These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi	**Study Identifiers:** NCT00580216, EudraCT 2007-004817-33
Drug substance(s): idrabiotaparinux (SSR126517E)	**Study code:** EFC10295

Title of the study: A multicenter, randomized, double-blind, assessor-blind, non-inferiority study comparing the efficacy and safety of once-weekly subcutaneous idrabiotaparinux (SSR126517E) with oral adjusted-dose warfarin in the prevention of stroke and systemic thromboembolic events in patients with atrial fibrillation (BOREALIS-AF)

Study center(s): Multinational, multicenter study, 437 active centers in 46 countries

Study period:

Date first patient enrolled: 14/Dec/2007

Date last patient completed: 08/Oct/2010

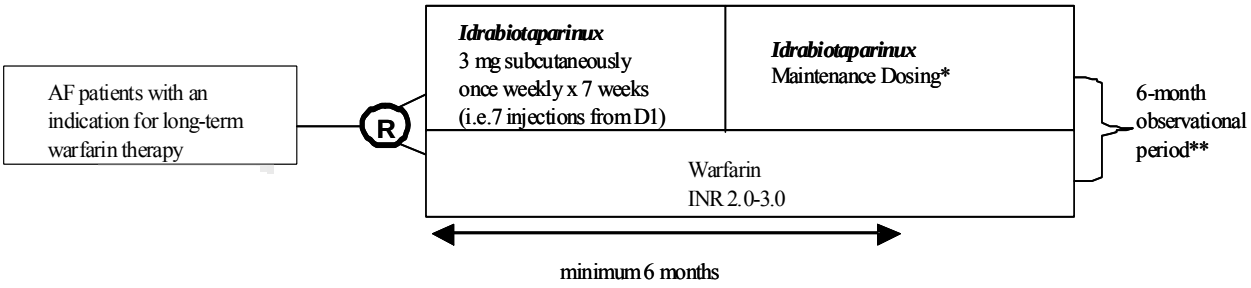
Phase of development: Efficacy and safety confirmatory Phase 3 study

Objectives:

The primary study objective was to evaluate whether once weekly subcutaneous (SC) injection of idrabiotaparinux was at least as effective as oral international normalized ratio (INR) adjusted-dose warfarin in the prevention of stroke or systemic embolic event in patients with atrial fibrillation (AF).

The main secondary study objective was to compare the incidence of the composite endpoint (stroke or, non-central nervous system systemic embolisms (CNS SE) or, myocardial infarction (MI) or, venous thrombo-embolic event (VTE) or, major bleeding or death) observed in the idrabiotaparinux group with the one observed in the warfarin group.

Methodology: This was a multinational, multicenter, randomized, double-blind, double-dummy, non-inferiority study with 2 parallel groups, idrabiotaparinux and warfarin.



*Maintenance Dosing: (1) For patients <75 years and baseline creatinine clearance ≥50 mL/ min, dosing was weekly injections of 2 mg. (2) For patients ≥75 years or baseline creatinine clearance [30-50 mL/min], dosing was weekly injections of 1.5 mg.

**Except patients randomized within the 3 months prior to the last patient randomized for whom the observational period ranged between 13 and 26 weeks up to the common study end date. However, due to the premature study discontinuation, all patients were to have 6-month observational period.

Methodology (continued):

Patients were randomized centrally by interactive voice response system (IVRS), to either idrabiotaparinux or warfarin for a period of at least 6 months, and were stratified by (1) center and (2) current use of vitamin-K antagonist (VKA). All patients received oral warfarin (or matching placebo) and weekly SC injections of idrabiotaparinux (or matching placebo). VKA treatment was stopped at randomization in patients receiving such pre-study treatment.

Warfarin dosing adjustments were made by actual or sham INR values. To preserve the double-blind design, INR measurements were made with an encrypted bedside, point-of-care device. Patients receiving idrabiotaparinux received sham INR values.

Avidin (SSR29261), a neutralizing agent for idrabiotaparinux-treated patients and administered by intravenous (IV) route, was used to reverse anticoagulation, in case of significant bleeding, emergency invasive procedure with a risk of uncontrollable bleeding or clinically significant overdosage, where rapidly reversing anticoagulation was clinically indicated. In such cases, study unblinding was required prior to administration of avidin. In case of planned invasive procedure with the potential of uncontrollable bleeding, one IV infusion of avidin or matching placebo was administered, without the need for breaking the blind, before the procedure, and after a 4-day interruption of study capsules. It could be repeated in the same circumstances if administration of idrabiotaparinux /idrabiotaparinux placebo was resumed after a previous double-blind administration of avidin or its placebo. Avidin (open label or double blind) could be administered during treatment with weekly injections and within 2 weeks following the last weekly injection.

