The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No: TDU4089

Title: A safety, pharmacokinetics and bioavailability study after single dose subcutaneous administration of Org31540/SR90107A 0.75, 2.5, and 8mg in young adult Japanese healthy male subjects.

Rationale: The safety and pharmacokinetics (PK) of fondaparinux sodium (FX) administered by intravenous (IV) injection has been investigated in healthy adult male volunteers in Japan. Phase II, dose-ranging studies conducted in Europe, North America and Australia in subjects undergoing total hip replacement or total knee replacement surgery, indicate that a subcutaneous (SC) daily dose of 2.5mg FX is optimal in the prophylactic management of venous thrombolic event and this dose has been used in phase III trials in the West. In view of the potential usefulness of the SC dose, it was considered relevant to assess the safety, PK and absolute bioavailability of FX following SC administration in healthy, young adult, Japanese, male subjects. The 0.75mg dose was set as the lower dose as it is the minimum efficacious dose, and the minimum dose at which PK parameters can be assessed. The 8mg dose was set as the higher dose as it is the maximum dose assessed in previous studies.

Phase: I

Study Period: 20 December 1999 to 17 March 2000

Study Design: Monocenter, open-label, ascending single dose study, with a 2-period randomized crossover for 2.5mg single dose SC versus IV

Centres: A single center in Japan

Indication: None

Treatment: Eighteen subjects were enrolled. Six subjects were assigned to each of the 3 dose groups according to the order in which they gave informed consent. In the 2.5mg group, 3 subjects were randomly assigned to each of the 2 subgroups:
Group 1: 0.75mg FX given as a single SC administration
Group 2: 2.5mg FX given as both a single SC administration and an IV infusion. Three subjects received treatment in the order SC followed by IV and 3 subjects received treatment in the order IV followed by SC. Single dose treatments were administered in 2 treatment periods separated by a 10-day wash-out period
Group 3: 8mg FX given as a single SC administration.

Objectives:
To assess the PK of FX 0.75, 2.5 and 8mg after single-dose SC administration
To assess the absolute bioavailability of FX 2.5mg after SC administration by comparison to a 2-hour IV infusion of 2.5mg.
To assess the safety of FX after single dose SC and IV administration

Statistical Methods:
Populations analyzed:
All subjects were included in the analysis of both PK and safety.
Statistical tests used:
Pharmacokinetics:
Standard descriptive statistics were provided for maximum plasma concentration (C_{max}), time when C_{max} occurred (t_{max}), apparent terminal half-life ($t_{1/2z}$), area under the plasma concentration curve versus time curve from time zero to the last measurable time point (AUC_{last}), area under the plasma concentration curve versus time curve from time zero to infinity (AUC), mean residence time (MRT), plasma clearance [CL(/F)], distribution volume in the terminal phase [V_z(/F)], total cumulated amount excreted in urine (Ae), fraction of the dose excreted in the urine (fe) and renal clearance (CL_r).
Dose effect was assessed by a mixed model analysis on log-transformed values of C_{max}, AUC_{last}, AUC, MRT, CL(/F), V_z(/F), Ae, fe and CL_r.
Dose proportionality of C_{max}, AUC_{last} and Ae was evaluated using a log-transformed Power model.
The absolute bioavailability of FX after SC administration (relative to IV administration) was assessed at the 2.5mg dose using a mixed model analysis.
Safety: All safety parameters including adverse events (AEs), vital signs and abnormal laboratory parameters were assessed by means of descriptive statistics.

Study Population: Healthy, Japanese males, aged 20 to 35 years of age, with body weight between 45 and 80kg and within ±20% of that calculated by [height (cm) – 100] x 0.9, excluding concomitant medical illness, and history of bleeding, diathesis, or thrombosis.

