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Study No.: AR3106116
Title: Clinical Evaluation of GSK576428 (Fondaparinux Sodium) in Prevention of Venous Thromboembolism (VTE) after Abdominal Surgery
Rationale: For the purpose of seeking approval of Fondaparinux Sodium (FPX) for the prevention of VTE in abdominal surgery patients in Japan, the present study was conducted to evaluate the efficacy and safety of FPX in abdominal surgery patients who are at "high risk" for VTE according to the Japanese Guideline for Prevention of Venous Thromboembolism. In Japan, no standardized VTE prophylaxis with anticoagulants has been established. To explore the incidence of VTE in the presence of general prophylaxis in the Japanese population, this study included a benchmark group of subjects receiving prophylaxis with intermittent pneumatic compression (IPC) alone.
Phase: III
Study Period: 22 May 2006 - 16 February 2007
Study Design: A multicenter, randomized, open-label study.
Centres: 22 centers in Japan. Subjects randomized at 20 centers.
Indication: Prevention of VTE in patients undergoing abdominal surgery who are at high risk for VTE
Treatment: FPX group: FPX 2.5mg was administered once daily by SC injection for 4–8 days. The first injection of the study drug was given 24±2 hours after surgical closure. The second and subsequent injections of the study drug were given at approximately the same time every day as far as possible (but more than 12 hours after the first dose). IPC was prohibited during the surgical and treatment periods. IPC group: IPC was initiated before or after surgery and continued until an appropriate timepoint. The procedures and methods usually employed at each individual study center were followed as a rule.
Objectives: <Primary> To evaluate the efficacy and safety of FPX 2.5mg/day, administered by SC injection, in the prevention of VTE (symptomatic PE and any DVT) after abdominal surgery in an open-label design. <Secondary> To exploratively evaluate the relative efficacy of FPX 2.5mg/day SC in the prevention of VTE (symptomatic PE and any DVT) after abdominal surgery by using the VTE (symptomatic PE and any DVT) rate in the IPC group as a benchmark.
Primary Outcome/Efficacy Variable: Rate of VTE (symptomatic PE and any DVT) during main efficacy period, adjudicated by Central Independent Adjudication Committee of Efficacy (CIACE)
Secondary Outcome/Efficacy Variable(s): Efficacy: <Secondary> Rate of the following events adjudicated by CIACE (main efficacy period and whole study period, respectively) Rate of symptomatic PE

Rate of any DVT
Rate of proximal DVT
Rate of distal only DVT
Rate of symptomatic VTE (symptomatic PE and symptomatic DVT)
Rate of symptomatic DVT

Safety:

<Primary>

Incidence of major bleeding during treatment period

Bleeding events 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:

- 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 ≥ 900 mL 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>

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:

<Rationale for Sample Size>

In the study EFC3557 (multinational, randomised, double-blind study of FPX vs dalteparin in prevention of VTE in high-risk abdominal surgery), FPX 2.5mg had a VTE rate up to Day10 of 4.7% (95% CI: 3.3–6.6) in cancer surgery patients. In addition, it has been reported by Japanese article that when prophylaxis with IPC and elastic stocking was given to "high risk" patients undergoing surgery for sigmoid colon cancer, rectal cancer or pancreatic cancer, the incidence of PE (symptomatic and asymptomatic) was 15.4% (4/26) in Japan. In this study, therefore, the residual VTE rate of 15% or lower was targeted to demonstrate a risk reduction to moderate risk or below."

Assuming FPX 2.5mg has a VTE rate of 4.7%, a sample size of 64 was required to detect that the upper bound of a 95% confidence interval is equal to or smaller than 15% (95% CI = 1.0–13.1 for n/N = 3/64).

This study included an IPC group in order to obtain general information about the residual incidence of VTE. To that end, about half of the sample size for the FPX group was considered necessary for the IPC group. Therefore, patients were randomized in a 2:1 ratio to receive FPX or IPC.

