1. Introduction

The company requested a new indication in the "Prevention of VTE in patients undergoing abdominal surgery who are at risk of thromboembolic complications". The application is supported by a single double-blind, dalteparin-controlled pivotal study, PEGASUS (EFC3357). No Scientific Advice was sought to discuss the design of the trial.

2. Clinical aspects.

Rationale for the proposed change

DVT and PE are potentially life-threatening events following major abdominal surgery. Current knowledge about the epidemiology of post-operative VTE in abdominal surgery is mainly based on published studies assessing the efficacy of low molecular weight heparin (LMWH) using no treatment or placebo-treated control groups. The reported rates of DVT detected by screening procedures, clinical VTE and clinical PE are about 15%, 0.9% and 0.5%, respectively.

The seventh ACCP guidelines (American College of Chest Physicians, 2004) for antithrombotic therapy agreed on the following risk factors for VTE: surgery, trauma (major or lower extremities), immobility, paresis, malignancy, cancer therapy, previous VTE, increasing age, pregnancy and post-partum, estrogen use, acute medical illness, heart and respiratoy failure, inflammatory bowel disease, nephrotic syndrome, myeloproliferative disorders, paroxysmal nocturanal hemoglobinuria, obesity, smoking, varicose veins, central venous catheterisation, inherited or acquired thrombophilia. "High risk" was defined as follows:

Table 1 Levels of thromboembolism risk in surgical patients without prophylaxis, 7th ACCP guidelines

"High risk"	Surgery in patients >60 years or age 40-60 with additional risk factors(prior VTE, cancer, molecular hypercoagulability)
"Highest risk"	Surgery in patients with multiple risk factors(age >40 years , cancer, prior VTE); hip or knee arthroplasty, hip fracture surgery; major trauma; spinal cord injury

Based on numerous trials it is generally accepted that unfractionated heparin (UFH) and LMWH reduce the rate of post-operative VTE with a relative reduction of approximately 50% or more, and appear to be approximately equally efficacious and safe in preventing VTE in general surgery patients. The residual incidence of surveillance DVT or VTE with LMWH prophylaxis in general surgery has been reported to be in the range of 6% to 15% (as assessed in 3 active-controlled published studies by Bergqvist in 1986, 1988 and 1995, and the ENOXACAN study), with higher rates in patients with malignancy.

Analysis of data submitted

PEGASUS was a Phase III, multicentre, multinational, randomised, parallel-group double-blind (double-dummy) and active-controlled study comparing the efficacy and safety of fondaparinux 2.5 mg once-daily sc injection with dalteparin (Fragmin) 5000 IU once-daily sc injection, up to Day 10, in the prevention of VTE in patients undergoing high-risk abdominal surgery.

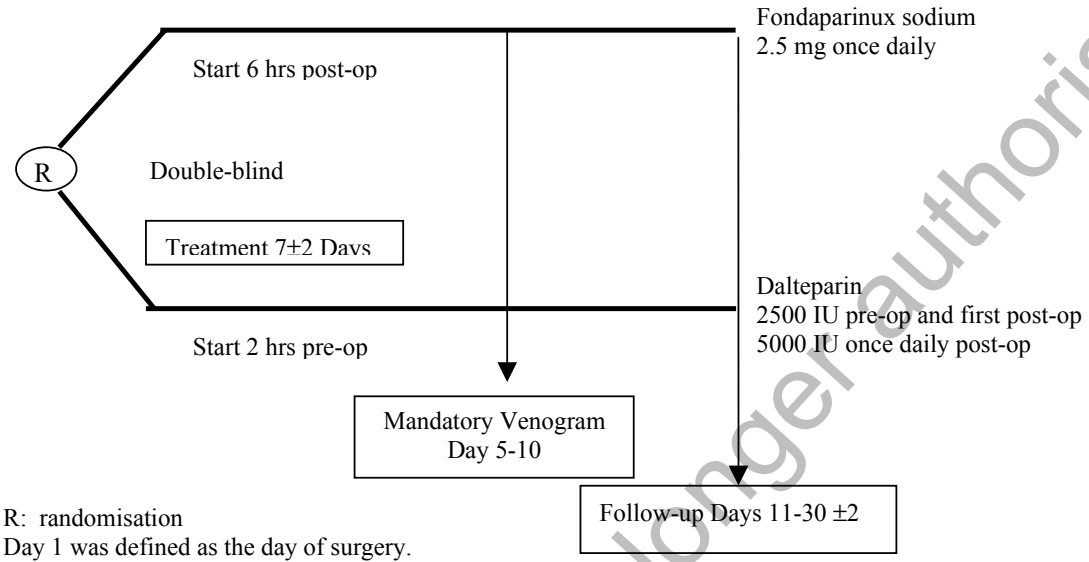
Clinical pharmacology

The applicant has adequately justified bioequivalence between the 12.5 mg/ml formulation used in the clinical trial and the 5 mg/ml intended for marketing by bridging two bioequivalence studies. It has been shown that fondaparinux concentration, volume of injection and sodium content of the formulation do not affect the bioavailability of fondaparinux and the 2 formulations can be considered bioequivalent.

The fondaparinux dose selected in this study was the same as that approved for prophylaxis in the MOSLL development programme. The dalteparin regimen used in the control group (2500 IU 2 hours pre-operatively and 12 hours after the pre-operative injection, and then 5000 IU once daily up to day 7±2) is approved and widely accepted for prophylaxis of patients at increased risk in general surgery.

Patients were screened from 30 days prior to surgery. Randomisation was to be performed at least 2 hours before anaesthesia induction for surgery (Day 1) and not more than 24 hours before the pre-operative injection. Patients were to be treated up to Day 7±2. A mandatory bilateral venogram had to be performed between Day 5 and Day 10, or earlier in case of symptomatic VTE, and in any case not more than one calendar day after the last study treatment injection. Patients were then followed-up from Day 11 up to Day 30±2.

Figure 1 - Study design



R: randomisation
Day 1 was defined as the day of surgery.

Basic *inclusion criteria* selected patients undergoing abdominal surgery under general anesthesia* (*spinal/epidural anesthesia were however allowed through an amendment during the study), planned to last longer than 45 min (from incision to incision closure), and satisfying one of the following conditions:

- over 60 years old with or without any other risk factor for VTE;
- over 40 years old and at risk for thromboembolic complications [patients who were obese (BMI>30 kg/m^2 for men and 28.6 kg/m^2 for women), or undergoing cancer surgery, or with a history of DVT or PE, or with congestive heart failure (NYHA grade III or IV), or chronic obstructive pulmonary disease, or inflammatory bowel disease].

