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Study No.: AR3106335
Title: Clinical Evaluation of GSK576428 (Fondaparinux Sodium) in Prevention of Venous Thromboembolism after Hip Fracture Surgery
Rationale: Fondaparinux sodium (FPX) is a selective inhibitor of activated factor X (factor Xa) and approved for the prevention of venous thromboembolic events (VTEs) in patients undergoing major orthopedic surgery of the lower limb such as hip fracture surgery, knee replacement surgery and hip replacement surgery. This study was conducted to evaluate the efficacy and safety of FPX 2.5mg in patients undergoing hip fracture surgery (HFS).
Phase: III
Study Period: 16 February 2006–26 October 2006
Study Design: A multicenter, open-label study
Centers: Nine (9) centers in Japan. Subjects received at least one dose of study drug at seven (7) centers.
Indication: Prevention of venous thromboembolic events (VTE) in the patients who are undergoing hip fracture surgery
Treatment: Patients received FPX 2.5mg, administered by subcutaneous injection, once daily for 10± 4 days (between Day 2 and Day 11± 5), (Day 1 was the day of surgery). The first injection of the study drug was given 24±2 hours after surgical closure. From Day 3 onwards, the injection of the study drug was given at about the same time every day as far as possible (but more than 12 hours after the first dose on Day 2). Venogram had to be obtained not later than 2 calendar days after the last study drug administration (between Day 11 and 17).
Objectives: To evaluate the efficacy and safety of FPX 2.5mg, administered by subcutaneous injection, in the prevention of VTE after HFS.
Primary Outcome/Efficacy Variable: Rate of VTE (deep vein thrombosis [DVT] or pulmonary embolism [PE]) during main efficacy period, adjudicated by the Central Independent Adjudication Committee of Efficacy (CIACE).
Secondary Outcome/Efficacy Variable(s): <u>Secondary Efficacy Endpoints</u> Rate of PE, rate of DVT, rate of proximal DVT and rate of distal only DVT (main efficacy period and whole study period, respectively). These events were adjudicated by the CIACE.
<u>Primary Safety Endpoint</u> Rate of major bleeding during treatment period. Bleeding events (Major and Minor bleeding) were adjudicated by the Central Independent Adjudication Committee of Safety (CIACS) according to the following criteria.
[Major bleeding] Clinically unusual bleeding meeting any of the following criteria:
<ul style="list-style-type: none"> - Fatal bleeding - Bleeding including retroperitoneal and intracranial bleeding, or bleeding into a critical organ (eye, adrenal gland, pericardium, spine) - Reoperation due to bleeding/hematoma at the operative site - Bleeding leading to a hemoglobin (Hb) fall ≥ 2 g/dL (1.6 mmol/L) within 48 hour of the bleed - Bleeding that required a transfusion of red blood cell or whole blood derived from ≥ 900mL of whole blood within 48 hours of the bleed (excluding the autologous transfusion except for the treatment of bleeding adverse event (AE)) - Bleeding leading to the bleeding index (BI) ≥ 2
BI: calculated as "number of units* transfused" within 48 hours of the bleed + pre-bleed Hb

(g/dL) – post-bleed Hb within 48 hours of the bleed (g/dL).

*: 450 mL of whole blood or red blood cell derived from 450 mL of whole blood is considered as 1 unit.

Secondary Safety Endpoints

Following event (treatment period and whole study period, respectively)

- Minor bleeding, Any bleeding (major and/or minor bleeding)
- Adverse events
- Deaths
- Numbers of transfused patients and units transfused

[Minor bleeding]

Clinically overt bleeding not meeting the criteria for major bleeding and considered more than expected in the clinical context.

Statistical Methods:

The HFS study (EFC2698) demonstrated the VTE rate of 8.3% in patients receiving FPX 2.5mg. In this study, the sample size of 45 has been set to allow the 2.5mg dose to reduce the VTE risk to the targeted “no derate risk” level, i.e., the leg DVT rate of 10± 0%, according to the Japanese guideline for Prevention of Venous Thromboembolism. More specifically, the upper limit of the 95% confidence interval for the VTE rate should be no more than or slightly more than 20%. Assuming that 10% are not evaluable for the primary efficacy variable VTE, 50 subjects have been set as the target number of subjects.

Analysis Populations

Full Analysis Set (FAS): The FAS population consisted of all patients who were assigned to study drug with the exception of:

- 1) those who did not receive study drug at all; and
- 2) those with no valid efficacy data (e.g., no evaluable venogram).

Per Protocol Set (PPS): The PPS population consisted of all patients in the FAS population who had no major protocol violations.

Safety Population (SP): The safety population consisted of all patients who received at least one dose of study drug.

Efficacy Evaluable Patients (EEP): The efficacy evaluable patients consisted of a subpopulation of SP who were judged to be evaluable for all DVT and proximal DVT or distal only DVT by the site of occurrence (total / side of operation / opposite side of operation / both sides).

Statistical Methods

[Efficacy]

The following two periods were used in efficacy analyses: main efficacy period (from the first study drug injection up to Day 17 or to first venogram, whichever occurred first), and whole study period (from the first study drug injection up to the follow-up).

FAS was the primary population for the efficacy analysis. Point estimates and 95% confidence interval for the VTE rate were calculated. PPS was also analyzed for the primary endpoint and the secondary endpoints of interest. EEP was the analysis population for DVT by site. Point estimates and 95% confidence interval for DVT rate were calculated by the site of occurrence (total / side of operation / opposite side of operation / both sides).

