
WHO Preferred Drug Name		VTE				VTE		
Concomitant intake	**N**	**n**	**%**	**95% CI**	**N**	**n**	**%**	**95% CI**
Heparin (UFH, LMWH)/heparinoid [a]								
With	17	3	17.6	[3.8;43.4]	17	4	23.5	[6.8;49.9]
Without	891	34	3.8	[2.7;5.3]	902	81	9.0	[7.2;11.0]
Anti-Platelet drugs other than ASA								
With	4	0	0.0	[0.0;60.2]	3	0	0.0	[0.0;70.8]
Without	904	37	4.1	[2.9;5.6]	916	85	9.3	[7.5;11.3]
Vitamin K antagonists								
With	5	2	40.0	[5.3;85.3]	8	1	12.5	[0.3;52.7]
Without	903	35	3.9	[2.7;5.3]	911	84	9.2	[7.4;11.3]
Dextran								
With	1	0	0.0	[0.0;97.5]	2	0	0.0	[0.0;84.2]
Without	907	37	4.1	[2.9;5.6]	917	85	9.3	[7.5;11.3]
NSAID								
With	436	22	5.0	[3.2;7.5]	443	31	7.0	[4.8;9.8]
Without	472	15	3.2	[1.8;5.2]	476	54	11.3	[8.6;14.5]
ASA								
With	39	1	2.6	[0.1;13.5]	35	5	14.3	[4.8;30.3]
Without	869	36	4.1	[2.9;5.7]	884	80	9.0	[7.2;11.1]
Penicillins								
With	188	9	4.8	[2.2;8.9]	188	18	9.6	[5.8;14.7]
Without	720	28	3.9	[2.6;5.6]	731	67	9.2	[7.2;11.5]
Cephalosporins								
With	631	28	4.4	[3.0;6.3]	655	58	8.9	[6.8;11.3]
Without	277	9	3.2	[1.5;6.1]	264	27	10.2	[6.8;14.5]
Anti-histamines & phenothiazines								
With	116	5	4.3	[1.4;9.8]	118	14	11.9	[6.6;19.1]
Without	792	32	4.0	[2.8;5.7]	801	71	8.9	[7.0;11.1]
Cardiac glycosides								
With	12	0	0.0	[0.0;26.5]	15	2	13.3	[1.7;40.5]
Without	896	37	4.1	[2.9;5.6]	904	83	9.2	[7.4;11.3]
Macrolide antibiotics								
With	2	0	0.0	[0.0;84.2]	3	1	33.3	[0.8;90.6]
Without	906	37	4.1	[2.9;5.6]	916	84	9.2	[7.4;11.2]
Tetracyclines								

With	0	0	NA	NA	1	0	0.0	[0.0;97.5]
Without	908	37	4.1	[2.9;5.6]	918	85	9.3	[7.5;11.3]
Other antibiotics								
With	29	0	0.0	[0.0;11.9]	29	3	10.3	[2.2;27.4]
Without	879	37	4.2	[3.0;5.8]	890	82	9.2	[7.4;11.3]
Vitamin C								
With	64	1	1.6	[0.0;8.4]	52	8	15.4	[6.9;28.1]
Without	844	36	4.3	[3.0;5.9]	867	77	8.9	[7.1;11.0]

NA = not applicable
aAs per-protocol, heparin flushes and heparin in cell saver equipment on Day 1 were not taken into account
Sponsor's table in NDA Vol. 117, pp. 97-98

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

Reviewer's Summary

Study 63118 was a multicenter, randomized, double-blind, double-dummy, parallel-group study comparing Org31540/SR90107A 2.5 mg once daily SC (n=1155) to enoxaparin 40 mg once daily SC (n=1154) in 2309 patients undergoing either an elective primary total hip replacement surgery, or a revision of hip replacement surgery.

Administration of drugs was started post-operatively in nearly all patients (99%) in Org31540/SR90107A group and 22% in 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.

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 2309 randomized patients in the study, 446 (19.6%) patients had missing primary efficacy endpoint due to non-evaluable venography/no VTE assessment up to day 11. They were similar in two treatment groups [232 (20.4%) in Org31540/SR90107A group and 214 (18.9%) in enoxaparin group]. The missing rate associated with venography procedure in this study was compatible to other studies in patients undergoing elective hip replacement surgery (21-29% in studies in NDA 20-164/000, Lovenox, FDA Medical Officer's Review, page 63 and 102; 31% in studies in NDA 20-287/S-008, Fragmin, FDA Medical Officer's Review, page 15).