The exclusion criteria were mainly related to contraindications to dalteparin use, known bleeding risk, creatinine above 2.0 mg/dl (180 micromol/L), difficulties in performing venography and patients for whom anticoagulant therapy was indicated due to a co-existing condition. Patients undergoing urological (except kideney) or gynaecological surgery, laparoscopic surgery, emergency post-trauma surgery, and patients undergoing vascular surgery were also excluded.

The *primary efficacy endpoint* was the composite of the following VTE outcomes: (i) mandatory venogram positive for any DVT between Day 5 and Day 10, (ii) symptomatic DVT and/or non-fatal PE, and (iii) fatal PE. A "non-evaluable" or no VTE assessment up to Day 10 (i.e.) was the only reason for exclusion from the primary efficacy analysis. The *secondary efficacy endpoints* were the components of the primary efficacy outcome considered separately during the same time period: DVT (any, proximal, and distal only) and symptomatic VTE (DVT and/or PE). Additional efficacy outcomes were symptomatic VTE up to Day 32 and initiation of curative treatment based on local VTE assessment.

The main *safety endpoint* was the incidence of major bleeding (MB) during the treatment period. MB was defined as: (i) a fatal bleeding, or (ii) bleeding at the surgical site leading to intervention, or (iii) non-surgical bleeding at a critical site (e.g., intracranial, retroperitoneal, intra-ocular, pericardial,

spinal or into adrenal gland), or leading to intervention, and/or with a bleeding index (BI)[1] ≥2. Other safety variables were: major bleedings between first injection and Day 32, minor bleeding (i.e. clinically overt bleeding not meeting the criteria of MB), transfusion requirements, adverse events (AEs)/serious adverse events (SAEs), deaths, and changes in laboratory parameters.

The "primary efficacy population" consisted of all randomised patients with a non-missing primary efficacy outcome. Patients were analysed "as randomised" in all efficacy analyses, and according to the treatment actually received (i.e., "as treated") in all safety analyses. The following periods were used in efficacy and safety analyses:

- main efficacy period: from the first study drug injection or the day of surgery (whichever occurred first) up to the first venogram or up to Day 10 (whichever occurred first), both days included. This period was used for primary efficacy outcome and secondary efficacy parameters;
- treatment period: from the first study drug injection up to 2 calendar days after the last study drug injection. This period was the main period for safety analyses;
- whole study period: from the first study drug injection up to Day 32. This period was used for symptomatic VTE and also for safety analyses.

A Central Independent Adjudication Committee (CIAC), whose members were unaware of treatment assignment, adjudicated efficacy and safety outcomes. Accumulated safety data were reviewed at regular intervals by an independent Data Monitoring Committee (DMC).

Exploratory analyses included baseline covariate analysis [country, gender, race, age, obesity, BMI, site of surgery, type of surgery, type of anesthesia, duration of surgery from incision up to incision closure, medical history/risk factors for VTE and baseline creatinine clearance (Clcr, calculated according to Cockroft and Gault)]. For each subgroup, point estimates and 95% CIs per treatment group were calculated, as well as 95% 2-sided CIs on the differences between the 2 treatment groups (fondaparinux sodium - dalteparin). A stepwise multiple logistic regression analysis was planned in order to test the treatment effect adjusted for the covariate prognostic factors taking into account the correlated nature of these variables.

Additional exploratory analyses were performed on the primary efficacy endpoint consisting of sensitivity analyses. These analyses considered 3 scenarios: "best case scenario" (all randomised patients without evaluation for primary endpoint were considered as "no VTE" patients); "realistic scenario" (the VTE rate for all randomised patients with a missing primary endpoint in any of the 2 groups was assumed to be the observed VTE rate) and "worst scenario" (all randomised patients without evaluation for the primary endpoint were considered as "VTE patients").
The primary efficacy outcome was further analysed according to selected concomitant medications which were reported to have a potential interaction with heparin according to the US Physicians' Desk Reference 1999.

Regarding the estimation of the *sample size*, the VTE rate in the control group was expected to be at least 7% based on previous studies in VTE prevention. The study was initially designed for a superiority analysis and a risk reduction of 40% with fondaparinux treatment was targeted. With a total of 2000 evaluable (non-missing efficacy assessment) patients, i.e. 1000 per group, the power to detect a significant difference (bilateral, α=0.05) between the dalteparin group and the fondaparinux group was greater than 75%. Thus, it was planned to randomise 2,900 patients in this study, estimating that 30% of patients would have a missing VTE evaluation.

During the conduct of the study, and prior to unblinding, as it appeared that the overall VTE rate was lower than the expected VTE rate, the Steering Committee decided to modify the study hypothesis from a 'superiority study' to a 'non-inferiority study', keeping the superiority objective in a sequential testing approach. A relative non-inferiority margin on the odds ratio (OR) of 1.7 was determined based on published literature, corresponding to a non-inferiority margin of 70% for the odds ratio reduction. Thus, the sequential procedure was as follows:

[1] BI=Number of units transfused + [pre-bleed hemoglobin (g/dl) – post-bleed hemoglobin (g/dl)

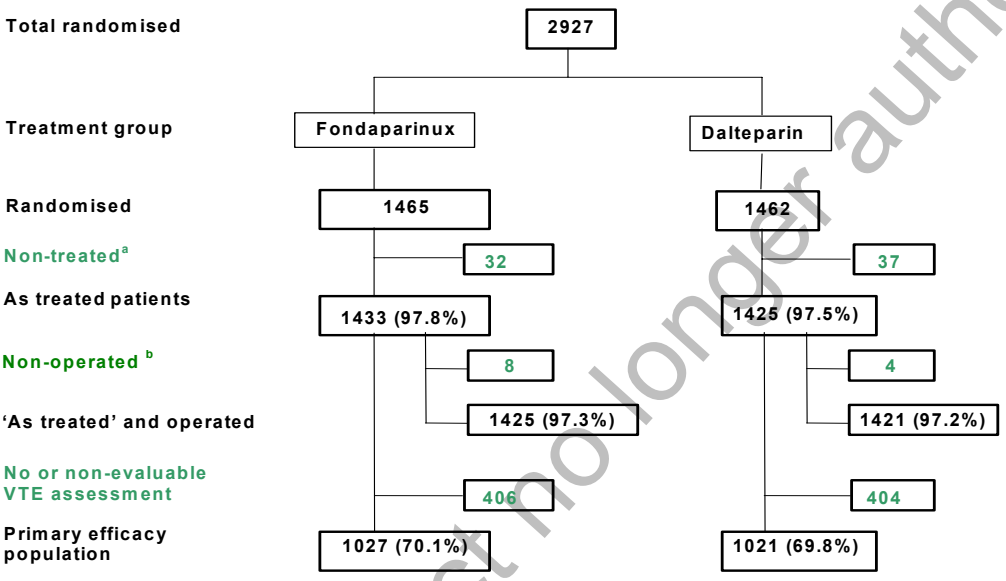
1. calculation of the odds ratio (OR) reduction (100 × (OR $_{\text{fondaparinux/dalteparin}}$ - 1)) and 95% CI for the primary efficacy endpoint. If the upper limit was < 70%, then;
2. comparison of the 2 groups using a 2-sided Fisher's exact test at the 0.05 significance level.

