EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report

for

ARIXTRA

International Nonproprietary Name:

fondaparinux sodium

Procedure No. EMEA/H/C/00403/II/0045

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. Scientific discussion

1.1 Introduction

Arixtra (fondaparinux) was the first of a new class of antithrombotic agents that selectively inhibit factor Xa. The antithrombotic activity of fondaparinux results from antithrombin (AT)-mediated selective inhibition of Factor Xa. By binding selectively to AT, fondaparinux potentiates (about 300 times) the innate neutralisation of Factor Xa by AT. Neutralisation of Factor Xa interrupts the blood coagulation cascade and inhibits both thrombin formation and thrombus development.
Subcutaneously (SC) administered fondaparinux 2.5 mg/day is currently approved in the EU for the prevention of venous thromboembolic events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs (MOSLL) or major abdominal surgery, in immobile medical patients at high risk of VTE, and for the treatment of patients with unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI) and ST-elevation myocardial infarction (STEMI). Fondaparinux is additionally approved in the EU for the treatment of acute deep-vein thrombosis (DVT) and acute pulmonary embolism (PE) at the dose of 7.5 mg/day SC (bodyweight < 50 kg, 5 mg/day; > 100 kg, 10 mg/day).

The scope of this variation is to extend the indication of fondaparinux sodium 1.5 and 2.5 mg/day SC, solution for injection, pre-filled syringe (Arixtra) for the "Treatment of acute symptomatic Superficial-Vein Thrombosis of the lower limbs without concomitant Deep-Vein Thrombosis (DVT)".

Superficial thrombophlebitis (ST) or superficial vein thrombosis frequently occurs as a complication, of an i.v. line and can also occur spontaneously. Spontaneous superficial vein thrombosis (SVT) of the legs is by far the most common form of ST. In the present submission, the term SVT will refer only to acute, spontaneous SVT of the lower limbs.
Clinical signs and symptoms of ST include the presence of a visible warm, red, tender, swollen area along the course of a superficial vein. ST occurs in an estimated 3-11% of the general population, more often in women (about 80% of cases) than in men. ST can occur in many locations but is most often found in the veins of the lower extremities. In 60 to 80% of such cases, ST is localized in the greater saphenous vein, in 10% to 20% in the lesser saphenous vein and in 10 to 20% in other veins of the legs, occurring bilaterally in 5 to 10% of patients.
In a majority of cases, the assumed self limiting nature of this frequent disease and good prognosis limits the therapeutic measure.
Treatment according to textbooks is polypragmatic and based on drugs with systemic or topical anti-inflammatory efficacy together with local measure like cooling. In some cases, ST could however be associated with deep-vein thrombosis (DVT), as they are present in 6 to 36% of patients with ST.
In the first large prospective epidemiological study conducted to date in patients with acute ST (the French POST study), about 600 patients had an isolated symptomatic SVT at inclusion of at least 5cm on CUS. 10.2% developed thromboembolic complications at 3 months (0.5% EP, 2.8% DVT, 3.3% extension of SVT, 1.9% recurrence of SVT), despite 90.5% having received anticoagulants. Although no agent is currently indicated for use in patients with ST, off-label use of various medications such as heparins has been used. In some patients with potential risk of associated VTS complications, there could be a medical need to treat TVS and prevent VTE complications according to experts.

This extension of indication is thus supported by one pivotal and unique double blind placebo controlled study: Study CALISTO. No reference treatment exists up to now and the CALISTO study is the first large clinical study conducted in this pathology. Patients diagnosed with SVT received 2.5 mg of the existing formulation of fondaparinux, once daily, via the established subcutaneous route for 45 days.
This represents an increase in the duration of clinical dosing from a maximum of 33 days in patients undergoing high fracture surgery to a period well in excess of one month. To support this extension of subcutaneous administration of fondaparinux in humans, and following the request form the Scientific Advice from the CHMP, an additional 6-month repeat dose toxicity study has been performed in rats.

In the present variation, the MAH proposed to update the following sections of the SPC (and the corresponding sections of the Package Leaflet):
- 4.1 Therapeutic indications
- 4.2 Posology and method of administration
- 4.4 Special warnings and precautions for use
- 5.1 Pharmacodynamic properties.

The last updated Risk Management Plan (RMP) was agreed with the CHMP in April 2009, which covers all currently approved indications for fondaparinux. An updated EU RMP was submitted specifically for this variation.

1.1. Non-clinical aspects

To support this new indication, and following a Scientific Advice from the CHMP, an additional 6 month repeat dose toxicity study has been performed in the rat. Fondaparinux sodium was give to Wistar Hannover Crl: WI (Han) rats (15/sex/group) at 0, 0.4, 2.0 and 10 mg/kg once daily by intravenous bolus injection. In addition 8 animals/sex were added to the control and high dose groups for a 6 week recovery period. There were no new toxicities and no adverse changes in animals at up to the maximum dose of 10 mg/kg/day. Toxicokinetic data showed no marked differences in systemic exposure between genders or between Weeks 13 and 26 at any dose level. At the no observed adverse effect level (NOAEL) of 10 mg/kg/day, mean AUC values were 25.2 µg.h/mL and 20.6 µg.h/mL, for males and females, respectively, at Week 26. These values represent at least 3 times those anticipated following subcutaneous dosing at 2.5 mg (i.e. the proposed clinical dose for the treatment of SVT) following a single dose to healthy volunteers.

The MAH has submitted an Environmental risk assessment to support the new indication. The MAH states: "Fondaparinux is a synthetic pentasaccharide and thus as a carbohydrate molecule is listed in the guidance amongst those substances which are considered unlikely to result in significant risk to the environment and therefore do not require an Environmental Risk Assessment."

1.2. Clinical aspects

Superficial thrombophlebitis (SVT) is a frequent complication of intravenous lines and can also occur spontaneously. Spontaneous SVT of the legs is by far the most common form of SVT.

SVT is most often seen in outpatients and high body weight and/or a history of varicose veins are recognised risk factors. Clinical signs and symptoms include the presence of a visible warm, red, tender, swollen area along the course of a superficial vein, often palpable as a cord. In 60 to 80% of cases involving the lower limbs, the SVT is located in the greater saphenous vein (GSV), in 10 to 20% in the lesser saphenous vein (LSV) and in 10 to 20% in other veins of the legs, occurring bilaterally in 5 to 10% of patients. SVT is estimated to be more frequent than DVT and pulmonary embolism (PE), with a claimed incidence of 125,000 new cases of clinically recognised SVT per year in the United States.
Duplex ultrasonography is often performed for confirmation of diagnosis and estimation of the extent of thrombosis.

SVT has historically been regarded as a benign, self-limiting disease, usually expected to resolve spontaneously within a few weeks and requiring little treatment other than symptomatic measures.
However, more recent studies have shown that SVT may be indicative of more widespread concomitant thrombosis. Systematic ultrasonography has revealed an incidence of concomitant DVT in 6% to 53% of patients with SVT, depending on the study. Furthermore, a clinical suspicion of concomitant PE has been described in 0% to 10% of patients with SVT, while systematic lung scanning has resulted in the detection of PE in up to 33% of patients with SVT.

With regard to physiopathology, there are links between SVT and DVT; the risk factors are common to both pathologies and SVT is itself a risk factor for DVT or PE. Risk factors that have been cited in association with SVT include previous thromboembolic episodes, long-haul flight, pregnancy, oral contraceptives, hormone replacement therapy, immobilisation, obesity, recent surgery, trauma and sclerotherapy. As with DVT or PE, there is a close relationship between SVT and thrombophilia or auto-immune diseases. Age is an additional risk factor; the older the patient, the fewer other risk factors are needed. However, venous insufficiency is much more common in the context of SVT (70% of cases), representing a crucial factor in the aetiology of this disease, in contrast to DVT.

Two mechanisms conceivably underlie the association between SVT and DVT or PE, namely: 1) migration of the SVT toward the deep venous system via the sapheno-femoral junction (SFJ), the sapheno-popliteal junction or a perforating vein, and 2) a state of hypercoagulability that may explain the non-contiguous coexistence of the two types of thrombosis.