Number of Subjects:	**FX 0.75mg**	**FX 2.5mg**		**FX 8mg**
	SC	**SC/IV**	**IV/SC**	**SC**
Planned N	6	3	3	6
Dosed N	6	3	3	6
Completed n (%)	6 (100)	3 (100)	3 (100)	6 (100)
Total Number Subjects Withdrawn N (%)	0	0	0	0
Withdrawn due to Adverse Events n (%)	0	0	0	0
Withdrawn due to Lack of Efficacy n (%)	0	0	0	0
Withdrawn for Other Reasons n (%)	0	0	0	0

Demographics	**FX 0.75mg**	**FX 2.5mg***	**FX 8mg**
N	6	6	6
Males	6	6	6
Mean Age in Years (sd)	24.5 (3.6)	22.5 (0.8)	22.3 (2.0)
Mean Weight in Kg (sd)	64.67 (6.97)	65.95 (4.53)	62.48 (8.44)
Asian (Japanese) n (%)	6 (100)	6 (100)	6 (100)

*Demographic data are those reported for Treatment Period I

Pharmacokinetics (PK):

Plasma

Plasma PK parameters for FX (N=6, unless stated otherwise)

Route Dose		**T_{max}[a] (h)**	**C_{max} (mg/L)**	**$t_{1/2z}$ (h)**	**AUC_{last} (mg.h/L)**	**AUC (mg.h/L)**	**CL/F (mL/min)**	**V_z/F (L)**	**MRT (h)**
SC 0.75mg	Mean	1.8	0.127	17.4	1.40	NC	NC	NC	NC
	SD	1.5-2.5[c]	0.015	4.47	0.387	NC	NC	NC	NC
	CV%	22.3	12.0	25.7	27.6	NC	NC	NC	NC
SC 2.5mg	Mean	2.0	0.335	16.1	5.15	6.62[b]	5.60[b]	7.81[b]	22.8[b]
	SD	1.5-2.5[c]	0.030	2.5	0.905	1.10	0.882	0.420	3.91
	CV%	19.6	8.8	15.5	17.6	16.6	14.7	5.4	17.1
SC 8mg	Mean	2.0	0.971	13.8	15.4	16.8	6.95	8.31	19.0
	SD	1.5-2.0[c]	0.125	0.66	1.26	1.54	0.600	0.535	1.38
	CV%	10.6	12.9	4.8	8.2	9.1	8.6	6.4	7.3
IV 2.5mg	Mean	2.0	0.414	14.2	5.11	6.53[b]	5.65[b]	7.22[b]	19.8[b]
	SD	2.0-2.0[c]	0.048	2.98	1.13	0.861	0.711	0.788	3.52
	CV%	0.0	11.7	21.0	22.2	13.2	12.6	10.9	17.8

CV%: coefficient of variation

NC: Not calculated (%AUC extrapolated >30%)

SD: Standard deviation

[a]Median

[b]N=5

[c]Range

Urine

Urine PK parameters for **FX** (N=6)

Route Dose		**Ae[a] (mg)**	**fe[a] (%)**	**CL_r (mL/min)**
SC 0.75mg	Mean	0.498	76.1	4.59
	SD	0.090	13.8	1.53
	CV%	18.2	18.2	33.3
SC 2.5mg	Mean	1.76	80.6	4.89
	SD	0.085	3.88	0.705
	CV%	4.8	4.8	14.4
SC 8mg	Mean	5.44	77.9	5.53
	SD	0.214	3.06	0.594
	CV%	3.9	3.9	10.8
IV 2.5mg	Mean	1.93	88.5	5.40
	SD	0.083	3.8	0.829
	CV%	4.3	4.3	15.4

CV%: coefficient of variation
SD: Standard deviation
[a]Ae and fe calculated to last quantifiable concentration in urine
fe (%) was calculated using the dose expressed as the acid form

	FX 2.5mg SC
Absolute bioavailability ratio estimate	1.01
(95% Confidence interval)	(0.92, 1.11)

Safety results:
An on-therapy AE was defined as an AE with onset from the time of administration of study medication until 120 hours after administration of study medication. An on-therapy serious adverse event (SAE) was defined as an SAE with onset from the time of administration of study medication until 120 hours after administration of study medication.

Adverse Events:	**FX 0.75mg**	**FX 2.5mg**		**FX 8mg**
	SC	**SC**	**IV**	**SC**
N	6	6	6	6
No. subjects with AEs n (%)	2 (33)	2 (33)	3 (50)	6 (100)
Most frequent AEs n (%)				
Coagulation disorder	2 (33)	3 (50)	3 (50)	4 (67)
Prothrombin decreased	0	0	0	5 (83)

Serious Adverse Events - On-Therapy
n (%) [n considered by the investigator to be related to study medication]

	FX 0.75mg	**FX 2.5mg**		**FX 8mg**
	SC	**SC**	**IV**	**SC**
	n (%) [related]	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**
Subjects with any SAE (fatal or non-fatal)	0	0	0	0

Publications:
No publication

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