A blinded central independent adjudication committee (CIAC) assessed all study outcomes deemed confirmed or uncertain by the site, all bleedings and all deaths. Cases of site-confirmed, uncertain stroke or systemic embolism were documented by appropriate imaging, eg, computed tomography (CT) scan or magnetic resonance imaging (MRI). Imaging reports and relevant clinical documentation were sent to the CIAC. CIAC adjudication was the basis for the study analyses.

During the course of the trial, an independent data monitoring committee (DMC) advised the executive committee on safety aspects of the trial. In parallel with safety, the DMC also reviewed efficacy data. Although there was no intention to terminate the study early for efficacy, monitoring boundaries were applied at these interim reviews.

All patients had an additional 6-month observational period after cessation of study treatment except last included patients who had at least a 3-month observational period.

Sanofi-aventis decided to discontinue the idrabiotaparinux development in the AF indication due to the perception that this compound did not appear to bring significant improvement in the care of these patients, in the context of recent therapeutic advances. As a consequence, the patient enrollment in the study was stopped on 21-Dec-2009 and all patients were to have a 6-month observational period.

Number of patients:	Planned: 9600	Randomized: 3773	Treated: 3760
	Efficacy: 3773	Safety: 3773	Pharmacokinetics: 809

Diagnosis and criteria for inclusion:

- Permanent, persistent or paroxysmal nonvalvular AF that was electrocardiogram-documented;

- With an indication for long-term VKA therapy based on the presence of previous ischemic stroke, TIA or systemic embolism and/or at least 2 of the following risk factors:

    a) hypertension requiring drug treatment,

    b) moderately or severely impaired left ventricular function and/or congestive heart failure,

    c) age ≥75 years,

    d) diabetes mellitus.

The risk of stroke in patients with nonrheumatic AF was assessed at baseline by the $CHADS_2$ score. The $CHADS_2$ score assigned a score from 0 to 6, based on the patient's age and other medical conditions (listed above).

Investigational medicinal product: Idrabiotaparinux	Avidin
Dose: pre-filled syringes for 6.0 mg/mL containing: • 0.5 mL of this solution for the 3.0 mg dosage, for all patients during 7 weeks (ie, 7 injections from Day 1); • 0.33 mL of this solution for the 2.0 mg dosage (actually 1.98 mg, rounded to 2.0 mg), for the injections from week 8 injection in patients with mild renal impairment (creatinine clearance ≥50 mL/min) and less than 75 years old; • 0.25 mL of this solution for the 1.5 mg dosage, for the injections from week 8 injection in patients with moderate renal impairment (creatinine clearance of 30-50 mL/min) or age ≥75 years.	Dose: 1 vial containing 105 mg of lyophilized powder to be diluted in 10 mL water or physiological saline for injection and 9.5 mL of this solution further diluted in approximately 100 mL of physiological saline.
Administration: SC injection; self injection was allowed.	Administration: 30-minute IV infusion

Duration of treatment: 6 months (26 weeks) before the common study end date for all patients randomized, except for the patients randomized within the 3 months prior to the last patient randomized who were all expected to be treated for 6 months;

Duration of observation: 9 months (39 weeks) after the date of randomization of the last patient, followed by an observation period [6 months (26 weeks) for all patients, except for patients randomized within the 3 months prior to the last patient randomized, for which the duration will range between 13 and 26 weeks, since limited by the common study date] up to the common study end date.

Due to the premature study discontinuation, the durations of treatment and observation were finally less than 6 months and 9 months, respectively, for the last patients randomized.

Reference therapy: Idrabiotaparinux placebo	warfarin placebo	Avidin placebo
Dose: pre-filled syringes containing 0.5 mL of this solution for all patients during 7 weeks; containing 0.33 mL of this solution for the injections from week 8 injection in patients with mild renal impairment (creatinine clearance ≥50 mL/min) and less than 75 years old; containing 0.25 mL of this solution for the injections from week 8 injection in patients with moderate renal impairment (creatinine clearance of 30-50 mL/min) or age ≥75 years	Dose: capsules in identical appearance for each strength	Dose: 1 vial containing 105 mg of sterile, pyrogen-free, lyophilized excipient powder, with the same appearance as avidin powder
Administration: SC injection; self-injection was allowed	Administration: oral	Administration: 30-minute IV infusion

Reference therapy: warfarin
Dose: 5 mg (white) or 1 mg (orange) capsules adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0-3.0). The INR should be checked at least once every month.
Administration: oral

Criteria for evaluation:

- **Efficacy assessment**

The primary efficacy variable was the composite of all CIAC-confirmed fatal or nonfatal strokes (ischemic, hemorrhagic and undefined) and non-CNS SE within the randomized treatment period.

