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Product name: **Arixtra**
Procedure No. **EMEA/H/C/403/II/10**

SCIENTIFIC DISCUSSION

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1. Introduction

This type II variation was submitted to request a new indication for the of 2.5 and 1.5 mg doses, namely the "prevention of VTE in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness". The application is supported by a single pivotal study, ARTEMIS/63129, clinical summaries of the key studies in MOSLL and PMS data (cut-off date of 31 August 2003).

1.1 Rationale for the proposed change

The incidence of confirmed asymptomatic venous thromboembolism (VTE) in general medical patients has been reported to be 10-25% in surveillance studies. There are several randomised controlled trials showing that conventional unfractionated heparin (UFH), as well as low molecular weight heparin (LMWH), can significantly reduce the incidence of VTE diagnosed with objective methods. The clinical relevance of these often non-symptomatic thrombi is partly controversial. The incidence of death from PE is 4-11% in autopsy studies of hospital in-patients, the majority of who are non-surgical patients. Various surveys have shown that systematic application of thromboprophylaxis in medical patients remains limited.

A recent systematic review of the field of VTE by The Swedish Council on Technology Assessment in Health Care (2002; "Prevention, Diagnosis, and Treatment of Venous Thromboembolism") evaluated and synthesised approximately 1,300 scientific studies and developed conclusions based on the following 4-grade scale:

Grade 1: Strong scientific evidence (for the conclusions).
Grade 2: Moderate scientific evidence.
Grade 3: Weak scientific evidence.
Grade 4: Insufficient evidence, including consensus of experts or completely lacking scientific base

The results for prophylaxis and treatment in medical conditions such as congestive heart failure, chronic obstructive lung disease and infections were the following:

- Both heparin agents reduce the risk for VTE in severely ill internal medicine patients (Grade 1).
- UFH does not reduce the risk for fatal PE (Grade 2)
- Neither LMWH nor UFH reduce mortality in severely ill internal medicine patients (Grade 3).
- The scientific evidence is insufficient for assessing whether they have an effect on symptomatic DVT (Grade 4).

The efficacy and safety of thromboprophylaxis in medical patients have already been demonstrated for two low molecular weight heparins. The MEDENOX and PREVENT trials provided, as single pivotal studies, adequate evidence of thromboprophylaxis with enoxaparin and dalteparin, respectively, in this indication. The fondaparinux ARTEMIS study is similar in design, conduct and size to the MEDENOX study.

2. Clinical aspects.

Artemis trial Methods

Artemis was a multicentre, multinational, randomised, double blind, placebo-controlled trial in patients at risk for thromboembolic complications due to restricted mobility during acute illness. Patients were randomly assigned to receive once-daily SC injections of either 2.5 mg fondaparinux or placebo. Treatment was scheduled to continue until Day 6 to 14.

Inclusion criteria were age ≥ 60 years, expected bed rest of at least 4 days and hospitalisation due to congestive heart failure New York Heart Association (NYHA) class III/IV, and/or acute respiratory illness in the presence of chronic lung disease, and/or acute infectious or inflammatory disease. Patients were examined for DVT by routine bilateral ascending venography of the legs between Day 6 and 15 (within one day after stopping study treatment), or earlier if DVT was clinically suspected. The exclusion criteria were consistent with those used in the MOSLL studies and were mainly related to a

known bleeding risk or difficulties to perform venography. In addition, patients for whom anticoagulant therapy was indicated due to a coexisting condition were to be excluded.

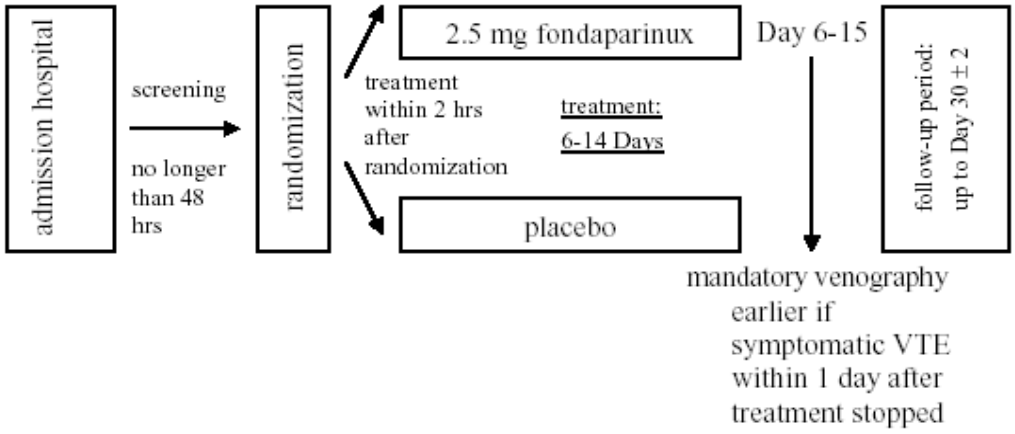
The *primary efficacy endpoint* was VTE recorded up to Day 15 or up to the first venogram, whichever came first, and defined as a composite of the following:

Venogram positive for DVT,
Symptomatic DVT,
Non-fatal PE,
Fatal PE (including death without another plausible cause).