The recent POST study, a prospective, epidemiological study conducted in patients with acute SVT, included consecutive patients reflecting the "real-world" routine clinical practice of angiologists in France. This showed that objectively confirmed DVT and/or symptomatic PE were concomitant with SVT in 24.9% (210/844) of patients at diagnosis. The thrombus in the deep vein was not contiguous to SVT in 41.9% of these SVT patients with DVT at presentation.
SVT patients with associated DVT or PE at presentation require treatment with curative doses of an anticoagulant agent.
Patients with acute isolated SVT (i.e. with no DVT or PE at presentation) are at risk of thromboembolic complications, which include recurrent disease or thrombus extension as well as DVT or PE. SVT recurrence and more importantly SVT extension are clinically important as they are associated with increased risk of DVT or PE, thereby prompting escalation of therapy to high dose anticoagulant agents or surgery, e.g. ligation of the SFJ or thrombectomy.

In the French epidemiological POST study (n=844), 8.3% of patients with isolated SVT at presentation experienced at least one symptomatic thromboembolic event at three months: 2.8% experienced symptomatic DVT (47% being proximal DVT), 0.5% symptomatic PE, 3.3% symptomatic extension of SVT and 1.9% symptomatic recurrence of SVT. It is noteworthy that these results were obtained despite more than 90% of the patients receiving one or more anticoagulant drugs (for a median duration of 11 days) on top of elastic stockings, almost half the patients also received topical or oral non-steroidal anti-inflammatory drugs (NSAIDs).

Male gender, severe venous insufficiency, varicose veins, a history of DVT or PE, a history of cancer or active cancer and disease characteristics, such as distance between the thrombus and the SFJ, have been reported to be risk factors for such thromboembolic complications of isolated SVT.

For a long time, acute isolated SVT was treated with oral analgesics or NSAIDs, in combination with compression (bandages or stockings), thrombectomy in patients suffering intense pain, and stripping of associated varicose veins. Various other therapeutic measures have been proposed in the literature for patients with acute isolated SVT, including immediate mobilisation (walking exercises) and local anti-inflammatory applications (gel, cream, spray, etc.).

Anticoagulation with unfractionated heparin (UFH) or LMWH at prophylactic or curative doses is currently the preferred option over routine surgery (commonly ligation of the SFJ). However, there are few published studies with UFH and LMWH in SVT patients, and all were small and had various methodological limitations. None provided clear conclusions on anticoagulant strategies for the effective prevention of symptomatic thromboembolic complications of SVT. It is also unclear to what extent different locations of SVT should influence the choice of treatment. Currently, patients with SVT involving the SFJ are considered at high risk of DVT or PE and require surgical ligation of the SFJ or thrombectomy.
Patients with an indication for primary surgery are not further discussed in the present submission.

Although guidelines regarding the management of SVT patients are available, they vary in their advice because of the weak evidence base to support clear recommendations. The 8th consensus of the American College of Chest Physicians (ACCP) suggested prophylactic or intermediate doses of LMWH or intermediate doses of UFH for at least 4 weeks for the treatment of SVT. This relatively weak Grade 2B recommendation is based on evidence of moderate quality, and acknowledges that the risk-to-benefit ratio of such a strategy is unclear. Additionally, the authors added that less extensive SVT (i.e. involving a short venous segment or distant from the SFJ) would probably not require anticoagulant treatment and that it was reasonable to use oral or topical NSAIDs for symptom control in such cases.
Recommendations issued by European national expert groups are heterogeneous regarding the use of anticoagulant therapy (ranging from "watchful waiting" to anticoagulant treatment for 6-12 weeks), and the recommended dose (prophylactic/intermediate/full) and duration of such treatment.

A survey conducted by GlaxoSmithKline in 2005 across 13 European countries using interviews of key experts in the field of SVT highlighted the heterogeneous management of SVT patients throughout Europe. In response to questions, experts cited all possible therapeutic alternatives, including ambulation (i.e. no treatment), surgery, graduated compression stockings (GCS), analgesic agents, venotonic agents, NSAIDs, aspirin or other antiplatelet agents, UFH (prophylactic or curative dose), LMWH (prophylactic or curative dose), and VKA.

Available data suggest that a low-dose (prophylactic) regimen of LMWH should be sufficient to treat patients with acute isolated SVT of the lower limbs. Substantial efficacy and safety data are available showing that fondaparinux 2.5 mg/day was at least as effective and safe as LMWH in the prevention of

VTE after surgery. Extrapolating these results, it was hypothesised that fondaparinux 2.5 mg/day should be at least as effective and safe as a prophylactic regimen of LMWH employed for the treatment of SVT patients. Although the reduced dose of fondaparinux 1.5 mg is recommended for VTE prophylaxis in patients with a creatinine clearance between 20 and 50 mL/min, this dosage regimen was not evaluated in the pivotal study supporting this application. The study investigators did not consider that a dose reduction in moderate renally impaired patients was appropriate for the treatment of SVT, as there were concerns that it may be less efficacious.
Furthermore, it is argued by the MAH that the SVT population was expected to be at a low risk of bleeding for two reasons: first, the low rates of surgical intervention expected in the population and second, published data with other anticoagulants in patients with SVT reported low rates of bleeding complications.
The clinical development programme supporting the efficacy and safety of fondaparinux in patients with acute symptomatic isolated SVT of the lower limbs builds on the already substantial data available for fondaparinux in the prevention and treatment of VTE. It consists of one pivotal Phase III study, the CALISTO study.

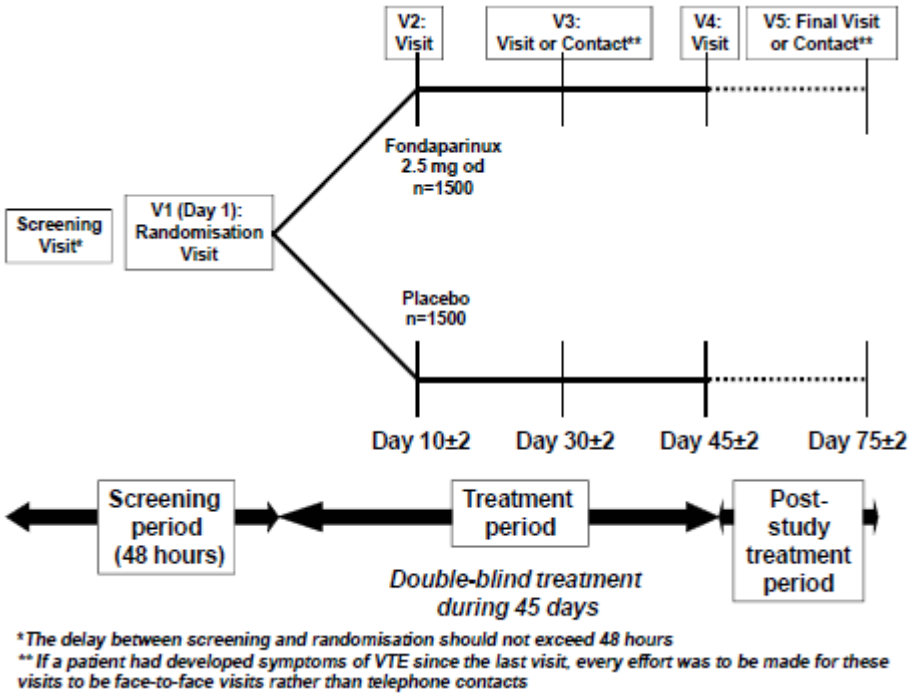
A CHMP Scientific Advice was sought during protocol development and after these discussions the protocol was revised. The primary efficacy endpoint was revised to include all-cause death, and an evaluation of efficacy and safety after a 30-day follow-up period was included. Furthermore patients at high risk for VTE such as those with recent DVT and active cancer were excluded as placebo treatment may not be regarded as ethically justified in these patients.