Additional outcomes included cardiovascular death, VTE and MI.

- **Safety assessment**

The primary safety outcome was clinically relevant bleeding as adjudicated by the CIAC.

Other safety outcomes were all deaths, major bleeding and intracranial hemorrhage, then adverse events (AEs)/serious adverse events (SAEs) and changes in laboratory parameters.

- **Pharmacokinetics and pharmacokinetic/pharmacodynamic assessment**

A 12-month nested PK sub-study (and anti-Xa assessments) of idrabiotaparinux was performed in parallel of the main study. All patients who agreed to participate in the PK sub-study were enrolled to ensure the sample representativeness (country of origin). Blood for trough concentrations during the initial as well as the age- and renal-adjusted idrabiotaparinux regimens was sampled prior to dosing and after treatment interruption at specified intervals.

At any time during the study period, blood samples for PK and anti-Xa activity measurements were drawn as close as possible to the occurrence of any efficacy outcome event or any bleeding reported as AEs (whether or not open-label avidin was administered), and also just before any invasive procedure (whether or not double-blind avidin was administered).

Statistical methods:

- **Analysis population**

The primary efficacy analysis population was the all randomized population. Patients were analyzed in the treatment group assigned by the IVRS (treatment group "as randomized"). Safety analyses regarding bleedings were also performed on the randomized population in order to allow for a benefit/risk assessment. Other safety analyses were performed on the randomized and treated population.

The avidin population included all randomized and treated patients from the idrabiotaparinux group who received at least one dose or partial of a dose of avidin (double blind or open label avidin). This population was used to document avidin administration.

- **Analysis period**

The analysis period was defined following the "intention-to-treat" principle and took into account all events up to the end of the pre-defined period, irrespective of whether the patient received or complied with the treatment assigned by randomization.

All patients were followed and analyzed until the common end date of the study. Due to the premature discontinuation of the study, the cut-off date for defining the randomized treatment period was 21-Dec-2009. For patients still receiving study treatment after this date, the end of analysis period was defined as the date of end of study treatment.

Statistical methods (continued):

- **Efficacy analyses**

The number of patient-years at risk and the number of patients with strokes and/or non-CNS SE during the randomized treatment period was presented by treatment group on the all randomized population, together with the annual event rate (event rate per 100 patient-years).

The idrabiotaparinux to warfarin hazard ratio with its 95% confidence interval (CI) was estimated using Cox's proportional hazards model, stratified by pre-study administration of VKA, with treatment group as the only factor.

Since the study was prematurely stopped before reaching the required number of events to show non-inferiority of idrabiotaparinux to warfarin, non-inferiority of idrabiotaparinux with respect to warfarin was not formally tested. Only descriptive analyses, including estimation of the hazard ratio and its 95% CI were provided.

- **Safety analyses**

The number of patient-years at risk and the number of patients with CIAC-confirmed clinically relevant bleeding during the randomized treatment period was presented by treatment group on the all randomized population, together with the annual rate (event rate per 100 patient-years).

Treatment-emergent AEs (TEAEs) are AEs that developed or worsened or became serious from first study drug administration to last study drug administration + 92 days.

The idrabiotaparinux to warfarin hazard ratio with its 95% CI was estimated using Cox's proportional hazards model, stratified by pre-study administration of VKA, with treatment group as the only factor.

- **Analysis of PK and PD variables**

The principal pharmacokinetic (PK) variable was the plasma concentrations, which were used to derive the PK parameters of idrabiotaparinux in patients with AF using population pharmacokinetics. The principal pharmacodynamic (PD) variable was the anti-Xa activity, measured without excess of antithrombin, relative to the maximal effect in a pool of plasma from healthy volunteers. The PK and PD variables were assessed in the subset of patients to follow the PK and PD before and after the dose adaptation on week 7.

Summary:

- **Summary of populations**

Table 1 - Analysis populations

	Idrabiotaparinux	Warfarin	All
Randomized population	1886	1887	3773
Randomized and treated population	1884	1876	3760
Avidin population	89 (4.7%)	NA	89 (2.4%)

Note: One patient was included twice in the study with two different subject IDs. Data from the duplicate subject ID was excluded from all analyses.
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).