Point estimates and 2-sided 95% CI per treatment group were calculated as well as 2-sided 95% CIs on the relative risk (fondaparinux/dalteparin) and difference (fondaparinux – dalteparin).

Results

The study was conducted at 131 active centres in 22 countries. The following chart provides an overview of the study population flow.

Figure 2 Participant flow - Number of patients by treatment group and population.



[a] *None of the 69 non-treated patients were evaluable for the primary efficacy analysis.*
[b] *Seven patients were non-operated patients, and 5 patients were considered as non-operated (3 in the fondaparinux group and 2 in the dalteparin group) because the surgery was delayed by 7 days or more.*
Note: Percentages are calculated on the randomised population

The percentage of patients excluded from the primary efficacy analysis was similar for both treatment groups (i.e. 30%) and corresponds to the percentage anticipated by the MAH.

Table 2 Demographic data and surgical characteristics by treatment group (primary efficacy population)

Parameter		Fondaparinux (N=1027)	Dalteparin (N=1021)
Age (years)	N	1027	1021
	Mean	64.8	64.2
Age (years) [n(%)]	<65	459 (44.7 %)	496 (48.6 %)
	[65-75]	373 (36.3 %)	347 (34.0 %)
	≥75	195 (19.0 %)	178 (17.4 %)
Height (cm)	Mean	168.0	168.2
Weight (kg)	Mean	74.19	74.30
Weight (kg) [n(%)]	<50	39 (3.8 %)	39 (3.8 %)
	[50-100]	922 (90.0 %)	912 (89.4 %)
	≥100	63 (6.2 %)	69 (6.8 %)
	Missing	3	1
Body mass index (kg/m²)	Mean	26.26	26.26
	Min-Max	15.4-60.8	15.7-61.0
Obesity [n(%)][a]	Yes	222 (21.9 %)	217 (21.4 %)
	No	792 (78.1 %)	796 (78.6 %)
Gender [n(%)]	Male	575 (56.0 %)	570 (55.8 %)
	Female	452 (44.0 %)	451 (44.2 %)
Race [n(%)]	Caucasian	1001 (97.5 %)	991 (97.1 %)
	Black	11 (1.1 %)	9 (0.9 %)
	Asian/Oriental	7 (0.7 %)	8 (0.8 %)
	Other	8 (0.8 %)	13 (1.3 %)
Baseline creatinine clearance (ml/min)[n(%)]	<30	11 (1.1 %)	8 (0.8 %)
	[30-50]	131 (12.9 %)	114 (11.3 %)
	[50-80]	441 (43.4 %)	447 (44.3 %)
	≥80	433 (42.6 %)	439 (43.6 %)
	Missing	11	13
Site of surgery [n(%)]	Colonic/rectal	577 (56.2 %)	569 (55.7 %)
	Gastric	161 (15.7 %)	195 (19.1 %)
	Hepatic + Cholecystectomy + Other biliary	167 (16.3 %)	183 (17.9 %)
	Hepatic	61 (5.9 %)	56 (5.5 %)
	Cholecystectomy	110 (10.7 %)	128 (12.5 %)
	Other biliary	21 (2.0 %)	29 (2.8 %)
	Pancreatic	62 (6.0 %)	60 (5.9 %)
	Kidney	13 (1.3 %)	10 (1.0 %)
	Herniotomy	91 (8.9 %)	73 (7.1 %)
	Others	167 (16.3 %)	139 (13.6 %)
	Other intestine	89 (8.7 %)	72 (7.1 %)
	Other	88 (8.6 %)	75 (7.3 %)
Cancer surgery [n(%)]	Yes	696 (67.8 %)	712 (69.7 %)
	No	331 (32.2 %)	309 (30.3 %)
Type of anesthesia [n(%)]	General only	704 (68.5 %)	664 (65.0 %)
	Spinal/Epidural	323 (31.5 %)	357 (35.0 %)
Duration of surgery	Mean	2:46	2:46

[a] Obesity = BMI > 30 for male / BMI > 28.6 for female.
[b] Duration of surgery = Time between incision and incision closure.

The past *medical history* and/or VTE risk factors were similar for both treatment groups, with more than 73.4% of the patients with a history of neoplastic disease, and DVT/PE, COPD, CHF, prothrombic states present in 3.7%, 7.5%, 4.1%, and 0.3 % of the patients, respectively (data not shown). More than two thirds (69 %) of the patients had cancer surgery (more than half had colonic-rectal surgery), and the median surgery duration was rather long (2 hours 30 minutes), both of which could be expected to contribute to an increased VTE risk. From a safety perspective it should be noted that more than one third of patients had a spinal/epidural catheter.

The numbers of patients who received physical therapy for thromboprophylaxis (physical therapy and/or elastic stockings) was very similar in both treatment groups (around 65%).

The mean and median *exposure* was 7 days, and 97.7% and 97.6% in the fondaparinux sodium group and the dalteparin groups, respectively, received study drug for 5-9 days, as required by the protocol. The follow-up (a recorded contact after day 28) was almost complete among patients that were treated and had not died. The number of patients with active preoperative injections by type of anesthesia received is displayed in Table 3.

Table 3 Number (%) of patients according to active preoperative injections and type of anesthesia - Primary efficacy population

Patients with	**Fondaparinux (N=1027)**	**Dalteparin (N=1021)**	**Total (N=2048)**
Total patients who received an active pre-operative injection	1 (0.1 %)	684 (67.0 %)	685 (33.4 %)
- General anesthesia only	1 (0.1 %)	590 (57.8 %)	591 (28.9 %)
- Spinal/epidural anesthesia (only or mixed)	0 (0.0 %)	94 (9.2 %)	94 (4.6 %)
No active pre-operative injection	1026 (99.9 %)	337 (33.0 %)	1363 (66.6 %)
- General anesthesia only	703 (68.5 %)	74 (7.2 %)	777 (37.9 %)
- Spinal/epidural anesthesia (only or mixed)	323 (31.5 %)	263 (25.8 %)	586 (28.6 %)

A total of 33% of dalteparin patients did not receive a pre-operative injection, mainly due to the use of a catheter for spinal/epidural anesthesia and/or analgesia (25.8%), and therefore, according to the approved dalteparin labelling and as pre-specified in the protocol, no preoperative injection was given. The omission of the pre-operative dalteparin dose is considered consistent with current clinical practice, in which the use of spinal anaesthesia and/or epidural catheters in abdominal surgery is common. For the few remaining patients (7.2%) it was due to spinal/epidural anesthesia being planned at first but ultimately not being performed, or to the preoperative injection being mistakenly forgotten.

