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<b>Study No.:</b> AR3106333
<b>Title:</b> Clinical Evaluation of GSK576428 (Fondaparinux Sodium) in Prevention of Venous Thromboembolism after Elective Total Hip Replacement Surgery
<b>Rationale:</b> 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 1.5mg and 2.5mg in patients undergoing elective total hip replacement (THR) surgery.
<b>Phase:</b> III
<b>Study Period:</b> 30 January 2006–18 July 2006
<b>Study Design:</b> A multicenter, randomized, double-blind, confirmatory study
<b>Centers:</b> Eight (8) centers in Japan. Subjects were randomized and received at least one dose of study drug at all centers.
<b>Indication:</b> Prevention of venous thromboembolic events (VTE) in the patients who are undergoing elective total hip replacement surgery.
<b>Treatment:</b> Patients received FPX 1.5mg or 2.5mg, administered by subcutaneous injection, once daily for 10–14 days (between Day 2 and Day 11–15), (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).
<b>Objectives:</b> To evaluate the efficacy and safety of FPX 1.5mg and 2.5mg, administered by subcutaneous injection, in the prevention of VTE after THR.
<b>Primary Outcome/Efficacy Variable:</b> 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)
<b>Secondary Outcome/Efficacy Variable(s):</b> <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"> <li>- Fatal bleeding</li> <li>- Bleeding including retroperitoneal and intracranial bleeding, or bleeding into a critical organ (eye, adrenal gland, pericardium, spine)</li> <li>- Reoperation due to bleeding/hematoma at the operative site</li> <li>- Bleeding leading to a hemoglobin (Hb) fall <math>\geq 2</math> g/dL (1.6 mmol/L) within 48 hour of the bleed</li> <li>- Bleeding that required a transfusion of red blood cells or whole blood derived from <math>\geq 900</math>mL of whole blood within 48 hours of the bleed (excluding the autologous transfusion except for the treatment of bleeding adverse event)</li> <li>- Bleeding leading to the bleeding index (BI) <math>\geq 2</math></li> </ul>

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 dose-response model on VTE rate, derived from the THR dose ranging study (DRI2643), predicted that FPX 1.5mg and 2.5mg should have a VTE rate of 6.5% and 4.0%, respectively. Therefore, the sample size of 45 per group in this study has been set to allow even the lower dose, 1.5mg, to reduce the VTE risk to the targeted "moderate risk" level, i.e., the leg DVT rate of 10± 0%, according to the Japanese guidelines for Prevention of Venous Thromboembolism. More specifically, the upper limit of the 95% confidence interval of the VTE rate should be no more than 20%. Assuming that 10% are not evaluable for the primary efficacy variable VTE, 100 subjects (50 per group) have been set as the target number of subjects.

### Analysis Populations

Full Analysis Set (FAS): The FAS population consisted of all patients who were randomized to either treatment with the exception of:

- 1) those who did not receive study drug at all; and
- 2) those with no valid post-randomization 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 randomized study drug.

Efficacy Evaluable Patients (EEP): The efficacy evaluable patients consisted of a subpopulation of randomized subjects 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 for each treatment group. 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 for each treatment group.

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 either an elective primary THR surgery or a revision of a THR; ≥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 <10×10<sup>4</sup>/μL); severe hepatic disorder; severe renal disorder (serum creatinine >2.0mg/dL [180μmol/L]); body weight <40kg; previous arterial or venous thromboembolism requiring treatment; 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 1.5mg	FPX 2.5mg
Planned, N	50	50
Randomized, N	59	56
SP, n (%)	58 (98.3)	56 (100)
FAS, n (%)	48 (81.4)	46 (82.1)
PPS, n (%)	47 (79.7)	46 (82.1)
Completed, n (%)	56 (94.9)	52 (92.9)
Total Number of Subjects Withdrawn, N (%)	2 (3.4)	4 (7.1)
Withdrawn due to Adverse Events, n (%)	1 (1.7)	4 (7.1)
Withdrawn due to Lack of Efficacy, n (%)	0	0
Withdrawn due to other reasons, n (%)	1 (1.7)	0
(%): Percentage of subjects relative to all randomized subjects		

**Demographics:**

	FPX 1.5mg	FPX 2.5mg
<b>N (SP)</b>	58	56
Males; Females	7:51	5:51
Mean Age, years (SD)	63.7 (10.3)	61.7 (10.9)
Race, n (%)	na	na

na: not available

**Primary Efficacy Results:**

	FPX 1.5mg	FPX 2.5mg
Subjects with VTE during the main efficacy period (FAS)	N=48	N=46
n (%)	4 (8.3)	1 (2.2)
95% confidence interval (CI) (%)	2.3-20.0	0.1-11.5