- **Patient disposition**

Due to the premature discontinuation of the study, none of patients completed the study treatment period and more than 77% of patients in both treatment groups prematurely discontinued the treatment due to sanofi-aventis' decision to stop the study on 21-Dec-2009. A total of 140 (7.4%) patients in the idrabiotaparinux group and 157 (8.3%) in the warfarin group permanently discontinued study drug due to AEs.

Table 2 - Patient disposition - Randomized population

	Idrabiotaparinux (N=1886)	Warfarin (N=1887)
Did not complete the study treatment period	1886 (100%)	1887 (100%)
Subject's request for treatment discontinuation	215 (11.4%)	230 (12.2%)
Reason for treatment discontinuation		
Adverse event	140 (7.4%)	157 (8.3%)
Lack of efficacy	3 (0.2%)	6 (0.3%)
Poor compliance to protocol	26 (1.4%)	19 (1.0%)
Lost to follow-up	1 (<0.1%)	3 (0.2%)
Other	1716 (91.0%)	1702 (90.2%)
sanofi-aventis' decision [a]	1455 (77.1%)	1492 (79.1%)
Status at end of study		
Alive	1799 (95.4%)	1786 (94.6%)
Dead	81 (4.3%)	91 (4.8%)
Lost to follow-up	6 (0.3%)	10 (0.5%)

Note: One patient was included twice in the study with two different subject IDs. Data from the duplicate subject ID was excluded from all analyses.
Percentages are calculated using the number of patients randomized as denominator.
[a] Patients who prematurely discontinued the treatment the 21-Dec-2009 or later.

- **Demographics and other baseline characteristics**

All demographic and baseline characteristics were similar in the 2 treatment groups for the randomized population.

Table 3 - Demographics and patient characteristics at baseline - Randomized population

	Idrabiotaparinux (N=1886)	Warfarin (N=1887)	All (N=3773)
Age (years)			
Number	1886	1887	3773
Mean (SD)	69.0 (9.6)	69.0 (9.8)	69.0 (9.7)
Median	69.8	70.2	70.0
Min : Max	28 : 96	29 : 95	28 : 96
Age group (years) [n (%)]			
Number	1886	1887	3773
<65	635 (33.7%)	607 (32.2%)	1242 (32.9%)
[65-75]	661 (35.0%)	711 (37.7%)	1372 (36.4%)
≥ 75	590 (31.3%)	569 (30.2%)	1159 (30.7%)
Sex [n (%)]			
Number	1886	1887	3773
Male	1165 (61.8%)	1144 (60.6%)	2309 (61.2%)
Female	721 (38.2%)	743 (39.4%)	1464 (38.8%)
Race [n (%)]			
Number	1886	1887	3773
Caucasian/White	1598 (84.7%)	1620 (85.9%)	3218 (85.3%)
Black	34 (1.8%)	20 (1.1%)	54 (1.4%)
Asian/Oriental	103 (5.5%)	102 (5.4%)	205 (5.4%)
Other	151 (8.0%)	145 (7.7%)	296 (7.8%)
Creatinine clearance (mL/min) [n (%)]			
Number	1863	1869	3732
<30	7 (0.4%)	3 (0.2%)	10 (0.3%)
[30-50]	298 (15.8%)	305 (16.2%)	603 (16.0%)
[50-80]	806 (42.7%)	756 (40.1%)	1562 (41.4%)
>80	752 (39.9%)	805 (42.7%)	1557 (41.3%)
Pre-study drug administration of VKA			
Number	1886	1887	3773
Yes	1061 (56.3%)	1055 (55.9%)	2116 (56.1%)
No	825 (43.7%)	832 (44.1%)	1657 (43.9%)

Risk factors for stroke/non-central nervous system systemic embolisms

The percentage of patients with risk factors for stroke or non-CNS SE at baseline was similar in the 2 treatment groups for the randomized population.

Overall, 99.9% of the patients had risk factors for stroke or non-CNS SE. The percentage of patients with previous ischemic stroke, TIA or non-CNS SE (high risk patients) was similar in the 2 treatment groups (31.1% in the idrabiotaparinux group and 29.6% in the warfarin group). The most frequent risk factor in both treatment groups was 'hypertension requiring drug treatment'.

Table 4 - Risk factors for stroke/non-CNS SE - Randomized population

	Idrabiotaparinux (N=1886)	Warfarin (N=1887)	All (N=3773)
Any risk factor of stroke/non-CNS SE	1883 (99.8%)	1886 (>99.9%)	3769 (99.9%)
Previous ischemic stroke, TIA or non-CNS SE	586 (31.1%)	558 (29.6%)	1144 (30.3%)
Hypertension requiring drug treatment	1760 (93.3%)	1773 (94.0%)	3533 (93.6%)
Moderately or severely impaired left ventricular function and/or congestive heart failure	1148 (60.9%)	1101 (58.3%)	2249 (59.6%)
Age ≥75 years	590 (31.3%)	569 (30.2%)	1159 (30.7%)
Diabetes Mellitus	622 (33.0%)	632 (33.5%)	1254 (33.2%)

Note: A patient can be counted in several categories.

