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Study No.: AR3111436
Title: Clinical Evaluation of GSK576428 (Fondaparinux Sodium) in the Treatment of Acute Deep Vein Thrombosis (DVT)
Rationale: The primary objective of this study is to evaluate the efficacy (as measured by the rate of recurrent Venous Thromboembolism: VTE) and safety of Fondaparinux Sodium (FPX) as an alternative to unfractionated heparin (UFH), a standard treatment in Japan, in the initial treatment of acute DVT.
Phase: III
Study Period: 11 June 2008 -18 November 2009
Study Design: A multicenter, randomised, open-label study.
Centres: 24 Centres in Japan. Subjects were randomised in 18 centres.
Indication: Treatment of acute DVT.
<p>Treatment: Eligible subjects were randomised to receive either FPX or UFH for 5 to 10 days as initial treatment in a 3:1 ratio. Concomitant warfarin therapy was initiated as soon as possible following the start of initial treatment and continued after completion of initial treatment until Day 90±7. The expected total duration of a subject's participation in the study was up to 107 days, from screening after the informed consent to the end of follow-up period.</p> <p><Initial treatment period: 5 to 10 days (Day 1 to Day 5-10)> After enrollment (randomisation), FPX or UFH was initiated as soon as possible (within 6 hours of randomisation). The day of the start of initial treatment was defined as Day 1. In the FPX group, the dose of FPX was determined based on a subject's body weight (<50kg, 5mg; 50 to 100kg, 7.5mg; >100kg, 10mg) and administered once daily by SC injection. In the UFH group, the dose of UFH was adjusted to maintain activated partial thromboplastin time (APTT) at 1.5 to 2.5 times control.</p> <p>Concomitant warfarin therapy was initiated as soon as possible (no later than 72 hours following the first study drug administration). FPX or UFH was administered for at least 5 consecutive days (not less than 5 injections of FPX or not less than 108 hours of UFH treatment). The study drug was stopped when a prothrombin time international normalized ratio (PT-INR) was ≥1.5 on two consecutive days. The duration of study drug administration should be no longer than 10 days. In case PT-INR was below 1.5 on Day 10, the treatment with study drug could be continued at the discretion of the investigator or subinvestigator.</p> <p><Follow-up period: after the last dose of FPX or UFH, up to Day 90 (±7)> After the last dose of FPX or UFH, warfarin therapy was continued up to Day 90 (±7). The dose of warfarin was adjusted to maintain the PT-INR 1.53. 0 (target 2.0 to 2.5).</p>
<p>Objectives: To evaluate the efficacy as measured by the rate of recurrent symptomatic VTE (i.e., symptomatic Pulmonary Thromboembolism :PE or symptomatic DVT) and safety of FPX as the initial treatment in subjects with acute symptomatic DVT in an open-label design</p>
<p>Primary Outcome/Efficacy Variable: Rate of recurrent or new symptomatic VTE* recorded (by multi-detector (row) computed tomography [MDCT]) from Day 1 (the first day of the initial treatment period) up to Day 90 (±7) (the last day of the follow-up period)</p>
*: PE and DVT were adjudicated blindly by the Central Independent Adjudication Committee of

Efficacy (CIACE).

Secondary Outcome/Efficacy Variable(s):

Efficacy:

<Secondary endpoints>

1. Rate of the following recurrent or new VTE* events recorded (by MDCT) from Day 1 up to Day 90 (± 7):
 - non-fatal symptomatic PE, non-fatal symptomatic DVT only, fatal VTE, and total VTE (including asymptomatic DVT and asymptomatic PE).
2. Perfusion lung scan results at the end of the initial treatment period (Day 5-10 [± 1]).

*: PE and DVT were adjudicated blindly by CIACE.

Safety*:

<Primary endpoint>

Rate of major bleeding** during initial treatment period

<Secondary endpoints>

Bleeding events**, adverse events

*: The main period of interest for safety was the initial treatment period

** : Bleeding events (major bleeding, minor bleeding and no bleeding) were adjudicated blindly by the Central Independent Adjudication Committee of Safety (CIACS) according to the following criteria.