[Safety]

The following two periods were used in safety analyses: treatment period (from the first study drug injection up to 2 days after the last study drug injection), and whole study period (from the first study drug injection up to the follow-up).

SP was the primary population for the safety analysis. Point estimates and 95% confidence interval only for major bleeding and minor bleeding only and any bleeding (major bleeding and/or

minor bleeding) were calculated.

All adverse events, whether or not related to the study drug, were coded by system organ class and preferred term using MedDRA Ver. 9.0

Study Population:

Major inclusion criteria: Patients undergoing HFS within 10 days following the time of fracture of the hip (proximal femur) (or following the time of fracture estimated from trauma); ≥20 years of age.

Major exclusion criteria: Patients were not eligible if any of the following criteria applied: Active, clinically significant bleeding (excluding drainage), documented congenital or acquired bleeding tendency/disorders (e.g., ulcer of the gastrointestinal tract, diverticulitis of the gastrointestinal tract, colitis, acute bacterial endocarditis, severe hypertension, severe diabetes, or history of hemorrhagic stroke); thrombocytopenia or previous history of thrombocytopenia (platelet count <10×10⁴μL); severe hepatic disorder; severe renal disorder (serum creatinine >2.0mg/dL [180μmol/L]; body weight <40kg; previous arterial or venous thromboembolism requiring treatment; multiple trauma affecting more than one organ system; planned bilateral replacement surgery or any other surgery of the lower limb during the study period; current malignant tumor; administration of any of the prohibited medications listed below within 1 week prior to the first study drug administration: heparin, low molecular weight heparin, heparinoids, anti-thrombin agents, oral anticoagulant, fibrinolytic agents, dextrans and anti-platelet agents.

Number of subjects:

	FPX 2.5mg
Planned, N	50
Assigned to study drug, N	48
SP, n (%)	48 (84.2)
FAS, n (%)	37 (64.9)
PPS, n (%)	36 (63.2)
Completed, n (%)	42 (87.5)
Total Number of Subjects Withdrawn, N (%)	6 (12.5)
Withdrawn due to Adverse Events, n (%)	3 (6.3)
Withdrawn due to Lack of Efficacy, n (%)	0
Withdrawn due to other reasons, n (%)	3 (6.3)
(%): Percentage of subjects relative to all subjects assigned to study drug	

Demographics (SP):

	FPX 2.5mg
	N=48
Males; Females	8:40
Mean Age, years (SD)	76.6 (14.4)
Race, n (%)	Not available

Primary Efficacy Results:

	FPX 2.5mg
Subjects with VTE during the main efficacy period (FAS)	N=37
n (%)	8 (21.6)
95% confidence interval (CI) (%)	9.8 38.2

Secondary Outcome Variable(s):

	FPX 2.5mg
Subjects with DVT by site during the main efficacy period (EEP)	
All DVT, n/N (%)	8/37 (21.6)
Proximal DVT, n/N (%)	1/38 (2.6)
Distal only DVT, n/N (%)	8/37 (21.6)
Subjects with symptomatic DVT during the main efficacy (SP) , n/N (%)	FPX 2.5mg

		0/48
Subjects with PE during the main efficacy (SP) , n/N (%)		FPX 2.5mg
		0/48
Safety Results:		
Subjects with bleeding events during treatment period (between Day 2 and 2 calendar days after the last injection) (SP)		FPX 2.5mg
		N=48
Major bleeding	n (%)	0
Minor bleeding	n (%)	0
Any bleeding (major and/or minor bleeding),	n (%)	0
Transfused patients and volume of transfusion during treatment period (between Day 2 and 2 calendar days after the last injection) (SP)		FPX 2.5mg
		N=48
Transfused patients	n (%)	1 (2.1)
Volume of transfusion	mL	280.0
Adverse events results: On-therapy AEs/SAEs were reported from first injection of study drug to up to 2 calendar days after last injection (Treatment period).		
Most Frequent Adverse Events - On-Therapy		FPX 2.5mg
		N=48
Subjects with any AE(s), n (%)		37 (77.1)
10 Most frequent AEs, n (%)		
Constipation		8 (16.7)
Insomnia		8 (16.7)
Oedema peripheral		4 (8.3)
Excoriation		4 (8.3)
Dermatitis contact		4 (8.3)
Restlessness		3 (6.3)
Pyrexia		3 (6.3)
Blood alkaline phosphatase increased		3 (6.3)
Abdominal pain upper		2 (4.2)
Diarrhea		2 (4.2)
C reactive protein increased		2 (4.2)
Platelet count increased		2 (4.2)
Arthralgia		2 (4.2)
Pain in extremity		2 (4.2)
Erythema		2 (4.2)
Nasopharyngitis		2 (4.2)
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]		
		FPX 2.5mg
Subjects with non-fatal SAEs		
		n (%) [related]
Ileus		1 (2.1) [0]
Femur fracture		1 (2.1) [0]
Subjects with fatal SAEs, n (%)		
		n (%) [related]
		0

Conclusion: See publication below

Publication: Fuji, T. and Fujita, S. Efficacy and safety of fondaparinux sodium for the prevention of venous thromboembolism after hip fracture surgery. The evaluation committee of efficacy and safety of fondaparinux sodium for the prevention of venous thromboembolism after hip-fracture surgery. *Kossetsu* 2008; 30(1): 206-209.