1.3.1 Clinical efficacy

The pivotal study supporting the application was a multicentre, randomised, double-blind, placebo-controlled, parallel group, phase III study in subjects with acute symptomatic isolated superficial vein thrombosis (SVT) of the lower limbs (i.e. without concomitant DVT). The occurrence of symptomatic events of venous thromboembolism [VTE], bleeding complications and death was evaluated. The patients were treated with fondaparinux sodium 2.5 mg or placebo subcutaneously once daily for 45 days. The patients were followed up after additional 30 days, i.e. at day 75. The study was conducted at 171 centres in 17 countries and 3002 subjects were included (1502 in the fondaparinux group and 1500 in the placebo group.) A majority of the patients were included in Russia, Hungary, Germany and Ukraine.

The design of the study is summarised in the figure below:

Fig. 1: The overall design of the pivotal study.



The CHMP agreed with that the primary endpoint includes only symptomatic events as this is a placebo-controlled trial for an indication where anticoagulant treatment is not clearly established. This is in contrast to trials with an active control in a therapeutic area where anticoagulant treatment is generally accepted, e.g. prophylactic treatment in high risk surgery, where also asymptomatic events often are included as a surrogate marker.

However, the Committee was of the view that the proposed treatment duration was not fully justified. In clinical practice when anticoagulant treatment has been used for SVT shorter treatment duration is probably common (e.g. 3-4 weeks). In response to this CHMP concern the MAH proposed an amended recommendation for treatment duration.

Another weakness of the study is that no laboratory tests were performed after the screening visit. Thus the possibilities to detect occult bleedings, e.g. from the gastrointestinal tract, was limited.

The inclusion criteria were as follows:

- Hospitalised or non-hospitalised male or female subjects 18 years of age or older;
- Subjects with acute symptomatic isolated SVT of the lower limbs at least 5 cm long documented by standard CUS; and
- Subjects able and willing to provide written informed consent.

The most important exclusion criteria were as follows:

<u>Exclusion criteria related to disease characteristics at presentation:</u>

- SVT following sclerotherapy or resulting as a complication of an intravenous line;
- Palpable hard cord without any inflammation and, on CUS, with an antero-posterior diameter <5 mm and uniformly hyperechoic (high probability of old SVT);
- Delay between symptom onset and randomisation >21 days;
- Delay between diagnosis by CUS and randomisation >48 hours
- Treatment of the current episode of SVT with oral NSAIDs for >72 hours prior to randomisation;
- Treatment of the current episode of SVT with aspirin at doses >325 mg per day for >72 hours prior to randomisation;

- SVT within 3 cm from the SFJ;
- Symptomatic or asymptomatic DVT on qualifying CUS;
- Documented presence of symptomatic PE;
- Requirement for ligation of the SFJ, thrombectomy or planned intervention for stripping of varicose veins during the study period;
- History of documented SVT occurring within the last 90 days;
- History of documented DVT or PE within the last 6 months; or
- SVT in subjects with active cancer (i.e., treated for cancer within the last 6months).

Exclusion criteria related to concomitant medication:

- Anticoagulant treatment
- Treatment with aspirin at a dose >325 mg per day or oral NSAIDs (at any dose) required or likely to be required during the study period.

Exclusion criteria related to study treatments:

- Known hypersensitivity to fondaparinux or its excipients; or
- Women of childbearing potential not using a reliable contraceptive method throughout the study period

Exclusion criteria based on risk of bleeding:
A number of such criteria were defined in line with the current contraindications, warnings and precaution in the approved SPC criteria and notably also the following:

- Calculated creatinine clearance <30 mL/min; or
- Body weight <50 kg.

The CHMP considered the inclusion and exclusion criteria to be adequate.

Five protocol amendments were implemented. The most important amendment number 4 increased the study size from 2500 subjects to a maximum of 3000. This was due to a somewhat lower event rate than expected.

None of the amendments were judged to affect the robustness of the study.

Patients were randomised according to a central randomisation scheme using an interactive voice response system.

After screening the patients were randomised at visit 1 (day 1) and they had visit 2 at day 10, visit 3 at day 30, visit 4 at day 45 (end of therapy) and visit 5 at day 75 (all visits were to be done at ± 2days).

The **primary efficacy endpoint** recorded up to day 47 was defined as a composite of

- symptomatic PE - confirmed according to local procedures (including ventilation-perfusion scan, helical computerised tomography [CT] scan or pulmonary angiogram);
- symptomatic DVT - confirmed on CUS or venography;
- symptomatic extension of SVT - defined as downstream (i.e., proximally) progression of the initial SVT by at least 2 cm AND to within 3 cm or less from the sapheno-femoral junction confirmed by CUS,
- symptomatic recurrent SVT - defined as a new episode in any other superficial venous location, confirmed by CUS, meeting the following criteria: the new SVT was in a different superficial vein and not directly contiguous upstream (i.e., distally) with the index SVT, or the new SVT was in the same superficial vein but clearly distinct from the index SVT with an open venous segment of at least 10 cm in length.

All suspected symptomatic events (i.e., for which a diagnostic test was performed, regardless of the result) were adjudicated by the independent Central Adjudication Committee, whose members were blinded to treatment assignments.

Secondary efficacy endpoints

VTE and/or death from any cause up to Day 77;

- Each component of the primary efficacy endpoint considered separately up to Day 47 and up to Day 77;
- A composite of symptomatic fatal or non-fatal PE and symptomatic DVT up to Day 47 and up to Day 77;
- A composite of symptomatic extension and recurrence up to Day 47 and up to Day 77
- Surgery to treat SVT up to Day 47 and up to Day 77.

Safety endpoints
The primary safety endpoint was major bleeding and/or death up to Day 47 or up to day of last injection + 4 days, whichever was longer.
Other safety endpoints included:

- major bleeding;
- clinically relevant non-major bleeding;
- minor bleeding;
- total (any) bleeding (major, clinically relevant non-major and minor bleeding);
- arterial thromboembolic event (e.g., stroke or myocardial infarction);
- death from any cause.

Major bleeding was defined as:

- fatal - and/or;
- in a critical area or organ (e.g., intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome) and/or;
- associated with a fall in haemoglobin ≥20 g/L (1.24 mmol/L) and/or;
- leading to transfusion of ≥2 units of packed red blood cells (PRBC) or whole blood.

Statistical analyses

Sample size was considered with respect to both the primary efficacy endpoint and safety evaluation, and an overall sample size of 2500 subjects (1250 per group) was determined.
Assuming a 45-day VTE incidence of 8% in the placebo group and a 50% reduction in the fondaparinux group to an incidence of 4%, the proposed sample size had 98.7% power to detect a difference between treatment groups using Fisher's exact test at a two-sided 5% level of significance.

The sample size was re-estimated by the Steering Committee in November 2008, based on a blinded review of the adjudicated incidence of VTE at Day 45. The overall blinded adjudicated event rate was 3.1%, observed in 2016 subjects who had completed the 45 day treatment period. Assuming a 50% reduction in the fondaparinux group, and a placebo rate of 4.1%, the Steering Committee recommended to increase the sample size to 3000 subjects (1500 per group), to ensure 90% power to detect a difference between treatment groups in the 45-day VTE incidence using Fisher's exact test at a two-sided 5% level of significance.

Analysis populations
Intention-to-Treat (ITT) Population: defined as all randomised subjects. The ITT Population was the primary population for all efficacy analyses.
As-Treated (AT) Population: composed of all randomised subjects who received at least one dose of the study treatment (exposed subjects). The AT Population was used for the safety analysis. Subjects were analysed according to the actual treatment received. If a subject received at least one dose of fondaparinux, he/she was assigned to the fondaparinux treatment group.

The Per-Protocol (PP) Population: composed of the subset of the ITT Population without any major protocol deviations. Major deviations were defined before the code was broken and were validated by the Steering Committee. The PP Population was not analysed because this population comprised more than 95% of the ITT Population.

A number of subgroup analyses were predefined but not presented here.

Premature withdrawal and missing data

It was not possible to distinguish whether a subject with a missing final event status did not have an event or if the final event status was missing. Therefore, based on the low marginal event rate, imputation of missing data for all endpoints was performed using the assumption that subjects did not have an event.

In the time-to-event analysis, subjects who discontinued the study without a final event status were censored at the withdrawal date or the date of last contact. All other subjects not having an event were censored at completion date.

Results

The majority of subjects randomised completed the study although slightly more subjects in the placebo group compared with the fondaparinux group withdrew from the study prematurely.
Thus the reported number of subjects completing the trial was high.

