SYNOPSIS

Title of the study: International, multicenter, randomized, parallel group, double-blind study, in patients with acute symptomatic deep vein thrombosis of the lower limbs, demonstrating the bioequipotency at steady state of equimolar doses of SSR126517E (3.0 mg) once a week and SR34006 (2.5 mg) once a week, documenting the safety and efficacy of both compounds during a 6-month treatment, and demonstrating the neutralizing effect of SSR29261 on the SSR126517E-induced anti-Xa activity (EFC5945, EQUINOX)

Investigator(s): [redacted]

Study centers: Multinational, multicenter study, 109 active centers in 20 countries.

Publications (reference): None

Study period:

Date first patient enrolled: 19/Apr/2006

Date last patient completed: 31/Jan/2008

Phase of development: Efficacy and safety confirmatory phase 3 study

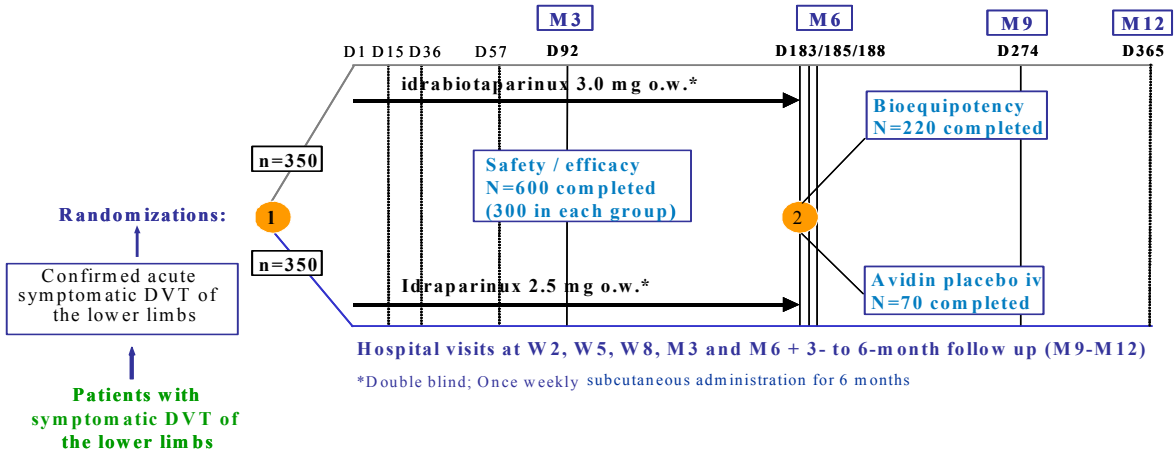
Objectives:

The primary objective of the bioequipotency assessment was to demonstrate the bioequipotency of idrabiotaparinux (SSR126517E) and idraparinux (SR34006) at Month 6 in patients with acute symptomatic deep vein thrombosis (DVT), as assessed by anti-Xa activity.

The primary objective of the avidin neutralizing effect assessment was to demonstrate the neutralizing effect of avidin (SSR29261) on the anti-Xa activity induced by idrabiotaparinux.

Secondary objectives were to describe the pharmacokinetic (PK) profile of idrabiotaparinux/idraparinux over time and for up to 6 months, and provide safety and efficacy data on idrabiotaparinux and idraparinux.

Methodology: This was an international, multicenter, double-blind, randomized, 3 treatments, 2 parallel groups phase 3 study in patients treated for acute symptomatic DVT of the lower limbs.



Patients with acute symptomatic DVT of the lower limbs, without confirmed symptomatic pulmonary embolism (PE) and without any other indication of fibrinolysis or anticoagulant treatment, were potentially eligible for this trial, if the diagnosis (including level of extension) was based on either 1 of the following:

- a non-compressible vein above the trifurcation of the calf veins on compression ultrasound (CUS),

- an intraluminal filling defect above the trifurcation of the calf veins on venography.

Patients were randomized centrally by an Interactive Voice Response System (IVRS) to either idrabiotaparinux or idraparinux (Day 1).

More than 36 hours pre-randomization treatment with therapeutic dosages of low molecular weight heparin, fondaparinux, or initiationof vitamin K antagonist treatment prior to randomization were not allowed. Based on a once weekly subcutaneous (SC) administration, treatment duration for all patients was 26 weeks (26 injections covering 6 months up to Day 182). A 27th injection was administered for the bioequipotency or for avidin-neutralizing effect assessments on Day 183. Patients with suspected efficacy or safety outcomes (recurrent DVT/PE or bleeding) underwent confirmatory testing (CUS or venography).