[Major bleeding]

- Fatal bleeding
- Clinical bleeding into a critical organ (retroperitoneal, intracranial, intraocular, adrenal gland, pericardium, spine, etc)
- Clinically overt bleeding associated with a fall in hemoglobin ≥ 2 g/dL (1.6 mmol/L) from the pre-bleeding value within 48 hours of the onset.
- Clinically overt bleeding which required a transfusion ≥ 2 units of packed red blood cell or whole blood.

[Minor bleeding]

All unusual clinically overt bleeding reported by investigator or subinvestigator as an AE and not adjudicated as a Major bleeding.

Pharmacokinetics:

Plasma concentrations of fondaparinux at two time points (pre-dose and 2 ± 1 hours post-dose) on any day between Day 5 and Day 7 (FPX group)

Statistical Methods:

<Justification for sample size>

Based on the incidence of recurrent symptomatic VTE in the FPX group of 3.9% reported in the overseas Study EFC2441 conducted in patients with symptomatic DVT, and assuming FPX has the same order of efficacy in the present Japanese study, the probability of detecting symptomatic VTE recurrence in at least one subject was estimated to be 65.8% with the sample size of 30 (27 efficacy evaluable subjects and 29 safety evaluable subjects). As for safety, the probability of detecting any bleeding in at least one subject was estimated to be 66.5% with the same sample size (the incidence of any bleeding in Study EFC2441 was 3.7%). The small-size UFH group was included in the study to exploratively evaluate the efficacy and safety of standard DVT treatment.

<Primary analysis populations>

- Full Analysis Set (FAS):

The FAS population consisted of all subjects enrolled excluding:

- 1) those who did not receive medication (FPX or UFH) at all ;
- 2) those with no valid efficacy data; and
- 3) those without a confirmed diagnosis of acute symptomatic DVT.

- Safety Population (SP):

The SP consisted of all subjects who received at least one dose of medication (FPX or UFH).

- Pharmacokinetic Population (PKP):

The PKP consisted of all subjects who received at least one dose of FPX and had plasma concentrations of fondaparinux.

<Efficacy analysis>

FAS was the primary population for the efficacy analysis. All randomised patients (ARP) and per protocol set (PPS) were also be analysed for the primary variable and the secondary variables of interest.

For the rate of recurrent or new symptomatic VTE recorded during the entire treatment period as the primary endpoint, point estimates and 95% confidence intervals were calculated by treatment group.

Similar analyses as for the primary efficacy variable were performed for the rates of recurrent or new various VTE events recorded during the entire treatment period as the secondary endpoints. Moreover, percentages of subjects with improvement in perfusion lung scan and descriptive statistics for the change from baseline in perfusion score were calculated.

<Safety analysis>

SP was the primary population for the safety analysis.

For the initial treatment period and for the entire treatment period, point estimates and 95% confidence intervals of the incidences of major bleeding and bleeding events were calculated by treatment group.

Adverse events (AEs) were summarized by system organ class (SOC)/preferred term (PT), severity and causal relationship, and the number and percentage of subjects with AEs were calculated.

<Pharmacokinetics analysis>

Pharmacokinetic analyses were performed on PKP.

Summary statistics (n, mean, SD, CV%, minimum, median, and maximum) of plasma concentrations of fondaparinux were calculated at each time point by dose level adjusted for body weight category. Moreover, scatter plots and box and whisker plots of plasma concentrations of fondaparinux at each time point were also prepared.

Study Population:

This study enrolled male or female patients aged ≥ 20 years with a confirmed diagnosis (by MDCT) of acute proximal DVT (the time from onset should be no longer than 10 days). The exclusion criteria included the followings: patients with symptomatic PE; patients for whom other therapies than anticoagulation (e.g., surgical thrombectomy, catheter intervention, thrombolytic therapy, and insertion of inferior vena cava filter) were indicated; therapeutic dosage of anticoagulants used for more than 24 hours prior to entry into the study; and active bleeding, bleeding tendency, concurrent thrombocytopenia, severe renal disorder, and other exclusion criteria to ensure the safety of subjects.