Table 1: Subject disposition

Population	Fondaparinux	Placebo	Total
Planned	1500	1500	3000
Randomized	1502	1500	3002
Completed [a], n (%)	1481 (98.6)	1467 (97.8)	2948 (98.2)
Withdrew after randomisation, n (%)	21 (1.4)	33 (2.2)	54 (1.8)
Reason for withdrawal from study			
Adverse event	2 (0.1)	1 (0.1)	3 (0.1)
Non-compliance	2 (0.1)	1 (0.1)	3 (0.1)
Lost to Follow-up	4 (0.3)	5 (0.3)	9 (0.3)
Did not meet treatment eligibility criteria	1 (0.1)	0	1 (0.0)
Investigator decision	0	4 (0.3)	4 (0.1)
Subject decided to withdraw from the study	9 (0.6)	18 (1.2)	27 (0.9)
Other	3 (0.2)	4 (0.1)	7 (0.2)

The total number of subjects with major protocol deviations was small (<5%) and comparable across treatment groups. The most common protocol deviation was use of prohibited concomitant medications and the rates were similar across treatment groups.

The PP population was more than 95 % of the ITT population, therefore separate analyses for the PP population was not performed.

Table 2: Study populations

Population	Fondaparinux	Placebo	Total
Intent-to-Treat (ITT)	1502	1500	3002
As-Treated (AT)	1499	1488	2987
Per-Protocol (PP)	1442	1424	2866

The median age of the patients was 58 years with 68% below the age of 65 and 8% above 75. Sixtyfour percent were females. Mean BMI was 29 with 37% above 30. The proportion of patients with

moderate renal impairment (CrCl 30-50) was 4.3% (n=129). Ninety-nine percent of the patients were of Caucasian ethnicity.

The study population was generally individuals who apart from SVT or other visible venous conditions were otherwise healthy without significant concomitant conditions.
The treatment groups were similar with respect to medical history related to VTE at screening. Few subjects had recent trauma or limited mobility. The majority of subjects used graduated compression stockings (76%), had visible venous disease at screening (any disorder; 94%), had varicose veins (89%).

The characteristics of the qualifying SVT were similar across treatment groups with a mean onset of 7.1 days from randomisation. The mean length of the qualifying SVT on CUS was 20.5 cm, predominately involved the GSV (93%), the SVT was in a varicose vein in the vast majority of cases (89%), was above the knee in approximately half the subjects (47%), and in the majority of subjects (82%) the distance between the head of the thrombus and SFJ was ≥10 cm.

The treatment groups were well balanced on the type of treatment used prior the study. The most commonly used medications were analgesics (26%), topical nonsteroidal anti-inflammatory drugs (NSAIDs; 40%) and aspirin or other anti-platelet agents (24%). Graduated compression stockings were used by 83% of subjects in each treatment group during the study.
Similarly, the treatment groups were well balanced with respect to the use of most medications during the study. One notable exception was the use of anticoagulants started during the study. In the placebo group 96 (6.4%) of subjects commenced anti-coagulant therapy during the study compared to 17 (1.1%) of fondaparinux subjects. An evaluation of the type and dose of agent used shows that both therapeutic and prophylactic doses of anti-coagulant were administered. The protocol prohibited the use of anti-coagulants concomitant to study medication, however in the event of confirmed VTE, the Investigator could stop study drug and initiate medical therapy at his/her discretion.
Overall the most commonly used medications during the study were analgesics, topical NSAIDs and aspirin or other anti-platelet agents. Graduated compression stockings were used by 83% of subjects in each treatment group.

The CHMP concluded that the study population is reasonably representative of the European target population. The treatment with anti-inflammatory agents and conservative measures, e.g compression stockings, probably reflects European clinical practice. The treatment groups were well balanced with regard to demographic characteristics, medical history, risk factors and concomitant treatment.

The mean duration of exposure across treatment groups was 42 days (median 45 days). More than 90% of subjects had 30 or more days of exposure to study drug.

A subject could discontinue investigational product, but remain in the study. Over twice as many subjects discontinued investigational product in the placebo group compared with the fondaparinux group, see table 3 below.

Table 3: Discontinuation of study drug, rates and reasons

Discontinuation of Investigational Product	Fondaparinux N = 1502	Placebo N = 1500	Total N = 3002
Permanent discontinuation [a], n (%):	82 (5.5)	189 (12.6)	271 (9.0)
Reason for Discontinuation of Investigational Product:			
Non-compliance n (%)	17 (1.1)	6 (0.4)	23 (0.8)
Investigator decision, n (%)	4 (0.3)	9 (0.6)	13 (0.4)
Subject withdrew from treatment, n (%)	20 (1.3)	44 (2.9)	64 (2.1)
Need for anti-thrombotic treatment, n (%)	10 (0.7)	49 (3.3)	59 (2.0)
Need for other prohibited treatment, n (%)	4 (0.3)	9 (0.6)	13 (0.4)
Other, n (%)	27 (1.8)	72 (4.8)	99 (3.3)

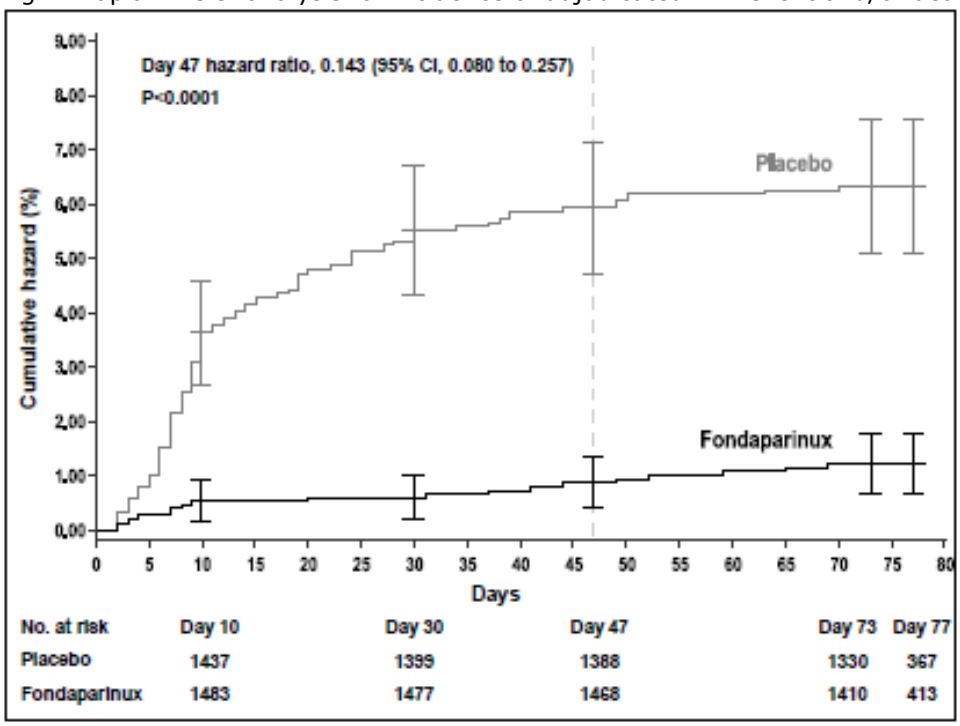
Primary end-points
The incidence of the composite primary end-point was significantly lower in the fondaparinux group as compared with placebo (relative reduction approximately 85%). The corresponding absolute reduction was 5.0% (95% CI; 3.7%, 6.3%) (See table 4 below).

Table 4: Primary end-point results, incidence of adjudicated VTE events or death from any cause up to day 47 (ITT population)

Day 47	Fondaparinux N = 1502	Placebo N = 1500
Adjudicated VTE Event and/or Death, n (%)	13 (0.9)	88 (5.9)
Within group CIs	(0.5%, 1.5%)	(4.7%, 7.2%)
Relative Risk Fondaparinux/Placebo (95% CI)	0.148 (0.083, 0.263)	
Fisher's Exact Test, p-value	<0.001	
Risk Difference (Fondaparinux – Placebo) (95% CI)	-0.050 (-0.063, -0.037)	

At Days 10, 30, 47, and 77 the reduction in risk of VTE/death associated with fondaparinux therapy compared with placebo was clinically and statistically significant. The plot below illustrates the time to event pattern.