Efficacy

The results for the *primary endpoint* and its individual components are given in the following table.

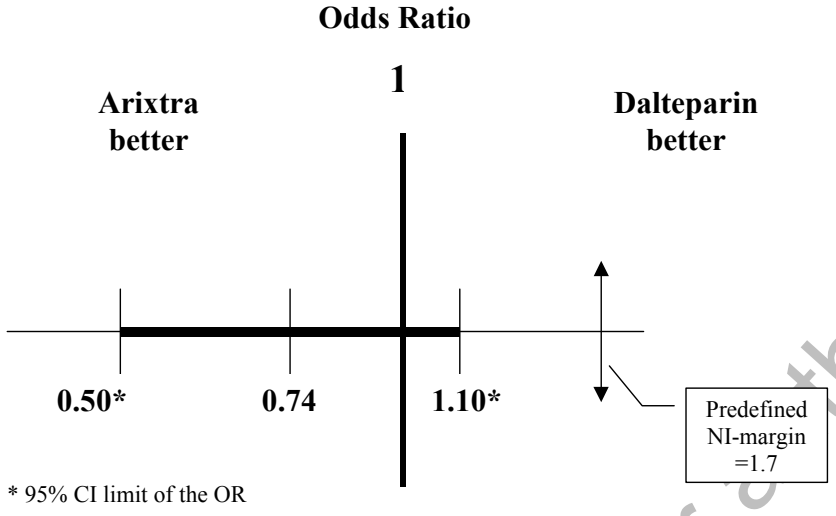
Table 4 Number (%) of patients with adjudicated VTE – Primary efficacy population

	Fondaparinux	**Dalteparin**	**Odds Ratio Reduction [CI]**
Primary efficacy outcome			
VTE	47/1027 (4.6%)	62/1021 (6.1%)	-25.8% [-49.7, 9.5]
Components of the primary efficacy outcome (secondary analysis)			
Any DVT	43/1024 (4.2 %)	59 / 1018 (5.8 %)	ND
Any proximal DVT	5 / 1076 (0.5 %)	5 / 1077 (0.5 %)	ND
Distal DVT only	40 / 1025 (3.9 %)	54 / 1022 (5.3 %)	ND
Symptomatic VTE	6 / 1465 (0.4%)	5 / 1462 (0.3%)	ND
Symptomatic DVT	2	2	ND
Non-fatal PE	2	0	ND
Fatal PE	3	3	ND

Two patients in the fondaparinux sodium group had distal DVT only in one leg and a proximal DVT in the other leg

Fondaparinux nominally reduced the risk of VTE in patients undergoing high-risk abdominal surgery, from 6.1% (dalteparin group) to 4.6% (fondaparinux group), resulting in an ORR [CI] of -25.8% [-49.7%, 9.5%] in favour of fondaparinux. The CI upper limit was much lower than the (very liberal) prespecified 70% limit, allowing the conclusion that fondaparinux is non-inferior to dalteparin

according to the study protocol criteria.This difference was however not statistically significant and mainly due to a reduction of asymptomatic distal DVT.



Regarding *ancillary analyses* of the primary endpoint, no statistically significant heterogeneity of treatment effect was demonstrated for any covariate analysed except for obesity (22% of the patient population; p=0.021) and cancer surgery (69% of the patient population; p=0.022). In general, VTE rates remained numerically lower in the fondaparinux group compared with dalteparin when treatment effect was adjusted on the covariate prognostic factors (especially in old age, moderate renal impairment and cancer surgery), with the exception of presence of obesity. As expected, overall, risk was increased with cancer, with increasing age, with increasing BMI, and with increasing duration of surgery. The adjusted percentage ORR for the treatment effect was –31.2% [-54.1%, 3.0%].

Table 5 - Relevant demographic data and surgical characteristics by treatment group

		Fondaparinux (N=1027)				Dalteparin (N=1021)			
			VTE				VTE		
	Covariate	**N**	**n**	**%**	**95% CI**	**N**	**n**	**%**	**95% CI**
Obesity[a]									
	Yes	222	19	8.6	[5.2;13.0]	217	13	6.0	[3.2;10.0]
	No	792	26	3.3	[2.2;4.8]	796	48	6.0	[4.5;7.9]
	Missing	13	2	15.4	[1.9;45.4]	8	1	12.5	[0.3;52.7]
Baseline Creatinine clearance									
	<30 ml/min	11	0	0.0	[0.0;28.5]	8	2	25.0	[3.2;65.1]
	30 – 50 ml/min	131	6	4.6	[1.7;9.7]	114	13	11.4	[6.2;18.7]
	50 - 80 ml/min	441	18	4.1	[2.4;6.4]	447	27	6.0	[4.0;8.7]
	≥80 ml/min	433	23	5.3	[3.4;7.9]	439	20	4.6	[2.8;6.9]
	Missing	11	0	0.0	[0.0;28.5]	13	0	0.0	[0.0;24.7]
Cancer surgery									
	Yes	696	33	4.7	[3.3;6.6]	712	55	7.7	[5.9;9.9]
	ORR 40.5% [-61.9%; -7.2%] p= 0.022[b]								
	No	331	14	4.2	[2.3;7.0]	309	7	2.3	[0.9;4.6]

[a] Obesity = BMI >30 for male / BMI >28.6 for female.
[b] the p value is not adjusted for multiplicity analysis

The results in the above table suggest that fondaparinux is more effective than dalteparin in the large cancer surgery subgroup, which was not the case in the overall PEGASUS population or in the non-cancer surgery subgroup. The incidence of VTE in the cancer surgery patients treated with dalteparin (7.7%) was broadly comparable to that observed in previous studies. Importantly, fondaparinux was superior to dalteparin in these patients, providing a clinically relevant and statistically significant

reduction of VTE (4.7%), with a ORR [95% CI] relative to dalteparin of 40.5% [-61.9%, -7.2%], p = 0.02, p value not adjusted for multiplicity.

Pre-specified sensitivity analyses were performed on all randomised patients. In all 3 scenarios considered the non-inferiority criterion on the primary efficacy endpoint was maintained. Further to a request from CHMP, the MAH conducted further sensitivity analyses assigning the best possible outcome to missing values in the control group and the worst possible outcome to missing values in the experimental group, and vice-versa (i.e. as per PtC on missing data, CPMP/EWP/1776/99). However, given the large relative difference between the proportion of patients excluded due to a missing VTE evaluation (i.e. 30%) and the low VTE rate observed in both groups (4.6% for fondaparinux versus 6.1% for dalteparin), little additional value was gained from these additional sensitivity analyses.