For patients completing the 6-month treatment period, this treatment period was followed by an observational period of 3 to 6 months, with a Month 9 visit (Day 274+7) and a phone/visit contact at Month 12 (Day 365+7).

At the end of the 6-month treatment period (26 injections), all patients who had completed the 6-month treatment period were to be re-randomized to either the idrabiotaparinux/idraparinux bioequipotency assessment or the avidin neutralizing effect assessment (the only exception was patients who in the Investigator's opinion might not interrupt their anticoagulant treatment at the end of the 6-month treatment period and therefore could not be re-randomized in the avidin sub-study).Two additional hospital/clinic visits (within 1 week: Day 185 and Day 188) were scheduled for patients allocated to avidin neutralizing effect assessment.

All symptomatic and confirmed recurrent DVT of the lower limbs/PE within 6 months after randomization, all bleedings reported by the Investigators and all deaths (cause of death) up to the end of the follow-up were adjudicated and confirmed by a Central Independent Adjudication Committee (CIAC).

In case of severe bleeding (as judged by the Investigator) or invasive procedure without the potential for controlling bleeding or overdose, during the treatment period and within the 13 weeks following permanent treatment interruption, whenever possible, after unblinding the treatment code, the patient could receive an intravenous (IV) infusion of avidin (just before the invasive procedure if it is the case), using an open-label kit.

Number of patients: Planned: 700 (350 in each group)

Outline of analysis populations

Population	Idrabiotaparinux	Idraparinux
All randomized	386	371
Randomized and treated	385	370
Bioequipotency sub-study:		
Allocated	130	131
Evaluable	114	114
Avidin sub-study:		
Allocated	33 active avidin 22 avidin placebo	26 avidin placebo
Evaluable	23 active avidin 18 avidin placebo	-[a]

[a]: not analyzed

Diagnosis and criteria for inclusion: Confirmed acute symptomatic DVT of the lower limbs above trifurcation, based on non-compressible vein above the trifurcation of the calf veins on CUS, or intraluminal filling defect above the trifurcation of the calf veins on venography.

Investigational products: Idrabiotaparinux: 0.5 mL pre-filled syringes for 3.0 mg	Idraparinux: 0.5 mL pre-filled syringes for 2.5 mg
Dose: 3.0 mg once-weekly	Dose: 2.5 mg once-weekly

Administration: subcutaneous (SC) injection. Self-injection was allowed.	Administration: SC injection. Self-injection was allowed.
Batch numbers: [redacted]	Batch numbers: [redacted]
Duration of treatment: 6 months **Duration of observation:** 9 to 12 months (3 to 6 months of post-treatment follow-up).	
Investigational product: Avidin Dose: - one 100 mg double-blind 30-minute infusion (2 vials of 55 mg to be reconstituted for a solution at 10 mg/mL) on Day 183, 4 hours after SC administration of idrabiotaparinux (avidin sub-study) - one 100 mg open-label infusion in case of severe bleeding or invasive procedure in the idrabiotaparinux group, whenever possible and appropriate (2 vials of 55 mg to be reconstituted for a solution at 10 mg/mL)	**Reference therapy:** Placebo avidin (on Day 183 in the avidin sub-study) Dose: NA
Administration: IV	Administration: IV
Batch numbers: double-blind: [redacted]; open-label: [redacted]	Batch number: [redacted]

Criteria for evaluation:

Bioequipotency assessment, avidin neutralizing effect assessment and time course to steady state

The pharmacodynamic (PD) variable was anti-Xa activity measured using a validated chromogenic method without excess antithrombin (AT) relative to the maximal effect in a pool of plasma from healthy volunteers. The PK variables consisted of the idrabiotaparinux and idraparinux concentrations, measured using a specific liquid chromatography tandem mass spectrometry (LC-MS/MS) method for idrabiotaparinux and an anti-Xa activity assay method with excess AT for idraparinux.

Safety assessment

The 2 main safety outcome events consisted of any clinically relevant bleeding (major and clinically relevant but not major), as confirmed by the CIAC, and death (cause of death validated by the CIAC).

Other safety outcomes were adverse events (AEs)/serious adverse events (SAEs), and changes in laboratory parameters.

