SYNOPSIS

Title of the study:	An International, multicenter, randomized, double-blind, double-dummy, parallel group, study of 3-month or 6-month treatment with SSR126517E (3.0 mg s.c. once weekly) versus oral INR-adjusted warfarin in the treatment of patients with symptomatic pulmonary embolism with or without symptomatic deep venous thrombosis (EFC6034)
Investigator(s):	[redacted]
Study center(s):	Multinational, multicenter study, 290 active centers in 39 countries.
Publications (reference):	Idrabiotaparinux for Acute Symptomatic Pulmonary Embolism. A randomized double-blind noninferiority trial. (Lancet-in Press)
Study period:	
Date first patient enrolled:	03/Aug/2006
Date last patient completed:	21/Oct/2010
Phase of development:	Efficacy noninferiority Phase 3 study

Objectives:

Primary efficacy objective

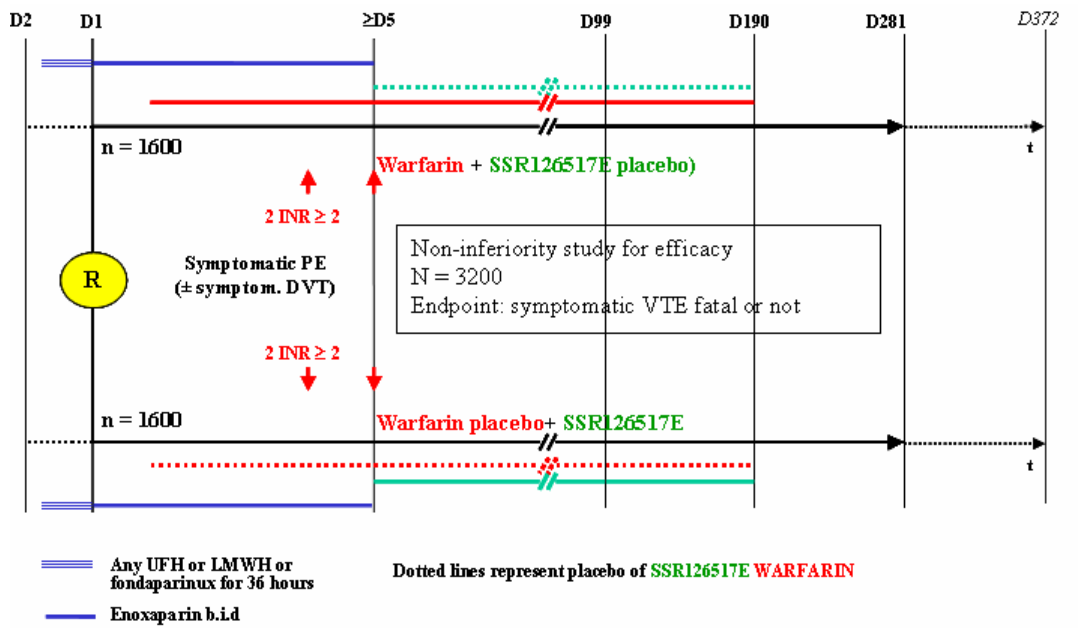
To evaluate whether a 3- or 6-month treatment with once-weekly idrabiotaparinux (SSR126517E) subcutaneous (SC) injections was at least as effective as a 3- or 6-month treatment with international normalized ratio (INR)-adjusted warfarin in the treatment and prevention of venous thromboembolic events (VTE) recurrence at 3 months in patients with symptomatic pulmonary embolism (PE) with or without symptomatic deep venous thrombosis (DVT).

Secondary efficacy objective

To evaluate whether a 6-month treatment with once-weekly idrabiotaparinux SC injections was at least as effective as a 6-month treatment with INR-adjusted warfarin in the treatment and prevention of VTE recurrence at 6 months in patients with symptomatic PE with or without symptomatic DVT.