Finally, no notable inconsistencies of the results were observed with regard to the primary efficacy end-point in the other subgroups (demographic subgroups, pre-existing disease categories, other risk factor groups, study centre or country). The numerical difference between treatments observed in the obese subgroup (22 % of the PEGASUS population) does not reach statistical significance.

As regards *secondary enpoints*, the rates of symptomatic VTE were similar between treatment groups up to the qualifying assessment and up to Day 32. During the whole study period, numerically fewer PEs were observed in the fondaparinux sodium group (9 including 4 non-fatal, 5 fatal) compared with the dalteparin group (11, including 9 non-fatal and 2 fatal respectively). The low number of events does not allow any conclusions.

Table 6 Number (%) of patients with symptomatic VTE up to the qualifying VTE assessment and up to Day 32 – All randomised patients

		Fondaparinux (N=1465)	**Dalteparin (N=1462)**
Patients with symptomatic VTE up to the qualifying VTE assessment			
VTE	n (%) 95% CI	6 (0.4 %) [0.2 ;0.9]	5 (0.3 %) [0.1 ;0.8]
DVT	n (%)	2 (0.1 %)	2 (0.1 %)
Non-fatal PE	n (%)	2 (0.1 %)	0 (0.0 %)
Fatal PE	n (%)	3 (0.2 %)	3 (0.2 %)
up to Day 32			
VTE	n (%) 95% CI	12 (0.8 %) [0.4 ;1.4]	14 (1.0 %) [0.5 ;1.6]
DVT	n (%)	4 (0.3 %)	4 (0.3 %)
Non-fatal PE	n (%)	4 (0.3 %)	2 (0.1 %)
Fatal PE	n (%)	5 (0.3 %)	9 (0.6 %)
VTE and/or all death[1]	n (%)	*47 (3.2%)*	*59 (4.0%)*

[1] *Provided in response to CHMP List of Questions*

Fatal PE represents a great proportion of the symptomatic VTE events. Of the 14 reported, 13 occurred in patients with cancer (rate of 0.67%). The repartition in both groups is as follows: 0.41% in the fondaparinux group (4/954) and 0.91% in the dalteparin group. This number of fatal PE is surprisingly high and is close to the rate reported in elderly patients undergoing hip fracture surgery in the PENTHIFRA study (0.9%) rather than the rate observed in the ENOXAN study in patients with cancer and additional risk factors undergoing digestive surgery (0.2%) - the rate of other symptomatic VTE events is quide low and remains similar to that observed in digestive surgery studies.

The numbers of patients receiving *curative treatment and prolonged prophylaxis of VTE* (heparin/LMWH or vitamin K antagonists) during the follow-up period were similar between the 2 treatment groups (36.9% fondaparinux vs. 37.9% dalteparin). It should be noted that the decision to initiate antithrombotic prophylaxis therapy following study drug was based on clinical judgement and independent of knowledge of the treatment allocation.

Finally, further to a request from CHMP, the MAH reanalysed the data to address some of the CHMP concerns. The results of the most relevant reanalyses are shown below

Table 7 Efficacy results analysed according to the per protocol population, as required in the PtC on switching between superiority and non-inferiority (CPMP/EWP/482/99).

Patients with VTE	Fondaparinux	Dalteparin	% Odds reduction Fondaparinux
Primary efficacy outcome PP Population n (%)	**(N=917)** 40 (4.4 %)	**(N=822)** 48 (5.8 %)	-26.5 [-52.2 ; 13.1]
Symptomatic VTE at Day 32 PP Population n (%)	**(N=1230)** 6 (0.5 %)	**(N=1146)** 11 (1.0 %)	-49.4 [-81.4; 37.2]
Symptomatic VTE/All Deaths at Day 32 PP Population n (%)	**(N=1230)** 34 (2.8 %)	**(N=1146)** 47 (4.1 %)	-33.5 [-57.6; 4.1]

The incidence of the primary endpoint in the PP population was very similar for both treatment groups to that observed for the "efficacy evaluable population" (see Table **), the observed odds reduction (-26.5%) is very similar to that of the primary analysis (-25.8%), and the 95%CI for the odds reduction in the PP population was consistent with that in the efficacy evaluable population, supporting the conclusion of non-inferiority to dalteparin. The results of the PP analysis demonstrate that fondaparinux preserves at least 90% (absolute effect retained 124% [95%CI: 90%, 159%]) of the historical LMWH/UFH benefit over placebo according to the Hasselblad method (Hasselblad and Kong, 2001).

Below are the results using the CHMP-recommended endpoint for VTE assessment in non-inferiority studies. This analysis is extremely underpowered as the number of qualifying events is dramatically reduced when asymptomatic distal DVT (representing the majority of venographic events) is not included in the composite endpoint and the study was not designed to evaluate non-inferiority under this restrictive endpoint definition. In both populations the incidence of events was <1% with the 95% CI for the odds ratio for the difference between the treatments being extremely wide and and do not allow to conclude that non-inferiority is demonstrated with regard to this composite endpoint.

Table 8 Effect of Treatment on the CHMP Recommended Endpoint for VTE assessment in non-inferiority studies (PtC)

Proximal DVT and/or PE	Fondaparinux	Dalteparin	% Odds Reduction Fondaparinux [95%CI]
Efficacy Evaluable Population	9/1080 (0.8%)	8/1080 (0.7%)	12.6 [-56.7, 193.0]
PP Population	6/961 (0.6%)	5/874 (0.6%)	9.2 [-66.8; 259.1]
Proximal DVT and/or PE and/or Death Per Protocol Population	17/972 (1.7 %)	22/891 (2.5 %)	-29.7 [-62.9 ; 33.3]

As recommended in the CHMP PtC document, the revised endpoint was also analysed with the inclusion of all deaths that occurred up to the qualifying VTE assessment. The inclusion of all deaths has the effect of increasing the event rate, with the 95%CI for the treatment effect becoming narrower. Based on this endpoint the odds reduction and the 95% CI are consistent with that seen for the protocol specified primary endpoint, with a trend favouring fondaparinux.

Safety

Most patients (92-93%) in both treatment groups received study drug for 5-9 days, as per the protocol.