Efficacy assessment

The main efficacy outcome was symptomatic recurrent DVT/PE (fatal or not), as validated by the CIAC.

Pharmacokinetics

Idraparinux and Idrabiotaparinux plasma concentrations were expressed in molar units (µM) to allow for a direct comparison.

Pharmacokinetic sampling times and bioanalytical methods:

Plasma idraparinux concentrations were measured by means of an anti-Xa activity validated chromogenic enzyme assay with addition of AT. Plasma concentrations of idrabiotaparinux and its debiotinylated metabolite (SSR115771) were measured using a specific validated physicochemical LC-MS/MS method.

For the bioequipotency assessment, 5 PK/PD samples per patient were drawn; for the avidin neutralizing effect assessment, 10 PK/PD samples per patient were drawn as described in the following table:

Sampling time for bioequipotency and avidin neutralization effect assessments

SUB-STUDY \ TIMES	T00H	T0H	T0.25H	T0.5H	T1H	T2H	T4H	T48	T120	T274
Bioequipotency		•[1]		•[2]			•[2]	•[2]	•[2]	
Avidin	✓[1]	✓[3]	✓[4]	✓[4]	✓[4]	✓[4]	✓[4]	✓[4]	✓[4]	✓[4]

1 just before the 27th SSR126517E/SR34006 administration (Day 183)
2 after the 27th SSR126517E/SR34006 administration (Day 183)
3 just before avidin administration, 3-4h after the 27th SSR126517E/SR34006 administration (Day 183)
4 after the start of the avidin infusion (Day 183)

PK/PD blood samples used to describe the PK/PD profile over the first 6 months, were drawn on Day 15±1, Day 36±1, Day 57±1, Day 92+7 just before the injection, on Day 183+7 and Day 274+7.

Statistical methods:

Analysis of pharmacokinetic and pharmacodynamic variables

- Idrabiotaparinux/idraparinux bioequipotency assessment at Month 6: A population PK/PD approach was used to derive the pharmacodynamic exposure parameters: maximal activity (A_{max}) and AUC of activity (AAUC) at Month 6. A standard bioequivalence methodology was used to assess bioequipotency. The individual exposure parameters were log-transformed and the 90%-confidence interval (CI) of the difference in mean log values between the treatment groups was estimated. The corresponding 90%-CI and point estimate of the ratio of the geometric means were obtained, applying the exponential function. Bioequipotency was claimed if the 90%-CI of the ratio was included in the [0.80;1.25] equivalence reference interval.

- Avidin neutralizing effect assessment on anti-Xa activity: The neutralizing effect of avidin on the anti-Xa activity induced by idrabiotaparinux was assessed by comparing between treatment groups the decrease between Log(observed anti-Xa activity) of idrabiotaparinux measured just before avidin or avidin-placebo infusion (T0h) and at the end of the infusion (T0.5h). Because of heterogeneous variances in the 2 groups (avidin-placebo and active avidin), a variance-weighted (Welch) analysis of variance (ANOVA) was used.

- Pharmacokinetic profile of idrabiotaparinux and idraparinux over time up to 6 months: the pharmacokinetic profile over time was described by means of the observed plasma concentrations at each timepoint (trough concentrations on Days 15, 36, 57, 92 and 183 after randomization), expressed as means, standard deviation (SD), geometric means and coefficient of variation (CV), by treatment group.

Safety analysis

Safety analyses were performed on the all treated population. The primary analysis concerned the 2 main safety outcome events occurring within 6 months (182 days, Day 182 was the day before the Month 6 visit, selected as the end of the analysis period in order to have an assessment period of fixed duration, and ending before the second randomization) of the first idrabiotaparinux/idraparinux injection. Rates and 95%-CI at 6 months were presented. The safety of idrabiotaparinux/idraparinux was also described as based on the number (%) of patients who reported treatment emergent (serious) adverse events [TE(S)AEs] from the first idrabiotaparinux/idraparinux injection to the end of the study (including the 3- to 6- months observational period). Other safety outcomes were summarized using descriptive statistics.

To document the safety of avidin in patients who received open-label avidin, and in patients of the idrabiotaparinux group who entered the avidin sub-study, TEAEs occurring from the start of the avidin infusion to the end of study were summarized by primary system organ classes and preferred terms.