Methodology: This was an international, multicenter, randomized in 2 parallel groups, double-blind, double-dummy, noninferiority study, in patients with symptomatic PE, with or without symptomatic DVT.

Flow-chart for the 3- and 6-month strata



Patients with confirmed symptomatic PE with or without acute symptomatic DVT were eligible for this study. Treatment with a therapeutic dose of any low molecular weight heparin (LMWH) or unfractioned heparin (UFH) or fondaparinux was allowed only within the 36 hours immediately preceding randomization. Randomization was performed as soon as the diagnosis of PE (and DVT if concomitant suspected symptomatic DVT) was confirmed.

Allocation to treatment was done centrally by Interactive Voice Response System (IVRS) and stratified by (1) center, (2) intended treatment duration, ie, 3 months or 6 months. At randomization, the planned duration of treatment (3 or 6 months) was prespecified by the Investigator and determined on the assessment of risk of VTE recurrence. Patients were randomized to either idrabiotaparinux + placebo of warfarin, or warfarin + placebo of idrabiotaparinux, with an initial treatment of at least 5 days with enoxaparin in both treatment groups. Measurements of INRs were centralized in order to provide Investigators with true (warfarin group) or mock (idrabiotaparinux group) INR values.

Whenever administered, the neutralizing effect of extractive avidin (SSR29261) on anticoagulation induced by idrabiotaparinux was documented.

A blinded central and independent adjudication committee (CIAC) assessed index PE (and DVT when applicable), all episodes of locally confirmed or doubtful PE /DVT recurrences, clinically relevant bleedings and deaths. Adjudication results were the basis for the final analyses. During the course of the study, an independent Data Monitoring Committee advised the Expert Executive Advisory Board on safety aspects of the study.

Patients in the 3-month stratum had an additional 13-week observational period after cessation of study treatment. Patients in the 6-month stratum had a 13-week up to 26-week observational period.

Number of patients: Planned: 3200 patients (1600 in each group)

Analysis populations

	Idrabiotaparinux	Warfarin	All
Randomized population	1599	1603	3202
3-month stratum	330 (20.6%)	336 (21.0%)	666 (20.8%)
6-month stratum	1269 (79.4%)	1267 (79.0%)	2536 (79.2%)
Per protocol population	1197 (74.9%)	711 (44.4%)	1908 (59.6%)
Randomized and treated population	1578	1595	3173
Avidin population	55 (3.5%)	0	55 (1.7%)

Note: For randomized population, patients are tabulated according to their randomized treatment (as randomized). For randomized and treated populations, patients are tabulated according to treatment actually received (as treated)

Diagnosis and criteria for inclusion: Confirmed acute symptomatic PE with or without symptomatic DVT of the lower limbs.

<table>
<tr><td>Investigational product: Idrabiotaparinux</td><td>Avidin (double blind/open label)</td></tr>
<tr><td>Dose: sterile, pyrogen-free, isotonic solution with sodium chloride and water for SC injection (6 mg/mL), prefilled syringes of:

- 0.5 mL of this solution for the 3.0 mg dosage for patients without severe renal insufficiency (SRI);

- 0.3 mL (1.8 mg) of this solution for patients with SRI.</td><td>Dose: sterile, pyrogen-free, lyophilized powder, supplied in stoppered, clear, glass vials, containing 55 mg of avidin, to be reconstituted prior to administration with 5.5 mL of water for injection or of physiologic saline, thus resulting in a solution for IV injection at 10 mg/mL.