Fig 2: Kaplan-Meier analysis for incidence of adjudicated VTE event and/or death (ITT)



The CHMP concluded that the difference in the incidences of the primary end point is considerable and statistically convincing. The curves appear to be essentially parallel after day 45. It would have been of interest to compare the incidence over time applying also shorter treatment duration (e.g. 3-4 weeks).

An analysis of the primary outcome using Investigator reported events was consistent with the primary endpoint based on adjudicated events.
The results of the sensivity analyses were consistent with the results of the primary analyses summarised above. One of sensivity analyses excluded the subjects with a missing final efficacy status. A second analysis focused on the incidence of adjudicated VTE events and/or death from any cause at any time during the study.

Up to day 77 the primary end point events were 18 in the fondaparinux group and 94 in the placeo group, i.e. 5 and 6 new events since day 47, respectively.

The CHMP concluded that there was no indication of a rebound phenomenon after discontinuation of treatment.

Secondary end-points
The incidences of the components of the primary endpoints are given below:

Table 5: Summary of the incidence of individual components of the primary end-point.

Adjudicated	Fondaparinux N = 1502	Placebo N = 1500
Day 47		
Number of subjects with adjudicated VTE, n (%)	12 (0.8)	87 (5.8)
Death, n (%)	2 (0.1)	1 (0.1)
Symptomatic PE, n (%)	0	5 (0.3)
Symptomatic DVT, n (%)	3 (0.2)	18 (1.2)
Symptomatic extension of SVT, n (%)	4 (0.3)	51 (3.4)
Symptomatic recurrence of SVT, n (%)	5 (0.3)	24 (1.6)
Day 77		
Number of subjects with adjudicated VTE, n (%)	17 (1.1)	93 (6.2)
Death, n (%)	2 (0.1)	1 (0.1)
Symptomatic PE, n (%)	0	6 (0.4)
Symptomatic DVT, n (%)	4 (0.3)	19 (1.3)
Symptomatic extension of SVT, n (%)	5 (0.3)	54 (3.6)
Symptomatic recurrence of SVT, n (%)	8 (0.5)	26 (1.7)

The majority of primary end point events consisted of extension or recurrence of SVT. Such a reduction of extension and recurrence of SVT is, however, to be regarded as clinically meaningful and most probably results in reduced pain and symptoms related to the inflammatory process which sometimes can result also in temporary walking disability.
The number of events with probably larger risks of severe complications (DVT or LE) was considerably lower. By treating 1500 patients 6 symptomatic cases of PE and 15 of DVT was prevented according to the results (p=0.015 and 0.001, respectively). It has been demonstrated by the MAH that treatment effects were similar in subgroups with different length of the SVT.

Interestingly a considerable reduction of surgery that was considered to be required to treat the SVT was reported in the fondaparinux group.

Table 6: Summary of surgery during the study (ITT)

	Fondaparinux N = 1502	Placebo N = 1500	Total N = 3002
Subjects with at least one surgical procedure, n (%):	24 (1.6)	69 (4.6)	93 (3.1)
Sapheno-popliteal vein ligation	3 (0.2)	2 (0.1)	5 (0.2)
Sapheno-femoral vein ligation	9 (0.6)	56 (3.7)	65 (2.2)
Varicose vein stripping in the GSV	14 (0.9)	18 (1.2)	32 (1.1)
Sclerotherapy of the GSV	1 (0.1)	1 (0.1)	2 (0.1)
Thrombectomy open surgery in the GSV	3 (0.2)	10 (0.7)	13 (0.4)
Local thrombectomy in the GSV	2 (0.1)	5 (0.3)	7 (0.2)
Varicose vein endovascular surgery in the GSV	0	2 (0.1)	2 (0.1)

The reported lower incidence of surgical interventions in the fondaparinux group provides important additional support for the clinical relevance of the reported reduction in the incidence of extension or recurrence of the SVT.

Subgroup analyses
The primary endpoint results were consistent over different demographic subgroups (women, men, age categories, BMI categories, different geographical regions, countries with large vs small inclusion rates etc) (detailed data not shown in this report).

The results were also consistent between treatment groups in different subgroups related to renal impairment, to history or no history of earlier VTE, to history of varicose veins or of earlier SVT, to distance from SFJ, to location above or below the knee.
Examination of the placebo event rates across the various sub-group categories suggests that the incidence of VTE and/or death by Day 47 tended to be higher in the following subgroups: age >75 years, weight >100 kg, creatinine clearance <50 ml/min, distance of the thrombus to the SFJ <10 cm, qualifying SVT involving the V Saphena Magna, qualifying SVT above the knee, a history of DVT or PE, history of SVT or multiple SVT and the absence of varicose veins. In addition placebo subjects who were not using NSAIDs at randomisation or not using antiplatelet agents or aspirin at randomisation also tended to have a higher rate of primary outcome events, relative to those who did use these agents at randomisation. However, subjects who apparently had no identifiable risk factors and who received placebo experienced an incidence VTE and/or Death by Day 47 of 4.1% (7/78 as compared to 2.3% or 2/89 in the fondaparinux group.

Conclusions on clinical efficacy

The single pivotal study supporting the application was adequately designed and seems to have been well performed. It provides convincing results with regard to the composite primary end point. It is crucial for the external validity of the study that DVT was effectively excluded at baseline and that is dependent on the quality of the CUS investigations. However, the consistency of the efficacy results in different countries and centres indicate that the quality of the investigations reflects current clinical standard.

The majority of primary end point events consisted of extension or recurrence of SVT. Such a reduction of extension and recurrence of SVT is, however, to be regarded as clinically meaningful and most probably results in reduced pain and symptoms related to the inflammatory process which sometimes can result in temporary walking disability. The reported significantly lower incidence of surgical interventions in the fondaparinux group provides additional support for the clinical relevance of the reported reduction in the incidence of extension or recurrence of the SVT.

The number of events with probably larger risks of severe complications (DVT or LE) was considerably lower. By treating 1500 patients 6 symptomatic cases of PE and 15 of DVT was prevented according to the results (p=0.015 and 0.001, respectively). The extension of the SVT at baseline was at mean over 20 cm and approximately half of them were located above the knee. It has, however, been demonstrated by the MAH that treatment effects were similar in subgroups with different length of the SVT.

The results were consistent over different demographic subgroups as well as in subgroups with different SVT characteristics and risk factors.

It is to be regarded as somewhat unfortunate that not different treatment duration was compared. In clinical practice when anticoagulant treatment has been used for SVT shorter treatment duration is probably common (e.g. 3-4 weeks). In response to the CHMP question the MAH has discussed this issue and proposed an amended recommendation for treatment duration of 4 to 6 weeks.

1.3.2 Clinical safety

Patient exposure

The exposure in SVT patients is derived from the pivotal study. It should, however, be taken into account that considerable experience exists from prophylactic treatment in surgery and in high risk medical patients with the same daily dosing but with shorter treatment duration. The mean duration of exposure across treatment groups was 42 days.

Table 7: Exposure in SVT treatment

Duration of Exposure (days)			
≤10, n (%)	35 (2)	95 (6)	130 (4)
11 to 30, n (%)	26 (2)	66 (4)	92 (3)
31 to 45, n (%)	1161 (77)	1091 (73)	2252 (75)
>45, n (%)	277 (18)	236 (16)	513 (17)
Mean (SD)	43.9 (13.45)	41.2 (11.04)	42.6 (12.38)
Median	45.0	45.0	45.0

Thus more than 90% of subjects had 30 or more days of exposure to study drug and even 17 % of subjects had more than 45 days of treatment. Treatment compliance was satisfactory. Of note, 91% of patients self-injected treatment.