**Secondary Outcome Variable(s):**

	FPX 1.5mg	FPX 2.5mg
Subjects with DVT by site during the main efficacy period (EEP)		
All DVT, n/N (%)	4/48 (8.3)	1/46 (2.2)
Proximal DVT, n/N (%)	0/53	0/52
Distal only DVT, n/N (%)	4/48 (8.3)	1/46 (2.2)

Subjects with symptomatic DVT during the main efficacy period (SP), n/N (%)		<b>FPX 1.5mg</b>	<b>FPX 2.5mg</b>
		0/58	0/56
Subjects with PE during the main efficacy period (SP), n/N (%)		<b>FPX 1.5mg</b>	<b>FPX 2.5mg</b>
		0/58	0/56
<b>Safety Results:</b>			
Subjects with bleeding events during treatment period (between Day 2 and 2 calendar days after the last injection) (SP)		<b>FPX 1.5mg</b>	<b>FPX 2.5mg</b>
		N=58	N=56
Major bleeding	n (%)	0	0
	95% CI	0.0-6.2	0.0-6.4
Minor bleeding	n (%)	1 (1.7)	2 (3.6)
	95% CI	0.0-9.2	0.4-12.3
Any bleeding (major and/or minor bleeding)	n (%)	1 (1.7)	2 (3.6)
	95% CI	0.0-9.2	0.4-12.3
Transfused patients and volume of transfusion during treatment period (between Day 2 and 2 calendar days after the last injection) (SP)		<b>FPX 1.5mg</b>	<b>FPX 2.5mg</b>
		N=58	N=56
Transfused patients	n (%)	5 (8.6)	2 (3.6)
Volume of transfusion	mean, mL (SD)	400.0 (0.0)	600.0 (282.8)
<b>Adverse events results:</b> On-therapy AEs/SAEs were reported from first injection of study drug to up to 2 calendar days after last injection (Treatment period).			
<b>Most Frequent Adverse Events - On-Therapy</b>		<b>FPX 1.5mg</b>	<b>FPX 2.5mg</b>
		N=58	N=56
Subjects with any AE(s), n (%)		49 (84.5)	45 (80.4)
10 Most frequent AEs, n (%)			
Myalgia		12 (20.7)	14 (25.0)
Insomnia		9 (15.5)	13 (23.2)
Constipation		5 (8.6)	10 (17.9)
Pruritus		3 (5.2)	9 (16.1)
Platelet count increased		7 (12.1)	5 (8.9)
Pain in extremity		1 (1.7)	4 (7.1)
Gamma glutamyl transferase increased		1 (1.7)	3 (5.4)
Headache		5 (8.6)	2 (3.6)
Dizziness		3 (5.2)	2 (3.6)
Dermatitis contact		2 (3.4)	2 (3.6)
Erythema		2 (3.4)	2 (3.6)
Blood alkaline phosphatase increased		2 (3.4)	2 (3.6)
Hepatic function abnormal		2 (3.4)	2 (3.6)
Rash		1 (1.7)	2 (3.6)
Haemorrhoids		1 (1.7)	2 (3.6)
Urticaria		0	2 (3.6)
Abdominal pain upper		5 (8.6)	1 (1.8)
Back pain		6 (10.3)	0
Diarrhoea		3 (5.2)	0
Nausea		3 (5.2)	0
Pyrexia		3 (5.2)	0
<b>Serious Adverse Events - On-Therapy</b>			
<b>n (%) [n considered by the investigator to be related</b>			

to study medication]	FPX 1.5mg	FPX 2.5mg
Subjects with non-fatal SAEs	n (%) [related]	n (%) [related]
	0	0
Subjects with fatal SAEs	n (%) [related]	n (%) [related]
	0	0
<b>Conclusion:</b>		
<ul style="list-style-type: none"> <li>• Results of the primary efficacy endpoint, rate of VTE, were 8.3% (4 subjects) and 2.2% (1 subject) in the FPX 1.5mg and 2.5mg groups, respectively..</li> <li>• The upper limit of the 95% confidence interval did not exceed the pre-specified limit of 20%</li> <li>• All reported VTEs were asymptomatic DVTs. Neither symptomatic VTE nor PE was observed.</li> <li>• The primary safety endpoint, major bleeding, did not occur. Minor bleeding was reported in 1 (1.7%) and 2 (3.6%) subjects in the FPX 1.5mg and 2.5 mg groups, respectively.</li> <li>• The most frequently reported AE both at 1.5mg and 2.5mg was myalgia. No serious adverse events were reported</li> </ul>		
<b>Publication:</b> None		