- 10 mL to be diluted up to 110 mL, to enable IV infusion of 100 mg.</td></tr>
<tr><td>Administration: once-weekly SC injection</td><td>Administration: IV infusion</td></tr>
<tr><td>Batch numbers: [redacted]</td><td>Batch numbers: [redacted]</td></tr>
<tr><td colspan="2">Duration of treatment: 3 months or 6 months of idrabiotaparinux (or its placebo), or INR-adjusted warfarin (or its placebo) depending on baseline risk of DVT/PE recurrence, determined by the Investigator prior to randomization.
Duration of observation:
- Screening phase last a maximum of 2 days (48 hours) and treatment with any UFH or LMWH or fondaparinux not exceed 36 hours.
- Treatment phase and observational period:
- For patients completed or not their 3-month (3-month treatment stratum) or 6-month (6-month treatment stratum) treatment period:
• all patients (3-or 6-month stratum) with 3-month visit 99 days (+ 7 days allowed),
• all patients in the 6-month stratum with 6-month visit 190 days (+ 7 days allowed).
- For patients with a completed study treatment period:
• 27 weeks in the 3-month treatment stratum: treatment period: 14 weeks, observational period: 13 weeks.
• 40 to 53 weeks in the 6-month treatment stratum: treatment period: 27 weeks, observational period: 13 weeks to 26 weeks.</td></tr>
<tr><td>Reference therapy: Warfarin</td><td>Other therapy: enoxaparin</td></tr>
<tr><td>Dose: 5 mg (white) or 1 mg (orange) masked in capsules adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0-3.0). The INR was to be checked at least once every month.</td><td>Dose: Locally marketed, prefilled syringes as locally registered for BID(1.0 mg/kg every 12 hours)</td></tr>
<tr><td>Administration: oral</td><td>Administration: SC injection</td></tr>
<tr><td>Batch numbers: 1 mg: [redacted]

5 mg: [redacted]</td><td>Batch number(s): Not applicable</td></tr>
</table>

Reference therapy: idrabiotaparinux placebo	warfarin placebo	avidin placebo
Dose: sterile, pyrogen-free, isotonic solution with sodium chloride and water for SC injection. Prefilled syringes: • containing 0.5 mL of this solution for patients without SRI; • containing 0.3 mL of this solution for patients with SRI.	Dose: capsules in identical appearance for each strength.	Dose: supplied in stoppered, clear, glass vials, containing 55 mg of sterile, pyrogen-free, lyophilized excipient powder, with the same appearance as avidin powder, and to be reconstituted and administered the same way as described above for avidin.
Administration: SC injection	Administration: oral	Administration: 30-minutes IV infusion
Batch numbers: [redacted]	Batch numbers: 1 mg: [redacted] 5 mg: [redacted]	Batch numbers: [redacted]

Criteria for evaluation:

Efficacy assessment

The primary efficacy outcome was symptomatic recurrent PE/DVT (fatal or not), as validated by the CIAC, within 99 days for patients from both strata (3- and 6-month treatment).

A secondary efficacy outcome for patients in the 6-month stratum was symptomatic recurrent PE/DVT, as validated by the CIAC, within 190 days.

Additional efficacy outcomes:

- The time to first symptomatic recurrent PE/DVT (fatal or nonfatal) within the patient's treatment period, ie, a combined analysis of the 3-and 6-month strata patients.

- The separate components of the efficacy outcomes within 99 days (all patients) and within 190 days (6-month stratum patients only).

Safety assessment

The principal safety outcome was any clinically relevant bleeding as classified by the CIAC (ie, major bleeding and other clinically relevant non major bleeding).

Pharmacokinetics and pharmacodynamics

Pharmacokinetics, assessments of anti-Xa and other biomarkers of coagulation (thrombin generation time (TGT) or diluted prothrombin time (dPT) in selected centers) were assessed using plasma samples collected in selected centers at non specified time point as well as fixed time point.

Pharmacokinetic sampling times and bioanalytical methods:

The PK variables consisted of the idrabiotaparinux and of its debiotinylated metabolite concentrations, measured using a validated specific liquid chromatography tandem mass spectrometry method.

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. Other biomarkers of coagulation TGT or dPT were also evaluated.

- Plasma samples were collected at non specified points in time:
(1) in all patients, in case of a locally confirmed or doubtful recurrent PE or DVT, and of any bleeding event reported as (S)AE;
(2) in patients receiving emergency open-label extractive avidin; or double blind avidin or its placebo in case of planned invasive procedure;
(3) just before any invasive procedure.

- Plasma samples were collected at fixed specified points:

(1) in all non SRI, patients in the 6-month stratum who agree to participate in this PK, anti-Xa and other biomarkers of coagulation:

− patients who completed their study treatment: at baseline only for other biomarkers of coagulation, at 3-month (Day 99), 6-month (Day 190) and 9-month (Day 281) visits, and between 3 and 6 months, and between 6 and 9 months, a random sample, concomitant to an INR measurement whenever feasible;

− patients who prematurely interrupted their study treatment : before 3 months (blood sampling at 3 months – Day 99) and between 3 and 6 months (blood sampling at 3 months (Day 99) and 6 months (Day 190).

(2) in SRI patients, just after the first injection of idrabiotaparinux or its placebo, at D15, and then, in patients in the 6-month stratum at the same time points as those defined above in the non SRI patients. In patients in the 3-month stratum: whether they complete or not their study treatment: at 3-month (D99) and 6-month (D190) visits.

Statistical methods:

Efficacy analysis

The efficacy analysis was performed on the randomized population (all patients with signed inform consent and a treatment kit number allocated and recorded in the IVRS database, regardless of whether the treatment kit was used or not). If the upper limit of the 95% confidence interval for the idrabiotaparinux to warfarin odds ratio, stratified on intended treatment duration (Mantel-Haenszel chi-square analysis), for the primary efficacy outcome (VTE recurrence within 99 days) is less than 2.0, idrabiotaparinux treatment was considered at least as effective as warfarin.

The secondary efficacy outcome (VTE recurrence within 190 days) for patients in the 6-month stratum was analyzed using a Cox's proportional hazards model and applying the same noninferiority margin. Time to first symptomatic recurrent PE/DVT within the patient's study treatment period for all patients was analyzed using Cox's proportional hazards model.

A per-protocol analysis was performed on the per-protocol population, defined as a subset of the randomized population containing the patients without a major efficacy-related protocol deviation.

Safety Analysis

All safety analyses regarding bleedings were performed on the randomized population. The randomized and treated population [subset of the randomized population containing the patients who actually received at least one dose or partial dose of study drug (enoxaparin, idrabiotaparinux, or warfarin)] was used for analyses of adverse events. Rates of clinically relevant bleedings were calculated in each treatment group. Cumulative incidences of clinically relevant bleedings were described by treatment group using the Kaplan Meier method.

Analysis of pharmacokinetic and pharmacodynamic variables

Pharmacokinetics

Concentrations from plasma samples collected at specific time points and included in the predefined time windows: C_{trough} concentrations at Day 99 and Day 190, and concentrations during the washout period on Day 281 were considered for descriptive statistics. The following descriptive statistics for idrabiotaparinux and its debiotinylated metabolite (SSR115771) concentrations were calculated: number of observations, arithmetic mean, standard deviation (SD), coefficient of variation (CV), geometric mean, median, minimum, and maximum.

Based on the idrabiotaparinux levels in the collected plasma samples at specific time points included in the predefined time windows (Day 99, Day 190 and Day 281), the validity of dose adjustment for patients with severe renal impairment was evaluated.

In patients receiving emergency avidin infusion, descriptive documentation of anticoagulant activity was performed through preavidin and postavidin measurement of idrabiotaparinux and its debiotinylated metabolite concentrations.

In patients who underwent a procedure, descriptive documentation of anticoagulant activity was performed through measurement of idrabiotaparinux and its debiotinylated metabolite concentrations before the procedure (and when applicable just after avidin administration), according to the outcome of the procedure (bleeding or no bleeding).