Number of Subjects:	FPX	UFH
Planned, N	30	10
Randomised, N	29	10
Completed, n(%)	22 (75.9)	8 (80.0)
Total Number Subjects Withdrawn, N(%)	7 (24.1)	2 (20.0)

Withdrawn due to Adverse Events n(%)	4 (13.8)	1 (10.0)
Withdrawn due to Lack of Efficacy n(%)	0	0
Withdrawn for other reasons n(%)	3 (10.3)	1 (10.0)
Demographics (FAS)	FPX (N=28)	UFH (N=9)
Females: Males	15:13	9:0
Mean Age, years (Standard Deviation(SD))	64.5 (19.7)	76.1 (12.2)
Asian-Japanese Heritage, n(%)	28 (100.0)	9 (100.0)
Body weight, n(%)	< 50 kg (Dose of FPX: 5 mg)	8 (28.6)
	50 – 100 kg (Dose of FPX: 7.5 mg)	20 (71.4)
	> 100 kg (Dose of FPX: 10 mg)	0
Primary Efficacy Results (FAS):		
Subjects with recurrent symptomatic VTE to Day 90(±7) (during all treatment period)	FPX (N=28)	UFH (N=9)
n(%) [95% Confidence Interval (CI)]	0 [0.0, 12.3]	0 [0.0, 33.6]
Secondary Outcome Variable(s) (FAS):		
Subjects with recurrent symptomatic/asymptomatic VTE (by type) to Day 90(±7) (during all treatment period)	FPX (N=28)	UFH (N=9)
Symptomatic VTE		
DVT only, n(%) [95% CI]	0 [0.0, 12.3]	0 [0.0, 33.6]
Non-fatal PE, n(%) [95% CI]	0 [0.0, 12.3]	0 [0.0, 33.6]
Fatal PE, n(%) [95% CI]	0 [0.0, 12.3]	0 [0.0, 33.6]
Asymptomatic VTE		
DVT only, n(%) [95% CI]	1 (3.6) [0.1, 18.3]	0 [0.0, 33.6]
PE, n(%) 95% CI]	0 [0.0, 12.3]	0 [0.0, 33.6]

Perfusion lung scan results (FAS):Day5-10 (± 1)			FPX (N=28)	UFH (N=9)
Entire group	n		27	9
	Improvement, n(%)		5 (18.5)	1 (11.1)
	No change, n(%)		22 (81.5)	8 (88.9)
	Worsening, n(%)		0	0
	Unassessable, n(%)		0	0
Subjects with asymptomatic PE	n		14	3
	Improvement, n(%)		4 (28.6)	1 (33.3)
	No change, n(%)		10 (71.4)	2 (66.7)
	Worsening, n(%)		0	0
	Unassessable, n(%)		0	0
Perfusion score (FAS)			FPX (N=28)	UFH (N=9)
Entire group	Baseline	n	27	9
		Mean(SD)	0.944 (0.087)	0.959 (0.048)
	Change from baseline, Day5-10 (± 1)	n	27	9
		Mean(SD)	0.015 (0.034)	0.004 (0.011)
Subjects with asymptomatic PE	Baseline	n	14	3
		Mean(SD)	0.914 (0.101)	0.918 (0.053)
	Change from baseline, Day5-10 (± 1)	n	14	3
		Mean(SD)	0.020 (0.038)	0.011 (0.019)
Safety Results:				
Subjects with Bleeding event during initial treatment period (SP)			FPX (N=29)	UFH (N=10)
Major bleeding, n(%) [95% CI]			1 (3.4) [0.1, 17.8]	0 [0.0, 30.8]
Minor bleeding, n(%) [95% CI]			1 (3.4) [0.1, 17.8]	0 [0.0, 30.8]
Any bleeding, n(%) [95% CI]			2 (6.9) [0.8, 22.8]	0 [0.0, 30.8]
All Adverse Events occurs during initial treatment period (SP)			FPX (N=29)	UFH (N=10)
Subjects with any AE(s), n (%)			19 (65.5)	7 (70.0)
Constipation			2 (6.9)	0
Haematochezia			2 (6.9)	0
Hepatic function abnormal			1 (3.4)	2 (20.0)
Diarrhoea			1 (3.4)	1 (10.0)
Nausea			1 (3.4)	1 (10.0)
Pyrexia			1 (3.4)	1 (10.0)
Delirium			1 (3.4)	1 (10.0)
Gastrointestinal haemorrhage			1 (3.4)	0
Blood alkaline phosphatase increased			1 (3.4)	0
Coagulation time prolonged			1 (3.4)	0
Oxygen saturation decreased			1 (3.4)	0
Injection site haemorrhage			1 (3.4)	0
Xerosis			1 (3.4)	0
Influenza			1 (3.4)	0
Nasopharyngitis			1 (3.4)	0
Pseudomembranous colitis			1 (3.4)	0
Upper respiratory tract infection			1 (3.4)	0
Haemorrhage subcutaneous			1 (3.4)	0
Pruritus			1 (3.4)	0
Skin haemorrhage			1 (3.4)	0