Table 9 Duration of exposure – "As treated" patients

	Fondaparinux (N=1433)	**Dalteparin (N=1425)**
Number of days on treatment[a]		
N	1433	1424
Median	7	7
Mean (SD)	6.8 (1.8)	6.9 (1.8)
Min-Max	1-10	1-10
Duration [n(%)]		
< 5 days	104 (7.3 %)	89 (6.3 %)
Between 5 to 9 days	1319 (92.0 %)	1323 (92.9 %)
> 9 days	10 (0.7 %)	12 (0.8 %)
Missing	0	1

[a] From first to last day of study drug treatment (active or not) ignoring temporary interruptions.

Bleedings

Most MBs occurred at the surgical site. During the treatment period the rate of MB was higher, though not statistically significant, in the fondaparinux group compared with dalteparin : 3.4% [95 %CI 2.5;4.5]vs 2.4% [95 % CI 1.7;3.3]. During the whole study period, the rate of MB was statistically significant higher in the fondaparinux group compared with dalteparin : 4.3% [95 % CI 3.3 ; 5.4] vs 2.7% [95 % CI 2.0.;3.7], absolute difference 1.5 [95 % CI 0.2 ; 2.9] p=0.032. During the treatment period, there were 2 fatal bleeds in each treatment group; during the follow-up period, no fatal bleeds occurred in the fondaparinux group, whereas 4 fatal bleeds were recorded in the dalteparin group (3 not related and 1 possibly related according to the investigators). No bleeding into a critical organ was recorded in either treatment group during the complete study time.

Table 10 Number (%) of patients with adjudicated bleeding events during the treatment period

Patients With		**Fondaparinux (N=1433)**	**Dalteparin (N=1425)**
Major bleeding	n (%) 95% CI	49 (3.4 %) [2.5;4.5]	34 (2.4 %) [1.7;3.3]
Minor bleeding only	n (%) 95% CI	31 (2.2 %) [1.5;3.1]	23 (1.6 %) [1.0;2.4]
Any bleeding	n (%) 95% CI	80 (5.6 %) [4.5;6.9]	57 (4.0 %) [3.0;5.2]

Table 11 Number (%) of patients with adjudicated bleeding events during the whole study period

Patients With		**Fondaparinux (N=1433)**	**Dalteparin (N=1425)**
Major bleeding	n (%) 95% CI	61 (4.3 %) [3.3;5.4]	39 (2.7 %) [2.0; 3.7]
Minor bleeding only	n (%) 95% CI	34 (2.4 %) [1.6;3.3]	24 (1.7 %) [1.1;2.5]
Any bleeding	n (%) 95% CI	95 (6.6 %) [5.4;8.0]	63(4.4 %) [3.4;5.6]

There was no significant heterogeneity between treatment groups across subcategories of the various covariates considered, although there was a general tendency to increased bleeding risk in patients with impaired renal function, and also with increasing age (data not shown), as noted earlier in the MOSLL studies. This probably reflects a combination of the well-known generally increased bleeding risk in these patients and an increased exposure (both drugs are dependent on renal function for their elimination). No significant increase in the percentage of patients experiencing major bleedings was

observed in cancer surgery patients. The observed increased bleeding incidence in patients undergoing surgery under general anaesthesia probably reflects a selection of patients with increased bleeding risk.

Table 12 Number (%) of patients with adjudicated major bleeding events during the treatment period according to various baseline covariates – "As treated" patients

	Fondaparinux (N=1433)				Dalteparin (N=1425)			
			Major Bleeding				Major Bleeding	
Covariate	**N**	**n**	**%**	**95% CI**	**N**	**n**	**%**	**95% CI**
Baseline Cl_{cr}								
<30 mL/min	14	1	7.1	[0.2;33.9]	14	2	14.3	[1.8;42.8]
[30-50[mL/min	179	12	6.7	[3.5;11.4]	168	4	2.4	[0.7;6.0]
[50-80[mL/min	613	22	3.6	[2.3;5.4]	613	15	2.4	[1.4;4.0]
≥80 mL/min	606	13	2.1	[1.1;3.6]	611	12	2.0	[1.0;3.4]
Missing	21	1	4.8	[0.1;23.8]	19	1	5.3	[0.1;26.0]
Type of anesthesia								
General only	959	41	4.3	[3.1;5.8]	924	27	2.9	[1.9;4.2]
Spinal/epidural (only or mixed)	466	8	1.7	[0.7;3.4]	497	7	1.4	[0.6;2.9]
Cancer surgery								
Yes	954	32	3.4	[2.3;4.7]	987	25	2.5	[1.6;3.7]
No	479	17	3.5	[2.1;5.6]	438	9	2.1	[0.9;3.9]
Duration of surgery [b,c]								
<Median [d]	696	23	3.3	[2.1;4.9]	682	16	2.3	[1.3;3.8]
≥Median	727	26	3.6	[2.3;5.2]	738	18	2.4	[1.5;3.8]
Missing	2	0	0.0	[0.0;84.2]	1	0	0.0	[0.0;97.5]

[a] Obesity = BMI >30 for males / BMI >28.6 for females.

[b] Patients for whom the surgery was delayed by 7 days or more and having received only pre-operative study drug were not considered.

[c] From incision up to incision closure.

[d] Median for duration of surgery was 2:30 hours.

As previously observed in the MOSLL studies, there was a tendency for an increased risk for MBs when the first fondaparinux injection was administered < 6 hours after surgery, as compared to ≥ 6 hours (3.4 and 2.8%, respectively).

Table 13 Number (%) of patients with adjudicated MB events during the treatment period and whole study period by adjudication criterion

	Bleeding site	During the Treatment Period[a]		During the Whole Study Period[b]	
		Fonda-parinux (N=1433)	Dalteparin (N=1425)	Fonda-parinux (N=1433)	Dalteparin (N=1425)
Any major bleeding		49 (3.4 %)	34 (2.4 %)	61 (4.3 %)	39 (2.7 %)
Fatal bleeding		2 (0.1 %)	2 (0.1 %)	2 (0.1 %)	6 (0.4 %)
Non-fatal bleeding into critical site		0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Non-fatal bleeding leading to (re)-operation		19 (1.3 %)	12 (0.8 %)	23 (1.6 %)	12 (0.8 %)
	Surgical	17 (1.2 %)	12 (0.8 %)	19 (1.3 %)	12 (0.8 %)
	Non-surgical	2 (0.1 %)	0 (0.0 %)	4 (0.3 %)	0 (0.0 %)
Non-fatal bleeding leading to intervention other than (re)-operation		10 (0.7 %)	2 (0.1 %)	14 (1.0 %)	3 (0.2 %)
	Surgical	10 (0.7 %)	2 (0.1 %)	14 (1.0 %)	3 (0.2 %)
	Non-surgical	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Bleeding index ≥2.0		18 (1.3 %)	18 (1.3 %)	22 (1.5 %)	18 (1.3 %)
	Surgical	11 (0.8 %)	12 (0.8 %)	12 (0.8 %)	13 (0.9 %)
	Non-surgical	7 (0.5 %)	7 (0.5 %)	10 (0.7 %)	6 (0.4 %)

[a] from first study drug injection up to 2 calendar days after the last injection
[b] from first study drug injection to Day 32

Fatal bleedings or bleedings into critical sites were not more common in the fondaparinux group, which provides some reassurance regarding the safety of fondaparinux in this setting.