Pharmacodynamics

Descriptive statistics for idrabiotaparinux anti-Xa activity (number of observations, arithmetic mean, SD, CV, geometric mean, median, minimum, and maximum) were calculated for PD anti-Xa samples collected at specific time points and included in the predefined time windows: A_{trough} activities on Day 99 and Day 190 and activities during the washout period on Day 281.

In patients receiving emergency avidin infusion, descriptive documentation of anticoagulant activity was performed through preavidin and postavidin measurement of idrabiotaparinux anti-Xa activity. The same description was done separately for patients who received avidin for a planned procedure and patients who received avidin following a bleeding.

In patients who underwent a procedure, descriptive documentation of anticoagulant activity was performed through measurement of idrabiotaparinux anti-Xa activity before the procedure (and when applicable just after avidin administration), according to the outcome of the procedure (bleeding or no bleeding).

Summary:

Efficacy results:

In this study idrabiotaparinux was demonstrated to be non inferior to warfarin for the prevention of recurrence in patients with PE with or without DVT, with a trend toward superiority.

Idrabiotaparinux was noninferior to warfarin on the primary efficacy endpoint (symptomatic recurrent PE/DVT, fatal or not) at 3 months with an odds ratio for idrabiotaparinux versus warfarin of 0.79 and p<0.0001 (95% CI 0.50-1.25). The prespecified non inferiority margin was 2.0. The incidence rate of symptomatic recurrent fatal or nonfatal PE at 3 months was similar between the 2 treatment groups while fewer patients experienced DVT in the idrabiotaparinux group (0.3%) versus in the warfarin group (1.1%).

The per-protocol analysis, performed on 1197 patients in the idrabiotaparinux group and 711 patients in the warfarin group, confirmed the non inferiority of idrabiotaparinux versus warfarin for incidence of VTE in patients with PE with or without DVT with an odds ratio for idrabiotaparinux versus warfarin of 0.55 and p<0.0001 (95 % CI 0.28 to 1.06) at 3 months. Time in therapeutic range was equal to 57%. Furthermore, protocol deviations were mainly related to TTR lower than 50% for patients in the warfarin group.

Idrabiotaparinux was non inferior to warfarin on the secondary efficacy endpoint (symptomatic recurrent PE/DVT, fatal or not) at 6 months with an odds ratio for idrabiotaparinux versus warfarin of 0.80 and p=0.0001 (95% CI 0.49 to 1.31). The incidence rate of symptomatic recurrent fatal or nonfatal PE at 6 months was similar between the 2 treatment groups, while fewer patients experienced DVT in the idrabiotaparinux group (0.6%) versus in the warfarin group (1.3%).

Combining the 3-month and 6-month periods and taking into account censored data using a time to event analysis, the cumulative incidence of symptomatic recurrent PE/DVT at 3 months was 2.2% in the idrabiotaparinux group and 2.7% in the warfarin group. At 6 months, these cumulative incidences were 2.6% and 3.4%, respectively. The incidence rate of fatal PE up to the end of the study was similar between the 2 treatment groups while fewer patients experienced nonfatal PE in the idrabiotaparinux group (1.0%) versus in the warfarin group (2.6%) or DVT in the idrabiotaparinux group (0.6%) versus in the warfarin group (1.9%).

Taking into account all events that occurred either during the treatment period or during the 3- to 6-month posttreatment follow-up period, the cumulative incidence rates of symptomatic recurrent PE/DVT at 12 months were 3.0% in the idrabiotaparinux group and 6.1% in the warfarin group.

Safety results:

In the 3-month stratum, idrabiotaparinux was better tolerated than warfarin, with an odds ratio for idrabiotaparinux versus warfarin of 0.67 and p=0.0098 (95% CI 0.49-0.91) on safety endpoint (any clinically relevant bleeding).

Within patients randomized in the 6-month stratum, there were fewer clinically relevant bleedings up to Day 190 in the idrabiotaparinux group (6.6%) compared to the warfarin group (8.1%), but this difference was not statistically significant.