Adverse events

The primary safety endpoint (major bleeding or death up to Day 47 or last dose + 4 days, whichever was longer) occurred in 3 (0.2%) fondaparinux subjects and 2 (0.1%) placebo subjects. In the fondaparinux group, these comprised 2 deaths (adjudicated cause cancer) and 1 major bleeding into a critical organ (intraocular which resolved without sequelae). The intraocular bleeding was an intra-retinal bleed in a patient with moderate renal impairment and hypertension. In the placebo group there was 1 death (due to acute heart failure, adjudicated cause 'other') and 1 major bleeding event (epistaxis which resolved without sequelae). There were no fatal bleedings in either group. No additional major bleeding and/or death events occurred after Day 47.

The incidence of adjudicated bleeding events (major, clinically-relevant non-major, and minor) was low (≤1.1%). A summary of the bleeding categories is given below.

Table 8: Incidence of adjudicated bleeding event to day 47 by category.

Adjudicated Criterion[a]	Fondaparinux N = 1499	Placebo N = 1488	Total N = 2987
Any Adjudicated Bleeding Event, n (%)[b]	15 (1.0)	14 (0.9)	29 (1.0)
Skin Haematoma >100 cm² and/or with pain	4 (0.3)	0	4 (0.1)
Gastro-intestinal bleeding	1 (0.1)	2 (0.1)	3 (0.1)
Epistaxis >5 min or repetitive	1 (0.1)	1 (0.1)	2 (0.1)
Haemoptysis	1 (0.1)	0	1 (0.1)
Urogenital	5 (0.3)	4 (0.3)	9 (0.3)
Intra-ocular	1 (0.1)	0	1 0.0)
Other bleeding resulting in clinical consequences for the subject	4 (0.3)	7 (0.5)	11 (0.4)

Most of the bleedings occurred before day 30. At day 77 there were 16 subjects in the fondaparinux group (1.1%) and 15 in the placebo group (1%) with any adjudicated bleeding event.

No clear differences between the treatment groups in bleeding tendency were reported. However, as pointed out above, no laboratory screening tests or more thorough clinical investigations were performed after the screening visit. Thus, the possibilities to detect occult bleedings were limited.

Of note, some bleedings were reported in listing of bleeding events but have not been adjudicated (criteria for bleeding event not satisfied): 5 in the fondaparinux group (2 urogenital, 1 very mild epistaxis, 1 gastrointestinal, 1 skin) versus one in the placebo group (type not specified). Thhe MAH has clarified that these 6 bleeding events did not meet the definition of any of the 3 pre-specified bleeding event definitions that were defined prospectively. If these six bleedings are included retrospectively in the comparison between the treatment groups it would result in a number of events (any bleeding) of 20 (1.3%) in the fondaparinux group and 15 (1.0%) in the placebo group.

Serious adverse events and deaths

A summary of the serious adverse events is tabulated below.

Table 9: Summary of the serious and significant adverse events

	Fondaparinux N = 1499	Placebo N = 1488	Total N = 2987
Deaths	2 (0.1)	1 (0.1)	3 (0.1)
Non-Fatal SAEs	10 (0.7)	16 (1.1)	26 (0.9)
AE leading to discontinuation of study treatment.	18 (1.2)	29 (1.9)	47 (1.6)
AEs leading to withdrawal from study	2 (0.1)	1 (0.1)	3 (0.1)

Table 10: Summary of drug-related treatment-emergent adverse events

Preferred Term	Fondaparinux N = 1499	Placebo N = 1488	Total N = 2987
Subjects with any drug-related event, n (%)	56 (3.7)	49 (3.3)	105 (3.5)
Injection site haematoma	25 (1.7)	16 (1.1)	41 (1.4)
Haematoma	5 (0.3)	2 (0.1)	7 (0.2)
Metrorrhagia	4 (0.3)	0	4 (0.1)
Vertigo	3 (0.2)	2 (0.1)	5 (0.2)
Epistaxis	3 (0.2)	2 (0.1)	5 (0.2)
Haemorrhagic diathesis	2 (0.1)	0	2 (0.1)
Abdominal pain	2 (0.1)	0	2 (0.1)
Dry mouth	2 (0.1)	1 (0.1)	3 (0.1)
Haemorrhoidal haemorrhage	2 (0.1)	1 (0.1)	3 (0.1)
Headache	2 (0.1)	1 (0.1)	3 (0.1)
Hematuria	2 (0.1)	2 (0.1)	4 (0.1)
Erythema	2 (0.1)	0	2 (0.1)
Asthenia	1 (0.1)	3 (0.2)	4 (0.1)
Hypersensitivity	1 (0.1)	2 (0.1)	3 (0.1)
Dysgeusia	0	2 (0.1)	3 (0.1)
Hypertension	0	2 (0.1)	2 (0.1)

Three subjects in the placebo group experienced arterial thromboembolic events (acute coronary syndrome, n=2, ischemic stroke, n=1) as compared to none in the fondaparinux group.

A somewhat greater number of subjects in the placebo group (n=29) discontinued the investigational product due to treatment emergent AE than subjects in the fondaparinux group (n=18).

Laboratory findings

No clinical laboratory tests were scheduled after screening except a pregnancy test in women of child-bearing potential.
Two subjects (both in the placebo group) were found to be pregnant after start of the investigational product.

Safety in special populations

No differences in bleeding rates between the treatment groups were recorded in patients with mild or moderate renal insufficiency.
No differences were seen in bleeding rates between treatment groups for patients on NSAID or aspirin during the trial.

Conclusions on clinical safety

The bleeding risk in patients with SVT is not expected to be much different from the general population of the same age and gender distribution. However, treatment with NSAID or aspirin is probably not uncommon in these patients and they are at increased risk for bleeding when treated with anticoagulants. This is adequately addressed in the SPC.
However no differences bleeding rates between the treatment groups were reported overall or in the subgroups of special interest as those mentioned above. This probably reflects that the target population generally has a rather low bleeding risk, as compared for example with surgical patients who are treated prophylactically with similar doses.
As pointed out above it may have been difficult to capture subclinical bleedings with the chosen study design.

The MAH has discussed the dose to be recommended in patients with renal impairment in response to the CHMP questions and proposes a recommendation for dosage reduction to 1.5 mg in patients with creatinine clearance in the range of 20 to 50 ml/min. This is consistent with the recommendation for the VTE prophylaxis indication.

1.4. Risk management plan

The MAH submitted an updated RMP (version 1.6). The new proposed indication has been accurately added to the RMP.

The MAH stated that feedback regarding the use of fondaparinux in SVT, (i.e., 12-18 months post launch) from key prescribers will be obtained and reported though a drug utilisation study. Furthermore the MAH has adequately discussed the possibility to extrapolate the results to different ethnic subgroups as almost only Caucasian patients were included in the single pivotal trial.

The MAH has committed to update the synopsis and protocol for the planned drug utilization study. Full clinical study protocol will be submitted to the CHMP by December 2010.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified Risks		
Bleeding events	Routine pharmacovigilance as described In RMP Section 3.1 Additional pharmacovigilance which includes: 1. Ongoing review of spontaneous reports of haemorrhage in patients treated with fondaparinux 2. Use of targeted follow-up questionnaire to ensure consistency of data collected for spontaneous reports of haemorrhage with respect to risk factors for haemorrhage.	Routine risk minimisation which includes: 1. Appropriate labelling • Bleeding risks are well-characterized and appropriately described in the current SPC, as shown below: *4.4 Special warnings and precautions for use* *Haemorrhage* *Fondaparinux should be used with caution in patients who have an increased risk of haemorrhage, such as those with congenital or acquired bleeding disorders (e.g. platelet count <50,000/mm3), active ulcerative gastrointestinal disease and recent intracranial haemorrhage or shortly after brain, spinal or ophthalmic surgery and in special patient groups as outlined below.* *[For 1.5 and 2.5mg:]* • *For prevention of VTE - Agents that may enhance the risk of haemorrhage should not be administered concomitantly with fondaparinux. These agents include desirudin, fibrinolytic agents, GP IIb/IIIa receptor antagonists, heparin, heparinoids, or Low Molecular Weight Heparin (LMWH). When required, concomitant therapy with vitamin K antagonist should be administered in accordance with the information of Section 4.5. Other antiplatelet medicinal products (acetylsalicylic acid, dipyridamole, sulfinpyrazone, ticlopidine or clopidogrel), and NSAIDs should be used with caution.*