$CHADS_2$ score

The percentage of patients in each class of risk according to the $CHADS_2$ score at baseline was similar in the 2 treatment groups for the randomized population: overall, 50.3% of patients were included with a moderate risk and 49.2% with a high risk of stroke.

Table 5 - $CHADS_2$ score at baseline - Randomized population

	Idrabiotaparinux (N=1886)	Warfarin (N=1887)	All (N=3773)
$CHADS_2$ score			
Number	1885	1887	3772
0	2 (0.1%)	1 (<0.1%)	3 (<0.1%)
1	8 (0.4%)	6 (0.3%)	14 (0.4%)
2	931 (49.4%)	968 (51.3%)	1899 (50.3%)
3	492 (26.1%)	516 (27.3%)	1008 (26.7%)
4	332 (17.6%)	289 (15.3%)	621 (16.5%)
5	102 (5.4%)	97 (5.1%)	199 (5.3%)
6	18 (1.0%)	10 (0.5%)	28 (0.7%)
$CHADS_2$ score by class of risk [a]			
Number	1885	1887	3772
Low risk	10 (0.5%)	7 (0.4%)	17 (0.5%)
Moderate risk	931 (49.4%)	968 (51.3%)	1899 (50.3%)
High risk	944 (50.1%)	912 (48.3%)	1856 (49.2%)

[a] Low risk means score ≤1, Moderate risk means score =2, High risk means score ≥3

Relevant and any prior medications

The percentage of patients with relevant and any prior medications taken before randomization was similar in the 2 treatment groups for the randomized population: before randomization, 35.4% of patients were treated with aspirin and 57.5% with VKA other than study drug. The percentage of patients with any relevant medications during the randomized treatment period was also similar in the 2 treatment groups for the randomized population (29.0% in the idrabiotaparinux group and 30.8% in the warfarin group).

- **Exposure**

Due to the premature discontinuation of the study, there was a high variability of the duration of exposure to study treatment, but overall exposure was similar in the 2 treatment groups for the randomized and treated population. The median duration was higher than 6 months in the 2 treatment groups (211 days in the idrabiotaparinux group and 209 days in the warfarin group) with a maximal duration of exposure above 25 months.

Table 6 - Exposure to study treatment - Randomized and treated population

	Idrabiotaparinux (N=1884)	**Warfarin (N=1876)**
Cumulative exposure to study treatment (patient years)	1238.4	1222.4
Duration of exposure to study treatment (days)		
Number	1884	1876
Mean (SD)	240.1 (174.4)	238.0 (175.1)
Median	211.0	209.0
Min : Max	1 : 757	1 : 768

Note: Patients are considered in the treatment group they actually received.

Duration of exposure is defined as date of last administration - date of first administration + 1 day, without any consideration of temporary discontinuation. In the warfarin group, open label VKA after permanent discontinuation of study drug is excluded.

In the warfarin group, the mean time in therapeutic range (TTR) was 57.7%

- **Efficacy results**

Stroke

The percentage of patients with CIAC-confirmed stroke or non-CNS SE was similar in the 2 treatment groups. The number of patients with CIAC-confirmed stroke or non-CNS SE within the randomization treatment period was lower than that assumed in the protocol (1.5% and 1.6% versus 2.9%).

Due to the premature discontinuation of the study, the number of patients with a primary outcome event needed for an 80% power was not reached (268 outcome events planned and 42 actually observed). The upper limit of the corresponding CI exceeded the defined non-inferiority margin of 1.38. However, a trend toward non-inferiority was observed.

Table 7 - CIAC-confirmed strokes or non-CNS SE within the randomized treatment period - Randomized population

	Idrabiotaparinux (N=1886)	**Warfarin (N=1887)**
Stroke or non-CNS SE within the randomized treatment period		
Number of patient-years at risk	1355	1355
Number of patients with event [n (% per year)]	20 (1.5%)	22 (1.6%)
95% CI	(0.9% to 2.3%)	(1.0% to 2.5%)
Idrabiotaparinux vs. Warfarin		
Hazard ratio	0.90	-
95% CI	(0.49 to 1.66)	-

Note: Hazard ratio and 95% CI determined using a Cox proportional hazards model, stratified on pre-study administration of VKA

- **Safety results**

Bleedings

The percentage of patients with any clinically relevant bleeding was lower in the idrabiotaparinux group (6.1% versus 10.0% in the warfarin group). The relative risk reduction of any clinically relevant bleeding within the treatment period in the idrabiotaparinux group versus the warfarin group was 39%.