Overall, Study 63118 was an adequate and well-controlled study. One center (0454, n=12) lost CRFs of 7 patients and data from this center were subsequently excluded from all analysis. A sensitivity analysis was further performed after including this center; the results were consistent with those from primary efficacy analysis after excluding this center.

Study 63118 demonstrated that Org31540/SR90107A 2.5 mg once daily SC is highly statistically significantly superior to enoxaparin 40 mg once daily SC 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).

The primary efficacy results in favor of Org31540/SR901 treatment were seen in nearly all participating countries (14/16). The efficacy results in favor of Org31540/SR901 were observed across all subgroups including gender, age, BMI, type of anesthesia, type of surgery (primary and revision), use of cement, duration of surgery, previous history of VTE, baseline creatinine level, previous use of antithrombotic medication, and concomitant antithrombotic medications.

Trial EFC2442 - [redacted]

Title of the Study

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

Study Period

December 21, 1998 to January 5, 2000

Investigators and Study Centers

The study was carried out by investigators at 139 centers in 3 countries: 94 in United Sates, 30 in Canada, and 15 in Australia.

Study Objectives

The objective of the study was to demonstrate superior efficacy of a once daily, postoperative, subcutaneous (SC) injection of 2.5 mg Org31540/SR90107A compared to twice daily post-operative, SC injections of 30 mg enoxaparin in the prevention of venous thromboembolic events (DVT or symptomatic PE) in patients having primary elective Total hip replacement (THR), or a revision of component(s) of a THR.

Overall Study Design

The study design of EFC2442 was the same as study 63118 except for using a different dosing regimen of enoxaparin and using a double-blind method without double-dummy. The randomization was performed post-operatively. The study population was the same as in Study 63118 with addition of established hemostasis on the calendar day of surgery,

no later than 8 hours after closure of the incision in the inclusion criteria. The efficacy and safety evaluations were the same as in study 63118 and were adjudicated by the same CIAC. The sample size estimation and statistical analysis were identical to 63118.

This was a multinational, multicenter, randomized, double-blind, parallel group study to compare 2.5 mg once daily SC Org31540/SR90107A to 30 mg every 12 hours SC enoxaparin in patients undergoing elective THR, or a revision.

Study Treatments

Patients were randomly assigned to 1 of 2 treatment groups:

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

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

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

Org31540/SR90107A was supplied by Sanofi-Synthelabo (Notre Dame de Bondeville, France) and was provided as an isotonic 10 mg/mL solution for subcutaneous injection in 0.25 mL prefilled syringes (2.5 mg) which were contained in an Autoject™ for blinding purposes. Each mL of Org31540/SR90107A contained 10 mg Org31540/SR90107A, — — sodium chloride, and —— water for injection.

Enoxaparin (Lovenox) was supplied in 0.3 mL (30 mg) pre-filled syringes which were contained in an Autoject™ for blinding purposes.

Placebo was supplied by Sanofi-Synthelabo (Paris, France) in Autojects™ identical to those of Org31540/SR90107A and enoxaparin, and contained isotonic sodium chloride for injection.

Dosing schedule

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

Dosing Schedule

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

a The morning injection Day 2 was at least 12 hours after the Day 1 dose and less than 24 hours post-surgical closure.
b Patients were required to receive injections for 7 ±2 days, including the day of surgery, and until the final (positive unscheduled or mandatory) venogram was obtained.
Sponsor's table in NDA Vol. 163, pp. 31

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

Randomization Process

Randomization for this study was contracted to [redacted] The randomization team at [redacted] generated a randomization list, within each study site, balanced with a block size of four, with a 2:2 ratio of Org31540/SR90107A and enoxaparin treatments. The randomization schedule, which consisted of center identifiers and treatment assignments (A, B) was uploaded into an Interactive Voice Response System (IVRS) at [redacted] to allow for centralized randomization of patients and centralized study drug management. The investigators were instructed to call the IVRS telephone number for each consecutive patient (numbered sequentially within a center) determined to have qualified for entry into the study. The IVRS informed the investigator of treatment kit number assignment for that patient. A patient was considered as randomized if a date and a treatment kit number were recorded in the "Treatment Assignment" form of the Case Report Form. Randomized patients who did not start or complete treatment were not to be replaced. Patients were randomized post-operatively.

Blinding procedures

Blinding for this study was accomplished by using an opaque auto injection system to conceal the study drug syringe. The syringe was pre-loaded inside an Autoject™ manufactured and marketed by [redacted] The enoxaparin, Org31540/SR90107A, and placebo Autoject™ were identical in appearance. Autoject™ for both treatment groups were color coded in an identical manner, yellow to indicate morning doses, and blue to indicate the first post-operative and subsequent evening doses.

Interim Analyses

There was no interim analysis in this study.