The number of transfused patients (whole blood or packed red blood cells) was similar between the 2 treatment groups. There were no significant differences between the 2 groups in the percentage of patients with Hb <8 g/dl and/or a decrease in Hb ≥2 g/dl during the treatment period.

Adverse Events
Despite a slight, non-significant, trend for an increased AE incidence in the fondaparinux group, the number of patients experiencing at least one AE, SAE or AE leading to study drug discontinuation were similar between the 2 treatment groups during the treatment period and the whole study period. An opposite trend for overall mortality was also noted.

Table 14 Number (%) of patients with at least one (S)AE during the whole study period up to Day 32

	Fondaparinux (N=1433)	Dalteparin (N=1425)
Patients with any (S)AE	703 (49.1 %)	668 (46.9 %)
Patients with any drug-related AE	89 (6.2 %)	64 (4.5 %)
Patients with any AE of severe intensity	152 (10.6 %)	141 (9.9 %)
Patients with SAE	261 (18.2 %)	243 (17.1 %)
Patients with drug-related SAE	31 (2.2 %)	19 (1.3 %)
Patients with treatment discontinuation due to (S)AE	62 (4.3%)	57 (4.0%)
Deaths [a]	40 (2.8 %)	55 (3.9 %)

[a] All deaths including fatal PE (which were not reported as SAE).

Table 15 Number (%) of patients with AEs during treatment period by WHO organ class and preferred term with incidence >2% in any treatment group

WHO organ class preferred term	Fondaparinux (N = 1433)	Dalteparin (N = 1425)
Any event	607 (42.4%)	583 (40.9%)
Gastro-intestinal system disorders	135 (9.4%)	127 (8.9%)
Platelet,bleeding & clotting disorders	120 (8.4%)	106 (7.4%)
Resistance mechanism disorders	102 (7.1%)	98 (6.9%)
Respiratory system disorders	95 (6.6%)	79 (5.5%)
Body as a whole - general disorders	88 (6.1%)	95 (6.7%)
Secondary terms	65 (4.5%)	62 (4.4%)
Cardiovascular disorders, general	59 (4.1%)	70 (4.9%)
Urinary system disorders	54 (3.8%)	59 (4.1%)
Skin and appendages disorders	49 (3.4%)	38 (2.7%)
Central & peripheral nervous system disorders	42 (2.9%)	50 (3.5%)
Heart rate and rhythm disorders	42 (2.9%)	42 (2.9%)
Metabolic and nutritional disorders	37 (2.6%)	43 (3.0%)
Red blood cell disorders	37 (2.6%)	30 (2.1%)
Psychiatric disorders	33 (2.3%)	37 (2.6%)
Musculo-skeletal system disorders	13 (0.9%)	11 (0.8%)
Liver and biliary system disorders	10 (0.7%)	7 (0.5%)
Myo endo pericardial & valve disorders	10 (0.7%)	11 (0.8%)
Autonomic nervous system disorders	6 (0.4%)	7 (0.5%)
Application site disorders	5 (0.3%)	6 (0.4%)
Reproductive disorders, male	3 (0.2%)	1 (0.1%)
Vascular (extracardiac) disorders	3 (0.2%)	5 (0.4%)
Vision disorders	3 (0.2%)	4 (0.3%)
White cell and res disorders	3 (0.2%)	7 (0.5%)
Reproductive disorders, female	2 (0.1%)	0 (0.0%)
Collagen disorders	1 (0.1%)	0 (0.0%)
Endocrine disorders	0 (0.0%)	1 (0.1%)
Foetal disorders	0 (0.0%)	2 (0.1%)

The slightly higher incidence of AEs within the platelet, bleeding & clotting disorders in the fondaparinux group was mainly due to the increased bleeding rate. The slightly higher incidence in respiratory system disorders in the fondaparinux group was largely due to a higher number of patients with pneumonia, which may be a chance finding.

Deaths

Table 16 No. of patients who died during the treatment period and whole study period, by adjudication criteria

	Fondaparinux 2.5 mg (N = 1433)	Dalteparin (N = 1425)
During treatment period		
Fatal PE	2 (0.1 %)	3 (0.2 %)
Haemorrhagic death	2 (0.1 %)	2 (0.1 %)
Not associated with VTE or bleeding	11 (0.8 %)	15 (1.1 %)
Total	15 (1.0 %)	20 (1.4 %)
During whole study period		
Fatal PE	5 (0.3 %)	9 (0.6 %)
Haemorrhagic death	2 (0.1 %)	6 (0.4 %)
Not associated with VTE or bleeding	33 (2.3 %)	40 (2.8 %)
Total	40 (2.8 %)	55 (3.9 %)

The numerically lower number of deaths not associated with VTE or bleeding in the fondaparinux group may have been a chance finding. However, due to the low event rate and the few observations, no firm conclusions can be drawn from these data.

Regarding *laboratory findings*, no difference was observed between the fondaparinux group and the active control group with regard to platelet counts in both PEGASUS and the pooled MOSLL studies, nor were notable differences observed between results from PEGASUS and the pooled MOSLL studies. Assessment of antiplatelet antibodies was mandatory only in the case of thrombocytopenia.

No cases of HIT were observed. No vital signs, physical examination or electrocardiogram data were specifically collected.

Safety in special populations
As discussed previously, increased age and/or decreased Clcr appeared to increase the risk of bleeding.

Discussion

Efficacy
The PEGASUS study, pivotal to this application, has demonstrated that fondaparinux 2.5 mg is non-inferior but not superior to dalteparin with regard to total VTE detected by venographic surveillance , there was a trend for a possible superior efficacy, but the difference was not significant.. However, the numerically reduced incidence of total VTE in the fondaparinux group is almost exclusively due to a reduction of asymptomatic distal thrombi, which probably reflects in part the relatively high proportion of this component of the composite end-point. The rate of proximal DVT and symptomatic VTE was very low. The difference observed for the primary endpoint is not accompanied by any reduction in the more clinically relevant parameters of proximal DVT or symptomatic VTE, and this has been reflected in section 5.1 of the SPC.