Efficacy analysis

Primary analysis: The efficacy analysis was performed on the all randomized population. The primary analysis concerned the main efficacy outcome events occurring within 6 months (182 days) of randomization. Rates were calculated by dividing the number of patients with an outcome event by the number of randomized patients (crude rates). These crude rates were presented with their 95%-CI.

Summary:

Population characteristics: Demographic and baseline characteristics were similar in the 2 treatment groups. A total of 40 (10.4%) patients in the idrabiotaparinux group and 45 (12.1%) in the idraparinux group permanently discontinued study drug prematurely.

Pharmacokinetic/pharmacodynamic results:

Bioequipotency

The point estimate of the idrabiotaparinux/idraparinux ratio (geometric means) for A_{max} was 1.11 (idraparinux being the reference). The 90% CI of the ratio for A_{max} was [1.00 – 1.23].

The point estimate of the idrabiotaparinux/idraparinux ratio (geometric means) for AAUC was 1.06 (idraparinux being the reference). The 90% CI of the ratio for AAUC was [0.96 – 1.16].

Avidin neutralizing effect assessment on anti-Xa activity

In the active avidin group, the SC administration of idrabiotaparinux followed 4 hours later by the 30-minute avidin IV infusion resulted in a 77.8% mean decrease in anti-Xa activity, ranging between 67.0% and 96.7% (respective percentages in the avidin-placebo group corresponded to a mean of 2.4%, and a range of -26.2% to 64.4%). The decrease in anti-Xa activity between the start and end of the avidin infusion was significantly greater in the active avidin group ($p=3.45 \times 10^{-15}$).

PK profile up to Month 6

The steady state of idrabiotaparinux was rapidly reached (2 weeks) in the course of the study, but the concentrations of the metabolite (SSR115771) reached quantifiable concentrations only 2 weeks after the start of the treatment. These concentrations then slowly increased up to Month 6.

The PK profile of the sum of idrabiotaparinux and metabolite (SSR115771) concentrations (compounds with the same anti-Xa activity) and that of idraparinux were superimposed over the course of the study up to Month 6.

Safety results: The number (%) of patients with any bleeding and major bleeding from the first study drug administration up to Day 182, the number (%) of patients who experienced TEAEs or TESAEs or who permanently discontinued study drug up to Day 182, or who died up to Day 182 were lower in the idrabiotaparinux group than in the idraparinux group (see table below).

Outline of safety results (number of patients [n (%)]) from the first study drug administration up to Day 182

	Idrabiotaparinux N=385 n (%)	Idraparinux N=370 n (%)
Any adjudicated bleeding	20 (5.2%)	27 (7.3%)
Any major bleeding	3 (0.8%)	14 (3.8%)
Any TEAE	223 (57.9%)	227 (61.4%)
Any TESAE[a]	47 (12.2%)	61 (16.5%)
Any TEAE leading to permanent discontinuation	20 (5.2%)	27 (7.3%)
Total deaths	6 (1.6%)	12 (3.2%)

a: including SAEs leading to death

Safety laboratory tests did not show any difference between idrabiotaparinux and idraparinux.

In the avidin sub-study, 2 patients experienced TESAEs 5 weeks and 5 months after the active avidin infusion, and 2 patients experienced TESAEs 12 days, 38 days and 5 months after the open-label avidin infusion. None was related to avidin, or to idrabiotaparinux. No AEs of an allergic or immuno-allergic type were observed following the avidin infusion. One case of death was observed 5 months after the avidin infusion.

For the anti-avidin antibody evaluation in the avidin sub-study, changes from negative to positive results or titer increase were never related to clinical symptoms of any type of hypersensitivity.

Efficacy results:

The number of patients with confirmed recurrent symptomatic VTE up to Day 182 is presented in the table below:

Outline of efficacy results (number of patients [n (%)]) from the first study drug administration up to Day 182

	Idrabiotaparinux N=386		Idraparinux N=371	
	n (%)	95% CI	n (%)	95% CI
Any VTE confirmed[a]	9 (2.3%)	(1.1 to 4.4)	12 (3.2%)	(1.7 to 5.6)
DVT confirmed[a]	3/3 (100%)	-	6/6 (100%)	-
PE confirmed (fatal or not)[a]	6/6 (100%)	-	5/7 (71.4%)	-

[a]: % calculated using the number of patients with CIAC-confirmed event (n) over the number of patients with a local confirmation of event (N)

Conclusions: [redacted]

Date of report: 11-Jan-2010