Taking into account all bleeding events that occurred either during the treatment or during the 3- to 6-month posttreatment follow-up period, the cumulative indicence rates of clinically relevant bleeding at 12 months were 7.6% in the idrabiotaparinux group and 9.5% in the warfarin group.

The percentage of patients experiencing treatment emergent AEs (TEAEs) or TESAEs or TEAEs leading to treatment discontinuation was lower in the idrabiotaparinux group than in the warfarin group. These differences are mainly due to bleedings less frequently reported in the idrabiotaparinux group.

The percentage of patients with any TEAE leading to death was overall similar in the 2 treatment groups. However, the number of patients who experienced treatment-emergent bleeding leading to death was lower in the idrabiotaparinux group than in the warfarin group and the number of patients who experienced TEAE other than bleeding leading to death was higher in the idrabiotaparinux group than in the warfarin group. The most frequent TEAEs were reported in the “infections and infestations”, “gastrointestinal disorders”, “respiratory, thoracic and mediastinal disorders”, “general disorders and administrative site conditions”, “nervous system disorders” and “musculo-skeletal and connective tissue disorders” SOCs.

The 2 treatment groups showed similar percentages of patients with postbaseline PCSA criteria in hematology and chemistry parameters during the study.

Overall, 55 patients received the avidin treatment after idrabiotaparinux injection, 20 in double-blind administration and 35 in open-label administration. Four patients received avidin administration following a bleeding (among them, 3 bleedings were major) and 2 patients received avidin administration due to an overdose. Out of these 4 patients having received avidin administration following a bleeding, 2 patients had a decrease in bleeding according to a global effect on bleeding size, and 1 decrease in bleeding was confirmed by the visual evolution of bleeding or a blood collection, on a complementary examination (eg, CT scan). Considering the small number of patients, the diversity of procedures and the clinical situation of each individual patient, it was difficult to conclude on avidin effect on clinically relevant endpoint.

Seventeen patients in the avidin population had TEAEs the day of the avidin infusion and 32 within 30 days after the avidin infusion. Twelve patients in the avidin population had TESAEs the day of the avidin infusion and 18 within 30 days after the avidin infusion. One patient in the avidin population had a TEAE leading to death the day of the avidin infusion and 5 within 30 days after the avidin infusion.

There was a total of 8 reports of pregnancies:

- 6 in the idrabiotaparinux group (1 in the posttreatment period, not described):
  - 1 patient had abortion reported as SAE which led to treatment discontinuation,
  - 1 patient lost to follow-up had pregnancy reported as SAE,
  - 1 patient had pregnancy reported as SAE during the posttreatment period and resulting in healthy newborn without any structural defects or functional deficits,
  - 2 patients had pregnancy reported as TEAEs leading to treatment discontinuation, resulting in healthy newborns without any structural defects or functional deficits;
- 2 in the warfarin group had pregnancy reported as TEAEs and resulting in healthy newborns without any structural defects or functional deficits.

Pharmacokinetic results:

After repeated SC administration of idrabiotaparinux concentrations were similar between Day 99 and Day 190, while the concentrations of its debiotinylated metabolite increased. On Day 281, 3 months after the last administration, idrabiotaparinux concentrations were below the limit of quantification, but low quantifiable levels of its debiotinylated metabolite were observed.

Similar concentrations of idrabiotaparinux and its debiotinylated metabolite and similar PD anti-Xa activity were observed between SRI and non SRI patients, and values observed for SRI patients remained in the range of those observed for non SRI patients.

Patients who received active avidin, showed a rapid and marked decrease in idrabiotaparinux concentrations, while concentrations of the debiotinylated metabolite remained constant before and after the avidin administration. Consistent with PK data, a marked decrease in anti-Xa activity was observed just after avidin infusion.

Conclusions: [redacted]

Date of report: 06-Oct-2011