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		If co-administration is essential, close monitoring is necessary. • *For treatment of superficial-vein thrombosis - Fondaparinux should be used with caution in patients who are being treated concomitantly with other medicinal products that increase the risk of haemorrhage.* *[For 5, 7.5 and 10mg:]* *Agents that may enhance the risk of haemorrhage should not be administered concomitantly with fondaparinux. These agents include desirudin, fibrinolytic agents, GP IIb/IIIa receptor antagonists, heparin, heparinoids, or Low Molecular Weight Heparin (LMWH). During treatment of VTE, concomitant therapy with vitamin K antagonist should be administered in accordance with the information of Section 4.5. Other antiplatelet medicinal products (acetylsalicylic acid, dipyridamole, sulfinpyrazone, ticlopidine or clopidogrel), and NSAIDs should be used with caution. If co-administration is essential, close monitoring is necessary.* • Fondaparinux is contraindicated in patients with severe renal failure, as shown below: *4.3 Contraindications (1.5 and 2.5mg)* *- severe renal impairment defined by creatinine clearance < 20 ml/min.* *4.3 Contraindications (5, 7.5 and 10mg)* *- severe renal impairment defined by creatinine clearance < 30 ml/min.* • Dosage in severe to moderate renal impairment (creatinine clearance 20-50 mL/min) reduced from 2.5 mg to 1.5mg (VTE prophylaxis only), as shown below: *4.2 Posology and method of administration* *Renal impairment -* • *Prevention of VTE - Fondaparinux should not be used in patients with creatinine clearance <20 ml/min (see section 4.3). The dose should be reduced to 1.5 mg once daily in patients with creatinine clearance in the range of 20 to 50 ml/min (see sections 4.4 and 5.2). No dosage reduction is required for patients with mild renal impairment (creatinine clearance >50 ml/min).*

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		• *Treatment of superficial-vein thrombosis - Fondaparinux should not be used in patients with creatinine clearance <20 ml/min (see section 4.3). The dose should be reduced to 1.5 mg once daily in patients with creatinine clearance in the range of 20 to 50 ml/min (see sections 4.4 and 5.2). No dosage reduction is required for patients with mild renal impairment (creatinine clearance >50 ml/min). The safety and efficacy of 1.5 mg has not been studied (see section 4.4.)*
Off label Use (VTE treatment and prevention)	Routine pharmacovigilance as described in RMP Section 3.1 Additional pharmacovigilance which includes: 1. Continued evaluation of spontaneous reports of haemorrhage reported in the setting of off-label use received globally. 2. The targeted follow up questionnaire issued for spontaneous reports of haemorrhage are issued regardless of treatment indication. Therefore, information obtained will help to characterize risk factors for haemorrhage reported from off-label use as well.	Routine risk minimisation which includes: 1. Appropriate labelling • Indications for use are clearly and accurately reflected in Section 4.1 of the SPC, as shown below: *4.1 Therapeutic indications* *Prevention of Venous Thromboembolic Events (VTE) in adultspatients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery.* *Prevention of Venous Thromboembolic Events (VTE) in adultspatients undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery (see section 5.1).* *Prevention of Venous Thromboembolic Events (VTE) in adult medical patients who are judged to be at high risk for VTE and who are immobilised due to acute illness such as cardiac insufficiency and/or acute respiratory disorders, and/or acute infectious or inflammatory disease.* *Treatment of adults with acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs without concomitant deep-vein thrombosis (see sections 4.2 and 5.1).* *Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in adultspatients for whom urgent (< 120 mins) invasive management (PCI) is not indicated (see sections 4.4 and 5.1).* *Treatment of ST segment elevation myocardial infarction (STEMI) in adultspatients who are managed with thrombolytics or who initially are to receive*

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		no other form of reperfusion therapy. *Treatment of adults with acute Deep Vein Thrombosis (DVT) and treatment of acute Pulmonary Embolism (PE), except in haemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy.*
Catheter thrombosis during PCI when fondaparinux is used as sole anti-coagulant adjunct to PCI	Routine pharmacovigilance as described in RMP Section 3.1 which includes: Additional pharmacovigilance which includes: 1. Use of targeted follow up questionnaire to ensure consistency of data collected for spontaneous reports of catheter thrombosis 2. Evaluate (post-approval) the appropriate use of fondaparinux in ACS patients who have to undergo PCI according to prescribing information.	Routine risk minimisation which includes: 1. Appropriate labelling: • Not recommending fondaparinux prior to or during primary PCI. • Recommendation against use of fondaparinux as sole anti-coagulation adjunct to non-primary PCI • Recommendation to use UFH for anti-coagulation during non-primary PCI in patients treated with fondaparinux As shown below: *4.4 Special warnings and precautions for use* *PCI and risk of guiding catheter thrombus* *In STEMI patients undergoing primary PCI, the use of fondaparinux prior to and during PCI is not recommended. Similarly, in UA/NSTEMI patients with life threatening conditions that require urgent revascularisation, the use of fondaparinux prior to and during PCI is not recommended. These are patients with refractory or recurrent angina associated with dynamic ST deviation, heart failure, life-threatening arrhythmias or haemodynamic instability.* *In UA/NSTEMI and STEMI patients undergoing non-primary PCI, the use of fondaparinux as the sole anticoagulant during PCI is not recommended, therefore UFH should be used according to local practice (see section 4.2).*

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Potential Risks		
Heparin Induced Thrombocytopenia	Routine pharmacovigilance as described in RMP Section 3.1 Additional pharmacovigilance which includes: 1. Use of targeted follow-up questionnaire to ensure consistency of data collected for spontaneous reports of HIT.	Routine risk minimisation which includes: 1. Appropriate labelling • Thrombocytopenia and the risk of HIT-type II are appropriately labelled in the SPC for fondaparinux (as shown below): *4.4 Special warnings and precautions for use* *Patients with Heparin Induced Thrombocytopenia* *Fondaparinux should be used with caution in patients with a history of HIT. The efficacy and safety of fondaparinux have not been formally studied in patients with HIT type II. Fondaparinux does not bind to platelet factor 4 and does not cross-react with sera from patients with Heparin Induced Thrombocytopenia (HIT) type II. However, rare spontaneous reports of HIT in patients treated with fondaparinux have been received. To date a causal association between treatment with fondaparinux and the occurrence of HIT has not been established.*
Risk of bleeding in non-primary PCI when UFH is used for anti-coagulation during the procedure in patients previously treated with fondaparinux	Routine pharmacovigilance as described in RMP Section 3.1 Additional pharmacovigilance which includes: • Conduct PASS. • Evaluate (post-approval) the adherence to the prescribing guidance for recommended use of fondaparinux in ACS patients who have to undergo PCI.	Routine risk minimisation activities which includes: 1. Appropriate labelling • Recommendation to use UFH for anti-coagulation during non-primary PCI in patients treated with fondaparinux taking into account individual bleeding risk including timing since last dose of fondaparinux (as shown below): *4.4 Special warnings and precautions for use* *PCI and risk of guiding catheter thrombus* *In STEMI patients undergoing primary PCI, the use of fondaparinux prior to and during PCI is not recommended. Similarly, in UA/NSTEMI patients with life threatening conditions that require urgent revascularisation, the use of fondaparinux prior to and during PCI is not recommended. These are patients with refractory or recurrent angina associated with dynamic ST deviation, heart failure, life-threatening arrhythmias or haemodynamic instability.* *In UA/NSTEMI and STEMI patients*