Table 8 - CIAC-confirmed clinically relevant bleeding within the randomized treatment period - Randomized population

	Idrabiotaparinux (N=1886)	**Warfarin (N=1887)**
Any clinically relevant bleeding within the randomized treatment period		
Number of patient-years at risk	1324	1297
Number of patients with event [n (% per year)]	81 (6.1%)	130 (10.0%)
95% CI	(4.9% to 7.6%)	(8.4% to 11.9%)
Idrabiotaparinux vs. Warfarin		
Hazard ratio	0.61	-
95% CI	(0.46 to 0.81)	-

Note: Hazard ratio and 95% CI determined using a Cox proportional hazards model, stratified on pre-study administration of VKA

The percentage of patients with fatal bleeding was lower in the idrabiotaparinux group (0.4% versus 0.7% in the warfarin group). The percentage of patients with major bleeding was lower in the idrabiotaparinux group (1.7% versus 1.8% in the warfarin group). The same percentage of patients experiencing intracranial hemorrhage was observed in the 2 treatment groups (0.9%).

Table 9 - CIAC-confirmed major bleeding within the randomized treatment period - Randomized population

	Idrabiotaparinux (N=1886)	**Warfarin (N=1887)**	**Idrabiotaparinux to Warfarin hazard ratio (95% CI)**
Major bleeding			
Number of patient-years at risk	1355	1355	0.92 (0.52 to 1.62)
Number of patients with event [n (% per year)]	23 (1.7%)	25 (1.8%)	
95% CI	(1.1% to 2.5%)	(1.2% to 2.7%)	
Intracranial hemorrhage			
Number of patient-years at risk	1357	1359	1.00 (0.45 to 2.22)
Number of patients with event [n (% per year)]	12 (0.9%)	12 (0.9%)	
95% CI	(0.5% to 1.5%)	(0.5% to 1.5%)	
Fatal bleeding			
Number of patient-years at risk	1362	1361	0.55 (0.18 to 1.64)
Number of patients with event [n (% per year)]	5 (0.4%)	9 (0.7%)	
95% CI	(0.1% to 0.9%)	(0.3% to 1.3%)	

Note: Hazard ratio and 95% CI determined using a Cox proportional hazards model, stratified on pre-study administration of VKA

The percentage of patients with any clinical relevant bleeding up to the end of the study was lower in the idrabiotaparinux group (6.2% versus 8.6% in the warfarin group) and the percentages of patients with major bleeding up to the end of the study were 2.1% in the idrabiotaparinux group and 1.8% in the warfarin group.

Overview of adverse events

The number (%) of patients who experienced any TEAEs or who permanently discontinued study treatment was lower in the idrabiotaparinux group (57.4% versus 59.9% in the warfarin group and 7.5% versus 8.5%, respectively). The number (%) of patients who experienced serious TEAEs or who died due to treatment-emergent bleeding was similar in the 2 treatment groups.

Table 10 - Overview of adverse event profile: Treatment emergent adverse events - Randomized and treated population

n(%)	Idrabiotaparinux (N=1884)	Warfarin (N=1876)
Patients with any TEAE	1082 (57.4%)	1124 (59.9%)
- Patients with treatment-emergent bleeding	253 (13.4%)	324 (17.3%)
- Patients with TEAE other than bleeding	1042 (55.3%)	1055 (56.2%)
Patients with any serious TEAE	384 (20.4%)	389 (20.7%)
- Patients with serious treatment-emergent bleeding	60 (3.2%)	73 (3.9%)
- Patients with serious TEAE other than bleeding	354 (18.8%)	344 (18.3%)
Patients with any TEAE leading to death	69 (3.7%)	68 (3.6%)
- Patients with treatment-emergent bleeding leading to death	10 (0.5%)	11 (0.6%)
- Patients with TEAE other than bleeding leading to death	60 (3.2%)	58 (3.1%)
Patients with any TEAE leading to permanent treatment discontinuation	142 (7.5%)	160 (8.5%)
- Patients with treatment-emergent bleeding leading to permanent treatment discontinuation	35 (1.9%)	44 (2.3%)
- Patients with TEAE other than bleeding leading to permanent treatment discontinuation	112 (5.9%)	118 (6.3%)

TEAE: Treatment emergent adverse event
n (%) = number and percentage of patients with at least one TEAE