Assuming that 20% are excluded from efficacy analyses, a total of 120 patients (80 in the FPX group and 40 in the IPC group) were randomized.

<Analysis Populations>

Safety Population (SP)

The SP consisted of all subjects who received at least one dose of study medication or who used IPC.

Full Analysis Set (FAS)

The FAS population consisted of all subjects enrolled excluding:

- 1) those who did not receive study medication at all in the FPX group or who did not use IPC at all in the IPC group;
- 2) those with no valid efficacy data; and
- 3) those who did not undergo abdominal surgery.

Per Protocol Set (PPS)

The PPS population consisted of all subjects in the FAS population who had no protocol deviation.

Efficacy Evaluable Patients (EEP)

The EEP consisted of subjects in the SP who had an adjudicated evaluable qualifying DVT (any DVT, proximal DVT or distal only DVT) assessment at the considered side (total/right/left/both).

<Efficacy>

The following two periods were used in efficacy analyses: main efficacy period (from the first study drug injection in the FPX group or the day after surgery in the IPC group up to the first venogram or Day 10 whichever occurred first), and whole study period (from the first study drug injection in the FPX group or the day after surgery in the IPC group up to the follow-up). (Day0 = day of surgery)

FAS was the primary population for the efficacy analysis. The point estimates and 95% confidence intervals for the VTE rate were calculated for each treatment group. PPS was also analyzed for the primary and secondary variables. The point estimates and 95% confidence intervals for the any DVT, proximal DVT and distal only DVT rates (total/right/left/both sides) were calculated for each treatment group.

<Safety>

The following two periods were used in safety analyses: treatment period (FPX group: from the first study drug injection up to 2 days after the last study drug injection, IPC group: from the start of IPC up to the first venogram), and whole study period (FPX group: from the first study drug injection up to the follow-up, IPC group: from the start of IPC up to the follow-up). The point estimates and 95% confidence intervals for the incidences of "major bleeding (with or without minor bleeding)", "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 or IPC, were coded by system organ class and preferred term using MedDRA Ver. 9.0.

Study Population:

Patients aged ≥ 40 years undergoing the following abdominal (between diaphragm and pelvic floor) surgery under general anesthesia lasting more than 45 minutes.

General or urologic surgery: Cancer surgery

Gynecologic surgery: Radical surgery for pelvic malignancy

However, subjects were excluded if any of the exclusion criteria based on contraindications and precautions for use of anticoagulants currently approved in Japan (e.g., active, clinically significant bleeding, bleeding tendency) or the exclusion criteria related to venography (e.g.,

severe renal disorder, hypersensitivity to contrast media) applied, or any of the prohibited medications was used within 1 week prior to the first study drug administration, or the use of IPC was contraindicated or inappropriate.		
Number of Subjects:	FPX	IPC
Planned, N	80	40
Randomised, N	83	44
SP, N	78	42
FAS, N	65	34
PPS, N	62	31
Completed, n (% of randomized population)	71 (85.5)	41 (93.2)
Total Number Subjects Withdrawn, N (% of randomized population)	7 (8.4)	1 (2.3)
Withdrawn due to Adverse Events n (% of randomized population)	2 (2.4)	0
Withdrawn due to Lack of Efficacy n (% of randomized population)	0	0
Withdrawn for other reasons n (% of randomized population)	5 (6.0)	1 (2.3)
Demographics	FPX	IPC
N (SP)	78	42
Females: Males	20:58	16:26
Mean Age, years (SD)	63.5 (9.7)	62.5 (8.1)
Asian/Japanese, n (%)	78 (100)	42 (100)
Primary Efficacy Results:		
VTE rate during the main efficacy period: FAS	FPX	IPC
n/N (%)	7/65 (10.8)	6/34 (17.6)
95% Confidence Interval	4.4 20.9	6.8 34.5
p-value	n/a	
Secondary Outcome Variable(s):		
DVT rate during the main efficacy period: EEP	FPX	IPC