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		undergoing non-primary PCI, the use of fondaparinux as the sole anticoagulant during PCI is not recommended, therefore UFH should be used according to local practice (see section 4.2).
Use of higher VTE treatment doses (5mg, 7.5mg, 10mg) for treatment of superficial-vein thrombosis	Routine pharmacovigilance as described in RMP Section 3.1 Additional pharmacovigilance which includes: 1. Ongoing review of spontaneous reports of haemorrhage in patients treated with fondaparinux 2. Use of targeted follow-up questionnaire to ensure consistency of data collected for spontaneous reports of haemorrhage with respect to risk factors for haemorrhage 3. Conduct a drug-utilisation study in order to evaluate the adherence to the proposed prescribing information regarding use of fondaparinux for treatment of superficial vein thrombosis	Routine risk minimisation which includes: 1. Appropriate labelling • Proper dosing instructions for the treatment of superficial-vein thrombosis are clearly provided in the proposed SPC as shown below: *4.2 Posology and method of administration* *Treatment of superficial-vein thrombosis* *The recommended dose of fondaparinux is 2.5 mg once daily, administered by subcutaneous injection. Patients eligible for fondaparinux 2.5 mg treatment should have acute, symptomatic, isolated, spontaneous superficial-vein thrombosis of the lower limbs, at least 5 cm long and documented by ultrasonographic investigation or other objective methods. Treatment should be initiated as soon as possible following diagnosis and after exclusion of concomitant DVT or superficial-vein thrombosis within 3 cm from the sapheno-femoral junction. Treatment should be continued for a minimum of 30 days and up to a maximum of 45 days in patients at high risk of thromboembolic complications (see sections 4.4 and 5.1). Patients could be recommended to self-inject the product when they are judged willing and able to do so. Physicians should provide clear instructions for self-injection.* • *Patients who are to undergo surgery or other invasive procedures. In superficial vein thrombosis patients who are to undergo surgery or other invasive procedures, fondaparinux, where possible, should not be given during the 24 hours before surgery. Fondaparinux may be restarted at least 6 hours post-operatively provided haemostasis has been achieved.*
Use of fondaparinux (2.5mg) in superficial-vein thrombosis patients with concomitant DVT.	Routine pharmacovigilance as described in RMP Section 3.1. Additional pharmacovigilance which includes: 1. Ongoing review of spontaneous reports representative of lack of effect received	Routine risk minimisation which includes: 1. Appropriate labelling: • Indications for use are clearly and accurately reflected in Section 4.1 of the SPC as shown below:

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	globally. 2. Conduct a drug-utilisation study in order to evaluate the adherence to the proposed prescribing information regarding use of fondaparinux for treatment of superficial vein thrombosis	*4.1 Therapeutic indications* *Treatment of adults with acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs without concomitant deep-vein thrombosis (see sections 4.2 and 5.1).* • Warning/Precaution to reinforce proper patient population (i.e. presence of superficial-vein thrombosis should be confirmed and concomitant DVT should be objectively excluded prior to initiation of therapy) *4.4 Special warnings and precautions for use* *Patients with superficial-vein thrombosis* *Presence of superficial-vein thrombosis greater than 3 cm from the sapheno-femoral junction should be confirmed and concomitant DVT should be excluded by compression ultrasound or objective methods prior to initiating treatment of fondaparinux. There are no data regarding the use of fondaparinux 2.5 mg in superficial-vein thrombosis patients with concomitant DVT or with superficial-vein thrombosis within 3 cm of the sapheno-femoral junction (see section 4.2 and 5.1).* *The safety and efficacy of fondaparinux 2.5 mg has not been studied in the following groups: patients with superficial-vein thrombosis following sclerotherapy or resulting as a complication of an intravenous line, patients with history of superficial-vein thrombosis within the previous 3 months, patients with history of venous thromboembolic disease within the previous 6 months, or patients with active cancer (see section 4.2 and 5.1).*
IMPORTANT MISSING INFORMATION		
Use in paediatric patients	Routine pharmacovigilance as described in RMP Section 3.1.	Routine risk minimisation which includes: 1. Appropriate labelling: • Section 4.2 indicates that fondaparinux is not recommended for use in children below 17 years of age (as shown below): *4.2 Posology and method of administration* *Paediatric population - Fondaparinux is not recommended for use in children below 17 years of age due to a lack of*

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		data on safety and efficacy.

1.5 Changes to the Product Information

Section 4.1 of the SPC of the 1.5 and 2.5 mg strengths was changed to include the new indication as follows: "Treatment of adults with acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs without concomitant deep-vein thrombosis"

As a result of the new indication further changes were made to sections 4.2, 4.4, 4.8 and 5.1. The Package Leaflet has been updated accordingly.

Additionally, the MAH took the opportunity to put change several sections of the SPC, Labelling and Package Leaflet to put them in line with the latest QRD template.

1.6. Overall conclusions and benefit-risk assessment

The scientific interest in different treatment alternatives of SVT has been relatively limited so far. There are few or no large well designed trials investigating the benefit and risks of anticoagulant therapy in these patients. This may in part be due to the historically common view that SVT is a rather benign disease that could primarily be treated conservatively with e.g. elastic stockings and local treatment. An exception has been SVT in the V saphena magna extending close to the sapheno-femoral junction where surgery often has been regarded as indicated. However, in recent years the evidence has increased that SVT may be associated with a higher incidence of thrombotic complications from the deep venous system than previously anticipated. Furthermore, anticoagulant treatment has probably been rather extensively used off-label in clinical practice in patients with more extensive SVT, which also is reflected in some of the current guidelines. Thus, in this perspective, the relatively large, placebo-controlled study evaluating anticoagulant therapy supporting this indication is of considerable scientific interest.

Efficacy: The single pivotal study supporting the application was generally of an adequate design and seems to have been well performed. It provides convincing results with regard to the composite primary end point. The majority of primary end point events consisted of extension or recurrence of SVT. Such a reduction of extension and recurrence of SVT is, however, to be regarded as clinically meaningful and most probably results in reduced pain and symptoms related to the inflammatory process which sometimes can result in temporary walking disability. The reported significantly lower incidence of surgical interventions in the fondaparinux group provides additional support for the clinical relevance of the reported reduction in the incidence of extension or recurrence of the SVT.
The number of events with probably larger risks of severe complications (DVT or LE) was considerably lower. By treating 1500 patients 6 symptomatic cases of PE and 15 of DVT was prevented according to the results (p=0.015 and 0.001, respectively). However, such a reduction of risk has been accepted for wide spread prophylaxis in surgical patients at moderate risk.
The results were consistent over different demographic subgroups as well as in subgroups with different SVT characteristics and risk factors. It has been demonstrated by the MAH that treatment effects were similar in subgroups with different length of the SVT.
The recommended treatment duration has been discussed in relation to the CHMP questions and a duration of a minimum of 4 weeks with maximum 6 weeks is reflected in the revised SPC.

Safety: The reported bleeding rates were low. The bleeding risk in patients with SVT is not expected to be much different from the general population of the same age and gender distribution. However, treatment with NSAID or aspirin is probably not uncommon in these patients and thus they are expected to be at a somewhat increased risk for bleeding when treated with anticoagulants.
However, no apparent differences in bleeding rates between the treatment groups were reported overall or in the subgroups of special interest as those mentioned above. This probably reflects that the target population generally has a lower bleeding risk, as compared for example with surgical patients who are treated prophylactically with similar doses. Further characterisation of the bleedings has been provided in the responses to CHMP questions and these analyses are judged not to change the overall

conclusions summarised above. In order to achieve similar exposure in patients with renal impairment (estimated CrCl 20-50 ml/min) as in the overall population and to reduce the risk for bleedings in these patients a reduced dose is recommended (1.5 mg). This is consistent with the dosing recommendation for prophylaxis in surgery patients.

As pointed out above it may have been difficult to capture subclinical bleedings with the chosen study design. No laboratory tests were done after screening and e.g. occult gastrointestinal bleedings could easily have been missed.

Conclusions on benefit risk balance
The benefit risk balance of the new indication is judged to be favourable.

2. Conclusion

On 22 July 2010 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.

Follow-up measures undertaken by the Marketing Authorisation Holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments (see Letter of Undertaking attached to this report):

Area	Description	Due date
Clinical	The MAH commits to perform a drug utilisation study in order to evaluate adherence to prescribing guidance regarding the use of fondaparinux for the treatment of superficial venous trombosis.	Full clinical study protocol to be submitted by Dec 2010

3. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope:

C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one

Extension of indication to include the treatment of adult patients with acute symptomatic spontaneous superficial vein thrombosis of the lower limbs without concomitant deep-vein thrombosis to the 1.5mg and 2.5 mg strengths.

Summary / scientific discussion:

The Scientific discussion of the CHMP Assessment Report will be published