As detailed earlier in this report, PEGASUS was initially designed as a superiority trial vs. dalteparin, and hence the choice of primary endpoint (i.e. total VTE including venographically detected asymptomatic distal DVTs). Due to the low VTE event rate, and prior to unblinding, the study hypothesis from changed to a "non-inferiority study". Regarding this switch to "non-inferiority", the CHMP noted a number of shortcomings with respect to the trial design. The pre-specified non-inferiority margin chosen by the company is highly questionable (70%) as it can hardly be accepted from a clinical perspective. Nonetheless, the upper limit of the CI of the ORR is well below the predefined non-inferiority margin, substantiating the conclusion that fondaparinux is clinically non-inferior to dalteparin for the chosen primary end-point. Support for this conclusion is also gained from the previously evaluated extensive development programme in MOSLL.

Secondly, for non-inferiority studies in this therapeutic area the CHMP recommends a composite end-point of proximal DVT and/or symptomatic VTE ("Points to Consider on clinical investigation of medicinal products for prophylaxis of intra- and post- operative venous thromboembolic risk"). A *post-hoc* analysis on this recommended composite endpoint (excluding distal DVT) shows very low event rates with extremely wide CIs in both groups, effectively precluding the demonstration of non-inferiority with regard to dalteparin for this revised endpoint. The MAH argues, and the CHMP essentially agrees, that the use of the more clinically relevant endpoint of proximal DVT and/or symptomatic VTE in a setting with such low event rates would require a very large study population and such a study would probably not be feasible. Thus, it remains difficult to estimate the size of clinically relevant differences from possible differences in the chosen primary end-point as it is dominated by asymptomatic events. Nevertheless, the different sensitivity analyses performed and the analyses on the per protocol (PP) populations, considered to be the more conservative approach for non-inferiority analyses and in line with CHMP guidance, provide support for the robustness of the primary efficacy analysis. Indeed, the results for the pre-specified primary endpoint as well as for symptomatic VTE and symptomatic VTE/all deaths at Day 32 for the PP population, provide reassurance that the trend favouring fondaparinux and the conclusion of non-inferiority to dalteparin based on the primary endpoint is maintained. Furthermore, in a retrospective analysis of the trial results in the large subpopulation (69%) undergoing cancer surgery a statistically significant reduction of total VTE rates was noted in the fondaparinux group, as mentioned in section 5.1 of the SPC.

The MAH has proposed a broad indication; however, PEGASUS targeted patients with high risk of VTE, quite similar to the "high risk" definition of the American College of Chest Physicians (ACCP) consensus of 2004. Moreover, in the subgroup of patients undergoing cancer surgery, who are at a higher risk of thromboembolic complications, fondaparinux was superior to dalteparin, providing a statistically significant reduction of the primary composite endpoint. Consequently, the CHMP has restricted the therapeutic indication to the use in patients who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery. Lastly,

patients undergoing urological (except kidney) or gynecological surgery, laparoscopic surgery and vascular were excluded from the study. This has been reflected in section 5.1.

Finally, the 1.5 mg dose was regrettably not tested in the PEGASUS trial. While the CHMP consider this regrettable, the company proposes, and the CHMP agrees, that the dosing recommendations for renally impaired patients in the setting of abdominal surgery at high risk of VTE should remain the same as are currently recommended for MOSLL and medical patients, pending the assessment of an overview of the clinical experience with regard to efficacy and bleeding incidence in renally impaired patients specifically requested by CHMP as a Follow up Measure.

Safety

There were more major bleedings on fondaparinux than on dalteparin during the treatment period. The difference in major bleedings became statistically significant during the whole study period. The bleedings observed after the acute treatment phase may very well be due to delayed clinical manifestation of bleedings that have started during or shortly after treatment. There is also a numerically increased incidence of minor bleedings in the fondaparinux group during the treatment period and the whole study period. As expected, most major bleedings occurred at the surgical site and were associated with a tendency to an increased need of re-surgery. In this respect, the MAH suggests that the clinical relevance of such bleedings may be considered minor, but such major bleedings, e.g. when occurring in patients with ischaemic areas in the heart or brain, or when necessitating blood transfusions and/o reoperation, cannot be considered to be of minor importance. Similar observations of an increased bleeding tendency were noted in the MOSSL prevention studies, where the same fondaparinux regimen was compared with enoxaparin. Reassuringly, in PEGASUS there was no evidence to suggest any difference for the clinically relevant endpoints of fatal bleeds, bleeds into critical organs, or the number of transfusions, and the incidence of major bleeding was comparable to that in the pre-operative randomisation MOSLL studies. The patient subgroups who are at an increased risk of bleeding are well characterised (patients with some degree of renal dysfunction and the elderly) , were similar in PEGASUS and the MOSLL studies and are adequately described in the SPC.

No other safety concerns are identified in the PEGASUS study. A slight, non-significant, trend for an increased AE incidence in the fondaparinux group was observed, but an opposite trend for overall mortality is also noted.

Conclusions and Benefit/ Risk Assessment

The conclusion from the PEGASUS trial with regard to anti-thrombotic efficacy, taking also the overall experience with fondaparinux into account (i.e. studies in MOSLL and medical patients), is that fondaparinux is essentially as least as effective as the dalteparin regimen in the prevention of surveillance VTE. The significantly lower VTE rates among the fondaparinux-treated patients that underwent cancer surgery as compared to the dalteparin patients support the conclusion that fondaparinux 2.5 mg may be somewhat more effective than 5000 IU dalteparin in patient undergoing abdominal cancer surgery. Such a difference, if real, can be expected to be more easily detected in patients with an increased VTE risk and cancer surgery patients constitutes such a major risk group.

Not unexpectedly, the tendency for increased efficacy is accompanied by a clear trend for increased major bleeding rates, but the rate of fatal bleedings or bleedings into critical sites was not increased as compared with dalteparin. Indeed, the rather extensive overall experience from prophylaxis with fondaparinux in high risk patients (undergoing MOSLL, abdominal surgery or being immobilised due to medical illness) indicates that the risk for fatal bleedings or bleedings into critical sites may not be more common than during prophylaxis with the approved alternatives or, alternatively, if an increased risk exists, it appears to be so small that it is difficult to detect also in clinical studies of considerable size (cf. the results from the MOSLL programme). However, as the preliminary results from the APOLLO trial (not included and not discussed in this report) may indicate, where an increase in the incidence of haemorrhagic deaths approaching 0.5% as compared to placebo was observed, prophylaxis with Quixidar in low risk patients could be associated with a negative benefit/risk balance. Indeed, when using a drug in prophylaxis in abdominal surgery, the treating physician should assess the baseline risk of VTE event and the benefit/risk ratio in terms of reduction of clinically significant VTE events versus safety concerns in terms of clinically significant bleedings. Bearing this in mind,

the CHMP has restricted the therapeutic indication to the use in patients undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery.