SYNOPSIS

Title of the study: A multicenter, randomized, double blind, double dummy, parallel group, dose ranging study of subcutaneous SR123781A with an enoxaparin calibrator arm in the prevention of venous thromboembolism in patients undergoing elective total hip replacement surgery (DRIVE; DRI5664)

Coordinating Investigator: [redacted]

Study centers: Patients were randomized and treated at 63 study centers in 14 countries.

Publications (reference): Not disclosed

Study period:

Date first patient enrolled: 01-Jun-2006

Date last patient completed: 06-Jun-2007

Phase of development: Dose-ranging

Objectives:

Primary objective

To demonstrate the efficacy of SR123781A (hexadecasaccharide [HDS]) in the prevention of venous thromboembolism (VTE: deep vein thrombosis [DVT] and/or pulmonary embolism [PE]) via demonstration of a dose-response in patients undergoing total hip replacement (THR) surgery

Secondary objectives

- To evaluate the safety (incidence of major bleeding) of HDS in the prevention of VTE after elective THR surgery
- To assess the HDS pharmacokinetic (PK) profile in patients undergoing elective THR surgery

Methodology: Multicenter, randomized, double blind, double dummy, parallel group, dose-ranging study testing once daily subcutaneous postoperative regimens of HDS with once daily subcutaneous injections of 40 mg enoxaparin, used as calibrator, for up to 10 days

Number of patients: Planned: 1020 (170 patients per treatment arm) Randomized: 1023

Summary of analysis population

Population	HDS					Enoxaparin	Total
	0.25 mg (N=172)	0.5 mg (N=164)	1 mg (N=172)	2 mg (N=170)	4 mg (N=176)	40 mg (N=169)	All (N=1023)
Safety (All randomized and treated)	171 (99.4)	163 (99.4)	170 (98.8)	168 (98.8)	171 (97.2)	166 (98.2)	1009 (98.6)
Primary efficacy	118 (68.6)	124 (75.6)	126 (73.3)	128 (75.3)	114 (64.8)	126 (74.6)	736 (71.9)
PP	113 (65.7)	115 (70.1)	114 (66.3)	118 (69.4)	103 (58.5)	117 (69.2)	680 (66.5)
PK [a]	171 (99.4)	163 (99.4)	170 (98.8)	168 (98.8)	171 (97.2)	-	-

[a]: Summary statistics of plasma HDS concentrations were prepared; no further PK analyses were performed.
PP=per protocol population (i.e. primary efficacy population, excluding patients presenting with at least one major protocol deviation)

Diagnosis and criteria for inclusion: Men and women aged ≥18 years undergoing elective THR surgery or a revision of at least one component of a THR performed ≥6 months prior to study entry

Investigational product:	SR123781A (HDS)
Dose:	0.25, 0.5, 1, 2, or 4 mg once daily starting 8 ± 1 hours postoperatively (ie, on Day 1)
Administration:	subcutaneous, once daily
Batch numbers:	[redacted]
Duration of treatment:	From 5 to 10 days for HDS and for enoxaparin

The recommended duration was from Day 1 (or Day 2 according to time of surgery) up to Day 10 for HDS and from Day -1 (or Day 1, depending on anesthesia and local labeling requirements) up to Day 10 for enoxaparin.

Duration of observation: 30 days

Follow-up period up to 30 days from randomization with a final follow-up visit at Day 30 ± 3 days.

Reference therapy:	enoxaparin
Dose:	40 mg starting 12 ± 1 hours preoperatively (ie, typically on Day -1) or in case of loco-regional anesthesia, postoperatively as per local labeling, according to Investigator's judgment
Administration:	subcutaneous, once daily
Batch numbers:	[redacted]

Reference therapy:	placebo
Dose:	placebo matching HDS once daily starting 8 ± 1 hours postoperatively (ie, on Day 1) placebo matching enoxaparin starting 12 ± 1 hours preoperatively (ie, typically on Day -1) or in case of loco-regional anesthesia, postoperatively as per local labeling, according to Investigator's judgment
Administration:	subcutaneous, once daily
Batch numbers:	[redacted]

Criteria for evaluation:

Efficacy: All efficacy endpoints were adjudicated by a blinded Clinical Events Adjudication Committee (CEAC).
The primary analysis was the incidence of the primary efficacy endpoint, which was a composite of the following VTE outcome events:

- Any DVT identified on mandatory venography of the lower limbs performed between Day 5 and Day 11
- Confirmed DVT and/or non-fatal PE in case of symptoms earlier than the date of the mandatory venography
- VTE related deaths (fatal PE and unexplained death) before the mandatory examination

Secondary endpoints: Incidence of the following outcome events up to the mandatory venography or a positive examination performed before the mandatory examination: any DVT; proximal DVT (globally and per side); isolated distal DVT; PE (either fatal or non-fatal); any confirmed symptomatic VTE (PE and/or DVT); initiation of curative treatment by the Investigator after local VTE assessment.

Safety:

The main safety endpoint was the incidence of major bleeding (surgical site bleeding leading to re-intervention, non-surgical site bleeding, fatal bleeding [major contributory factor of death]) between first study drug administration and 3 calendar days after last study drug injection.
Further safety parameters: minor bleedings, transfusion requirements, all deaths, serious adverse events (SAEs), adverse events (AEs), withdrawals due to AEs and changes in laboratory parameters.

Pharmacokinetics: Plasma concentrations of HDS on Days 1, 3, and 5 and the last treatment day; population PK analysis

Pharmacokinetic sampling times and bioanalytical methods:

Blood samples for PK analysis were collected on Day 1 (3 to 5 hours after the first drug administration), Day 3 (just before the daily administration), Day 5 (just before and 6 - 12 hours after the daily administration), and on Day 10 or last treatment day (3 to 5 hours after the daily administration).
The bioassay for HDS in plasma (expressed in mg/L) was based on the inhibition of a specified quantity of factor Xa by the antithrombin III (AT III)-HDS complex (with AT III added in excess). The lower limit of quantification was 0.030 mg/L.

Statistical methods:

Analysis populations: Four analysis populations were defined:

Primary efficacy population: all randomized patients who received at least one double-blind study drug injection (active or placebo), who underwent elective THR, and had an evaluation for the primary efficacy endpoint.
Per-protocol (PP) population: a subset of patients in the primary efficacy population, excluding patients presenting with at least one major protocol deviation.
Safety population (all randomized and treated): all randomized patients who were treated with at least one double-blind study drug injection (active or placebo), with patients assigned to treatment groups as treated rather than as randomized.
PK population: all patients with evaluable samples collected within the specified time windows.

Efficacy analysis: The incidence of the primary efficacy endpoint was analyzed across HDS treatments groups for the primary efficacy population using a two-sided Cochran-Armitage trend test using the values of the logarithm of the doses as score, and a logistic regression model including logarithmic dose levels as the only independent variable. Comparisons between HDS treatment groups were performed using a step-down approach. The 4 mg HDS dosage (the highest dosage) was compared with the 0.25 mg dosage (the lowest dosage) using the two-sided Fisher's exact test. If the p-value was ≤5%, sequential pair-wise comparisons were to be performed with the 2 mg, 1 mg, and 0.5 mg dosages at the same significance level until a comparison was not significant, at which point the procedure stopped. For each comparison, point estimates and 95% confidence intervals (CIs) on the absolute difference and the relative risk were computed. There was no statistical comparison of HDS with enoxaparin. As a supportive analysis, the primary analysis of efficacy was also performed with the PP population. Incidence of the most important secondary endpoints (ie, any DVT on either side, any proximal DVT on either side, and any symptomatic VTE) were analyzed across HDS treatment groups using a 2-sided Cochran-Armitage trend test. Sequential pair wise comparisons were performed as described for the primary efficacy endpoint.

Safety analysis: The incidence of major bleeding events and any bleeding events was analyzed across treatments groups as described for the primary analysis of the primary efficacy variable. Other safety data were summarized using descriptive statistics.

Pharmacokinetic analysis: PK data were summarized using descriptive statistics. No further PK analyses, including planned PK population analyses, were performed due to the discontinuation of the development of HDS.

Summary:

Efficacy results:
Event rates for the primary endpoint decreased from 21.2% in the lowest dose group (0.25 mg HDS) to 17.7% for the 0.5 mg HDS dose, 13.5% for the 1 mg HDS dose, 7.0% for the 2 mg HDS dose, and finally to 4.4% (4 mg HDS dose). The calibrator arm with enoxaparin had an event rate of 8.7%. A statistically significant dose-response effect was seen for HDS across doses for the prophylaxis of VTE after elective THR (Cochran-Armitage trend test, $p<0.0001$). The 2 mg and 4 mg HDS doses were significantly superior to the 0.25 mg dose ($p=0.0015$ and 0.0001, respectively; two-sided Fisher's exact test; risk reduction: 67% and 79%, respectively). The comparison with the 1 mg dose of HDS was not significant ($p=0.13$; risk reduction: 36%). Risk reduction for the 0.5 mg HDS dose was 16%. The dose-dependent effect on VTE events was supported by the PP analysis and by a logistic regression analysis (logarithmic dose level as the only independent variable) ($p<0.0001$). There was no indication that treatment effects varied between treatment groups according to any subgroup or covariate evaluated.

Similar findings were reported for components of the primary endpoint, with HDS dose-dependent reductions reported for any DVT and for proximal DVT (Cochran-Armitage trend test, $p<0.0001$ for both endpoints). For the prevention of any DVT, the 2 mg and 4 mg HDS doses were significantly superior to the 0.25 mg dose ($p=0.0015$ and 0.0001, respectively; two-sided Fisher's exact test; risk reduction: 67% and 79%, respectively). For the prevention of proximal DVT, the 1 mg, 2 mg, and 4 mg doses were significantly superior to the 0.25 mg dose ($p=0.029$, 0.0077, and 0.0034, respectively; two-sided Fisher's exact test; risk reduction: 80%, 90% and 100%, respectively).

No patients had confirmed adjudicated symptomatic VTE up to Day 11 or the day of mandatory venography in any treatment group. For the HDS groups, the incidence of curative treatment up to Day 11 or the day of the mandatory venography and after the qualifying VTE assessment decreased with increased dose of HDS.

Safety results:

The mean duration of exposure ranged from 7.9 (standard deviation [SD] 2.2) days for the 4 mg HDS group to 8.5 (SD 1.7) days for the 0.5 mg HDS group (enoxaparin group: 8.5 [SD 1.7] days). More than 85% of patients in each group were treated for 5 to 10 days.

Bleeding events: The number (%) and 95% CI of patients with confirmed adjudicated bleedings during the on-treatment period was as follows:

	HDS					Enoxaparin
	0.25mg (N=171)	0.5mg (N=163)	1mg (N=170)	2mg (N=168)	4mg (N=171)	40mg (N=166)
Major bleeding	2 (1.2%)	1 (0.6%)	1 (0.6%)	1 (0.6%)	10 (5.8%)	1 (0.6%)
	(0.1 to 4.2)	(0.0 to 3.4)	(0.0 to 3.2)	(0.0 to 3.3)	(2.8 to 10.5)	(0.0 to 3.3)
Minor bleeding only	5 (2.9%)	8 (4.9%)	4 (2.4%)	10 (6.0%)	32 (18.7%)	5 (3.0%)
	(1.0 to 6.7)	(2.1 to 9.4)	(0.6 to 5.9)	(2.9 to 10.7)	(13.2 to 25.4)	(1.0 to 6.9)
Any Bleeding	7 (4.1%)	9 (5.5%)	5 (2.9%)	11 (6.5%)	42 (24.6%)	6 (3.6%)
	(1.7 to 8.3)	(2.6 to 10.2)	(1.0 to 6.7)	(3.3 to 11.4)	(18.3 to 31.7)	(1.3 to 7.7)

There was a statistically significant dose-dependent trend in the incidence of major bleeding events (Cochran-Armitage trend test, p=0.0037). The incidence of major bleeds was significantly higher for the 4 mg dose group compared with the 0.25 mg dose only (p=0.035; two-sided Fisher's exact test; risk increase: 5.0-fold). One patient (0.25 mg HDS group) suffered a fatal bleeding event (described below). All other major bleeding events were adjudicated as surgical site bleeds leading to intervention or non-surgical site bleeding events with a bleeding index ≥ 2. The incidence of any bleeding event followed the same pattern as for major bleeding events (dose-response effect: Cochran-Armitage trend test, p <0.0001) and was significantly higher for the 4 mg dose group compared with the 0.25 mg dose (p <0.0001; two-sided Fisher's exact test); risk increase: 6.0 fold). In subgroup analyses, the incidence of any bleeding event was higher for patients with a longer duration of surgery (>2 hours) in the 4 lower dose HDS groups and in the enoxaparin group (but not the 4 mg HDS group) than for those with surgery of ≤2 hours.

The distribution of patients requiring blood transfusions and decreases in hemoglobin levels were consistent with the distribution of bleeding events.

Deaths: There were 2 deaths during the study; 1 patient in the 0.25 mg HDS group died during the on-treatment period and 1 patient in the 4 mg HDS group died after the on-treatment period. One patient (0.25 mg HDS group) died about 12 hours after the end of surgery due to a major hemorrhage from the surgical wound/drainage site; the patient developed a myocardial infarction (MI) due to uncontrolled and insufficiently treated hemorrhage, which he could not compensate and consequently died; the main cause of death was adjudicated as the hemorrhage, which was possibly related to study medication. One patient (4 mg HDS group) suffered brain hypoxia on Day 7 of the study (more than 3 days after the last dose of study medication) and died 8 days later (unrelated to study medication). The patient, who was polytoximanic, showed signs of agitation in the post-operative phase and was consequently sedated with diazepam. It appears that the sedation led to depressed breathing, which led to brain hypoxia and death.

Treatment emergent AEs (TEAEs): Patients who received the 4 mg HDS dose had more TEAEs, with a higher intensity, filling more seriousness criteria and with more events related to the study drug. The higher rate of drug-related TEAEs for this group consisted predominantly of bleeding events. The overall incidence of any TEAE (number [%] of patients) according to treatment reflected the difference in incidence of bleeding events in each group, as follows:

	HDS					Enoxaparin
	0.25mg (N=171)	0.5mg (N=163)	1mg (N=170)	2mg (N=168)	4mg (N=171)	40mg (N=166)
Any TEAE	58 (33.9)	68 (41.7)	54 (31.8)	55 (32.7)	103 (60.2)	60 (36.1)
Any drug-related TEAE	13 (7.6)	12 (7.4)	9 (5.3)	17 (10.1)	51 (29.8)	7 (4.2)
Any TEAE of severe intensity	4 (2.3)	2 (1.2)	3 (1.8)	1 (0.6)	16 (9.4)	2 (1.2)
Any serious TEAE	4 (2.3)	3 (1.8)	5 (2.9)	1 (0.6)	20 (11.7)	3 (1.8)
Any TEAE leading to death	1 (0.6)	0	0	0	1 (0.6)	0
Any TEAE leading to permanent study drug discontinuation	2 (1.2)	0	2 (1.2)	1 (0.6)	12 (7.0)	3 (1.8)

Safety results (cont'd):

The most frequent TEAEs on HDS were injury, poisoning and procedural complications (reported by >10% of patients in all HDS groups) and gastrointestinal disorders (reported by >10% of patients in the 4 mg HDS group only). All other system organ class (SOC) categories of TEAEs were reported by <10% of patients in all HDS groups. The most frequent TEAEs on HDS were bleeding TEAEs: post-procedural hemorrhage reported by 18.1% of patients in the 4 mg HDS group compared with 6.5% to 7.6% of patients in the lower dose HDS groups; post-procedural hematoma reported by 8.2% of patients in the 4 mg HDS group compared with 0% to 1.8% of patients in the lower dose HDS groups. Frequent TEAEs not related to bleeding had a similar incidence across all HDS groups.

The most frequent serious TEAEs reported by ≥1% of patients were bleeding events and were mainly reported for the 4 mg HDS dose group: post-procedural hemorrhage (5.3%, 4 mg HDS group; 1.8%, 0.25 mg HDS group); post-procedural hematoma (1.2%, 4 mg HDS group); hemorrhage (1.2%, 4 mg HDS group). All other serious TEAEs were reported by at most 1 patient in each group.

The most frequent TEAEs leading to discontinuation of HDS were bleeding events: post-procedural hemorrhage (3.5%, 4 mg HDS group; 1.2%, 0.25 mg HDS group); post-procedural hematoma (1.2%, 4 mg HDS group). All other TEAEs leading to discontinuation of study medication were reported by at most 1 patient in each group.

Bleeding TEAEs:
Bleeding TEAEs were more frequent for patients in the 4 mg HDS group (32.2%) than for the lower dose HDS groups (8.8% to 13.5%) (enoxaparin event rate: 10.2%). The most frequent bleeding TEAEs were post-procedural hemorrhage (18.1% of patients in the 4 mg HDS group compared with 6.5% to 7.6% of patients in the lower dose HDS groups) and post-procedural hematoma (7.6% of patients in the 4 mg HDS group compared with 0% to 1.8% of patients in the lower dose HDS groups). Note: It should be noted that for one patient (No. 100003008), "post procedural hematoma" was coded as an AE instead of as a bleeding AE, therefore this event was not counted in the summary of bleeding TEAEs but was counted as a TEAE; consequently, the incidence of this event as a TEAE was slightly higher (8.2%; see above). Ecchymosis was reported by 4.1% of patients in the 4 mg HDS group compared with 0% to 1.2% of patients in the lower dose HDS groups. For all other bleeding TEAEs, there was no marked difference between the incidence in the 4 mg HDS group and the lower dose HDS groups. Other bleeding TEAEs included hematoma and subcutaneous hematoma, and hemorrhage (gastrointestinal, urinary tract, and location not specified).

Other safety:
There was no clinically significant difference between HDS dose groups in the percentages of patients with predefined clinically significant abnormal values for laboratory safety variables, excluding hemoglobin (mentioned above). There was no clinically meaningful change in vital signs between treatment groups.

Pharmacokinetic results: No PK analyses were performed due to the discontinuation of the development of HDS.

Conclusions: [redacted]

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