Summary of treatment–emergent adverse events

The primary system organ classes (SOC) in which TEAEs were reported with idrabiotaparinux (with a frequency ≥10%) were 'infections and infestations' (18.3% in the idrabiotaparinux group and 19.0% in the warfarin group), 'cardiac disorders' (14.3% and 13.8%, respectively), 'gastrointestinal disorders' (13.0% and 15.5%, respectively), 'injury, poisoning and procedural complications' (12.8% and 14.1%, respectively) and 'nervous system disorders' (10.6% and 10.2%, respectively). A lower percentage (with a difference ≥1%) was observed in the idrabiotaparinux group compared to the warfarin group for the following SOCs 'respiratory, thoracic, and mediastinal disorders' (9.7% and 11.4%, respectively), 'gastrointestinal disorders', and 'injury, poisoning, and procedural complications'.

The percentage of patients with treatment-emergent bleeding was lower in the idrabiotaparinux group (13.4% versus 17.3% in the warfarin group).

Summary of deaths

Table 11 - Number (%) of patients who died during the study by adjudication criterion - Randomized and treated population

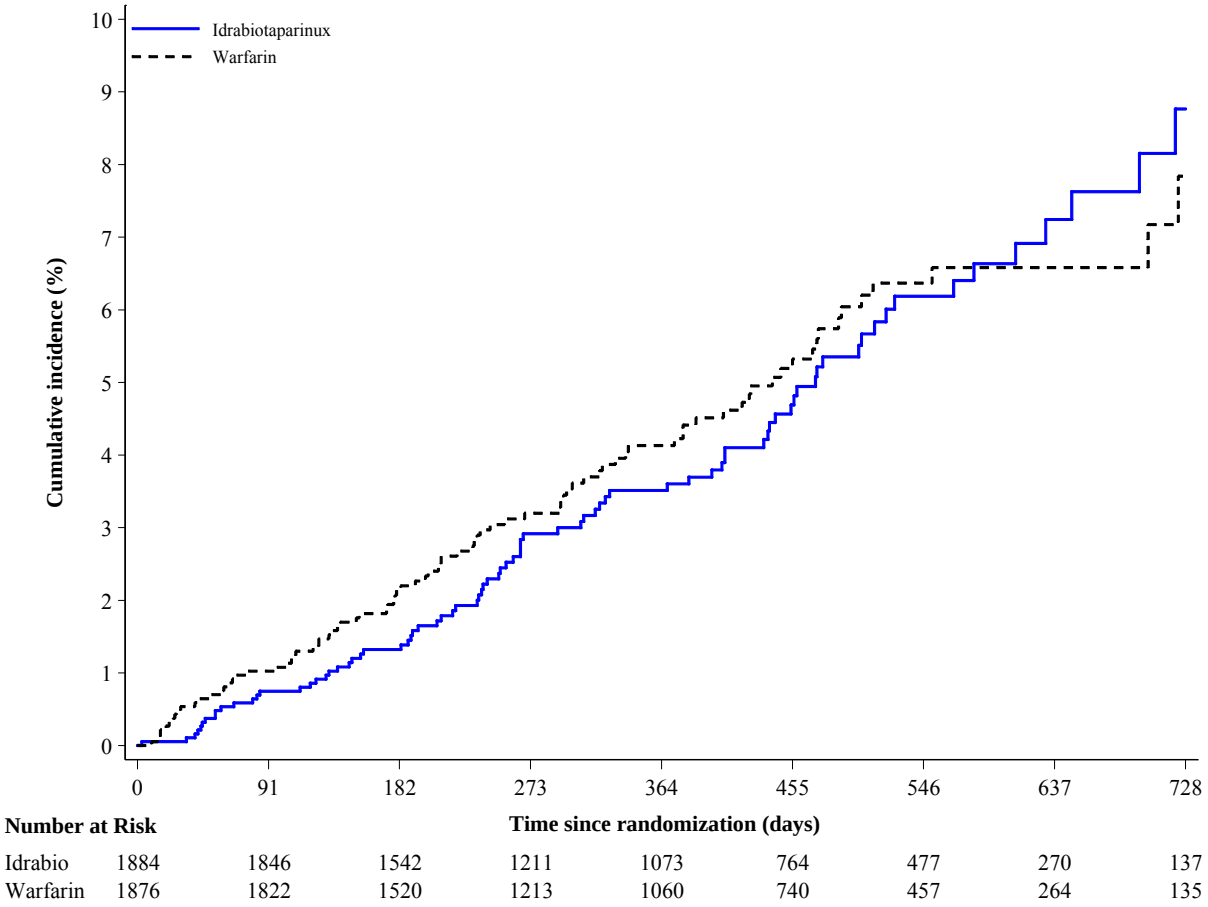
	Idrabiotaparinux (N=1884)	Warfarin (N=1876)
Death on-study[a]	81 (4.3%)	90 (4.8%)
Adjudication result		
Cardiovascular death	51 (2.7%)	56 (3.0%)
Stroke	2 (0.1%)	7 (0.4%)
Non-CNS SE	0	2 (0.1%)
MI	3 (0.2%)	2 (0.1%)
PE	0	1 (<0.1%)
Other cardiovascular death	46 (2.4%)	44 (2.3%)
Bleeding	10 (0.5%)	12 (0.6%)
Bleeding due to intracranial haemorrhage	6 (0.3%)	10 (0.5%)
Gastrointestinal bleeding	2 (0.1%)	2 (0.1%)
Other bleeding	2 (0.1%)	0
Other known cause	20 (1.1%)	22 (1.2%)
Not adjudicated	0	0