Back pain		1 (3.4)	0	
Periarthritis		1 (3.4)	0	
Insomnia		1 (3.4)	0	
Operative haemorrhage		1 (3.4)	0	
Epistaxis		1 (3.4)	0	
Arteriosclerosis		1 (3.4)	0	
Enteritis		0	1 (10.0)	
Vomiting		0	1 (10.0)	
Blood pressure decreased		0	1 (10.0)	
Blood urea increased		0	1 (10.0)	
White blood cell count decreased		0	1 (10.0)	
Heparin-induced thrombocytopenia		0	1 (10.0)	
Decreased appetite		0	1 (10.0)	
Serious Adverse Events occurs during initial treatment period (SP)		FPX (N=29)	UFH (N=10)	
Subjects with non-fatal SAEs, n (%) [related]		1 (3.4) [1]	1 (10.0) [0]	
Gastrointestinal haemorrhage		1 (3.4) [1]	0	
Delirium		0	1 (10.0) [0]	
Subjects with fatal SAEs, n (%)		0	0	
Pharmacokinetic results:				
Plasma concentrations of fondaparinux between Day 5 and Day 7 (PKP)		FPX 5 mg [body weight: <50kg] (N=8)	FPX 7.5 mg [body weight:50- 100kg] (N=20)	Total (N=28)
pre-dose	n	8	20	28
	Mean(SD), ng/mL	428.149 (137.894)	482.052 (162.097)	466.651 (155.032)
2±1 hours post-dose	N	8	20	28
	Mean(SD), ng/mL	1028.581 (257.532)	1242.570 (240.734)	1181.430 (260.130)

Conclusion:

- No recurrent symptomatic VTE (primary efficacy endpoint) was reported in the FPX and UFH groups.
- Recurrent asymptomatic VTE (secondary efficacy endpoint) was reported in only 1 subject in the FPX group.
- In the assessment of perfusion lung scan results and perfusion scores (secondary efficacy endpoint), improvement effects observed were similar between the FPX group and UFH group.
- Major bleeding was reported in only 1 subject in the FPX group in the initial treatment period.
- Adverse Events reported in at least 2 subjects in the initial treatment period include constipation and haematochezia reported in 2 subjects each in the FPX group and hepatic function abnormal reported in 2 subjects in the UFH group.
- Serious Adverse Events reported in the initial treatment period were gastrointestinal haemorrhage in 1 subject (3.4%) in the FPX group and delirium in 1 subject (10.0%) in the UFH group. No death was reported in this study.