Any DVT, n/N(%)	7/65 (10.8)	6/35 (17.1)
Proximal DVT, n/N(%)	0/68	0/37
Distal DVT only, n/N(%)	7/65 (10.8)	6/36 (16.7)
Symptomatic VTE rate during the main efficacy period: SP	FPX	IPC
n/N (%)	0/78	0/42
PE rate during the main efficacy period: SP	FPX	IPC
n/N (%)	0/78	0/42
Safety Results:		
Primary Safety Results:		
Number (%) of subjects with bleeding events during the treatment period: SP	FPX	IPC
Major bleeding, n/N(%)	0/78	0/42
95% Confidence Interval	0.0 4.6	0.0 8.4
Minor bleeding, n/N(%)	2/78 (2.6)	0/42
95% Confidence Interval	0.3 9.0	0.0 8.4
Any bleeding (major and/or minor bleeding), n/N(%)	2/78 (2.6)	0/42
95% Confidence Interval	0.3 9.0	0.0 8.4
Number (%) of subjects requiring transfusion during the treatment period: SP	FPX	IPC
n/N(%)	1/78 (1.3)	0/42
Adverse event results - treatment period: SP		
	FPX (N=78)	IPC (N=42)
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects with any AE(s), n(%)	38 (48.7)	12 (28.6)
10 most frequent AEs in each treatment group		

Alanine aminotransferase increased	3 (3.8)	2 (4.8)
Aspartate aminotransferase increased	3 (3.8)	2 (4.8)
Hepatic function abnormal	3 (3.8)	1 (2.4)
Eczema	3 (3.8)	0
Gamma-glutamyltransferase increased	3 (3.8)	0
Constipation	2 (2.6)	2 (4.8)
Diarrhoea	2 (2.6)	2 (4.8)
Dermatitis contact	2 (2.6)	0
Haemorrhage subcutaneous	2 (2.6)	0
Pruritus	2 (2.6)	0
Rash	2 (2.6)	0
Fibrin D dimer increased	2 (2.6)	0
Blood alkaline phosphatase increased	2 (2.6)	0
Ileus paralytic	2 (2.6)	0
Pyrexia	2 (2.6)	0
Erythema	0	2 (4.8)
Intestinal obstruction	0	2 (4.8)
Blood bilirubin increased	0	1 (2.4)
Abdominal pain	0	1 (2.4)
Ileus	0	1 (2.4)
Chest discomfort	0	1 (2.4)
Excoriation	0	1 (2.4)

Postoperative fever	0	1 (2.4)
Post procedural vomiting	0	1 (2.4)
Gastrointestinal injury	0	1 (2.4)
Post procedural nausea	0	1 (2.4)
Urinary incontinence	0	1 (2.4)
Shoulder pain	0	1 (2.4)
Atelectasis	0	1 (2.4)
Dyspnoea	0	1 (2.4)
Pneumonia aspiration	0	1 (2.4)
Anaemia	0	1 (2.4)
Serious Adverse event results - treatment period: SP		
	FPX (N=78)	IPC (N=42)
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]	n (%) [related]	n (%) [related]
Subjects with non-fatal SAEs, n(%) [related]	1 (1.3) [0]	3 (7.1) [0]
Wound decomposition	1 (1.3) [0]	0
Ileus	0	1 (2.4) [0]
Intestinal obstruction	0	1 (2.4) [0]
Alanine aminotransferase increased	0	1 (2.4) [0]
Aspartate aminotransferase increased	0	1 (2.4) [0]
Pneumonia aspiration	0	1 (2.4) [0]
Subjects with fatal SAEs, n(%)	FPX (N=78)	IPC (N=42)
n (%)	0	0

Conclusion: See publication below

Publications: Sakon, M., Tsukamoto, T., et al. Clinical evaluation of fondaparinux for prevention of venous thromboembolism after abdominal surgery. (A randomized open-label study of fondaparinux and intermittent pneumatic compression as a benchmark). Journal of Clinical Therapeutics & Medicines 2008; 24(7):679-689.