[a] Includes all deaths that occurred after the start of treatment up to end of study (defined as last protocol planned visit, or last contact date, or the resolution/stabilization of all treatment emergent SAE, whichever comes last)

The cumulative incidence of death during the study up to 455 days (15 months) was 4.7% in the idrabiotaparinux group compared to 5.3% in the warfarin group.

A Kaplan-Meier plot of cumulative incidence of death during the study is presented in Figure 1 below.

Figure 1 – Kaplan-Meier cumulative incidence of death during the study – Randomized and treated population



Number at Risk

Idrabio	1884	1846	1542	1211	1073	764	477	270	137
Warfarin	1876	1822	1520	1213	1060	740	457	264	135

The number (%) of patients with TEAEs leading to death was similar in the 2 treatment groups.

Summary of serious adverse events

Table 12 - Number (%) of patients with treatment emergent SAEs that occurred with a HLT percentage ≥1% in any treatment group by Primary SOC, HLGT, HLT and PT - Randomized and treated population

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	Idrabiotaparinux (N=1884)	Warfarin (N=1876)
Any class	384 (20.4%)	389 (20.7%)
INFECTIONS AND INFESTATIONS	57 (3.0%)	67 (3.6%)
HLGT: Infections - pathogen unspecified	46 (2.4%)	56 (3.0%)
HLT: Lower respiratory tract and lung infections	24 (1.3%)	35 (1.9%)
Pneumonia	18 (1.0%)	30 (1.6%)
CARDIAC DISORDERS	170 (9.0%)	140 (7.5%)
HLGT: Cardiac arrhythmias	70 (3.7%)	56 (3.0%)
HLT: Supraventricular arrhythmias	56 (3.0%)	44 (2.3%)
Atrial fibrillation	44 (2.3%)	36 (1.9%)
HLGT: Coronary artery disorders	48 (2.5%)	35 (1.9%)
HLT: Ischaemic coronary artery disorders	42 (2.2%)	32 (1.7%)
Angina unstable	28 (1.5%)	19 (1.0%)
HLGT: Heart failures	60 (3.2%)	59 (3.1%)
HLT: Heart failures nec	59 (3.1%)	57 (3.0%)
Cardiac failure	37 (2.0%)	36 (1.9%)

SAE: Serious adverse event, SOC: System organ class, HLGT: High level group term, HLT: High level term, PT: Preferred term
MedDRA 13.0
n (%) = number and percentage of patients with at least one treatment emergent SAE
Note: Table sorted by SOC internationally agreed order and HLGT, HLT, PT by alphabetic order
Only SOC with at least one HLT with a percentage ≥1% in at least one group are presented

Among the 384 (20.4%) patients with an SAE in the idrabiotaparinux group, 41 (2.2%) were related to idrabiotaparinux and among 389 (20.7%) with an SAE in the warfarin group, 50 (2.7%) were related to warfarin.

Summary of TEAEs leading to permanent treatment discontinuation

The number (%) of patients with TEAEs leading to permanent treatment discontinuation was 142 (7.5%) in the idrabiotaparinux group and 160 (8.5%) in the warfarin group. The most frequent TEAEs (>1%) leading to permanent treatment discontinuation were reported in 'general disorders and administration site conditions' (1.3% and 0.7%, respectively), 'nervous system disorders' (1.0% in the idrabiotaparinux group and 0.7% in the warfarin group), 'cardiac disorders' (1.0% and 1.3%, respectively) and 'gastrointestinal disorders' (0.8% and 1.7%, respectively).

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