Secondary efficacy outcomes were the separate components of the primary efficacy outcome during the same time period: any DVT, any proximal DVT, distal only DVT and symptomatic VTE (DVT, non-fatal PE or fatal PE). Additional efficacy outcomes were symptomatic VTE up to Day 32 and initiation of antithrombotic curative treatment based on local VTE assessments.

The study design is illustrated in Figure (9.1) 1.

Figure (9.1) 1 - Study Design



A venogram had to be performed within one day after stopping study treatment on Day 6-15, but earlier in case of symptomatic VTE or if the treatment was stopped prematurely. Three committees, blinded to treatment allocation, were formed to monitor different aspects of the study and adjudicate the primary efficacy outcome and the primary safety outcome (major bleedings).

Patients were examined for DVT by routine bilateral ascending venography of the legs between Day 6 and 15 (within 1 day after stopping study treatment), or earlier if DVT was clinically suspected. Clinically suspected VTE had to be confirmed by objective tests (i.e. venography for suspected DVT; lung scanning, pulmonary angiography or helical computed tomography for suspected PE). Suspected fatal PE had to be confirmed (if possible) by autopsy. Patients were to be followed-up at Day 30±2.

The primary efficacy analysis was performed on all randomised patients with a non-missing primary efficacy outcome during the primary efficacy period (from the day of first study drug injection, or randomisation for randomised but non-treated patients, up to the first venogram or up to Day 15, whichever came first).

A 10-14% rate of VTE in the placebo group was assumed based on the MEDENOX study (14.9% placebo VTE rate). The sample size was calculated using a 5% two-sided type I error, a power of 85%, and an assumed risk reduction of 60%. Based on an expected 30% of patients with an inadequate or no venogram, at least 800 patients were included in the trial.

The *analysis* of the primary efficacy outcome was the comparison of the two groups (fondaparinux - placebo) using a 2-sided Fisher's exact test at an error level of 5%. Point estimates and 2-sided 95%

confidence intervals (CIs) (binomial method) per treatment group were calculated as well as 2-sided 95% CIs (normal approximation) on odds ratio, relative risk and the difference between the 2 treatment groups. Point estimates and 95% CI per treatment group were calculated for all secondary parameters. Exploratory analyses included baseline covariate analysis: gender, race, age, weight, history of VTE, baseline creatinine clearance (Clcr) according to Cockroft and Gault, the main reason for hospitalisation and cancer. For each subgroup, point estimates and 95% CIs per treatment group were calculated.

Artemis trial Results

Eight hundred and forty nine patients were randomised. Ten patients (1.2%) were not treated with study drug, mainly because of unmet selection criteria or withdrawn informed consent. Of the 839 treated patients, 92 (11.0%) prematurely discontinued study drug. The majority of premature discontinuations of study drug were due to withdrawal of consent by the patient, followed by adverse events (AE)/serious adverse events (SAE). Most cases of premature treatment discontinuation occurred before Day 6 in both treatment groups (40/48 in the fondaparinux group and 35/44 in the placebo group). No statistically significant difference regarding the overall rate of permanent discontinuation was found between the treatment groups.

As defined in the protocol, a missing VTE evaluation (i.e. non-evaluable or no VTE assessment) up to Day 15 was the only reason for exclusion from the primary efficacy analysis.

Table 1 Number (%) of patients excluded from primary efficacy analysis by reason for exclusion - All Randomised Patients

Deviation	**Fondaparinux (N=429)**	**Placebo (N=420)**
No VTE assessment up to Day 15 [a, b]	78 (18.2%)	66 (15.7%)
Non-evaluable VTE assessment up to Day 15	30 (7.0%)	31 (7.4%)
Total patients excluded from primary efficacy analysis	108 (25.2%)	97 (23.1%)

[a] Note that patients adjudicated as negative in the absence of a venogram are also excluded
[b] Includes all non-treated patients (4 in the fondaparinux group and 6 in the placebo group)

Most of the missing VTE evaluations correspond to venograms not performed. The percentage of patients excluded from the primary efficacy analysis was similar for both treatment groups and was lower than the projected 30% non-evaluable patients in the protocol.

As regards *patient demographics*, both treatment groups were similar with respect to demographic and baseline characteristics, except regarding the history of VTE which was higher in the primary efficacy population in the placebo group (*6.2%)* compared to the fondaparinux group (*2.5%)*.

Table 2. Summary of demographic and baseline characteristics

Parameter		Fondaparinux (N=321)	Placebo (N=323)
Age (years)	Mean ± SD	74.3 ± 8.3	74.0 ± 8.2
[n (%)]	< 65	49 (15.3 %)	46 (14.2 %)
	≥ 65 - <75	110 (34.3 %)	117 (36.2 %)
	≥ 75	162 (50.5 %)	160 (49.5 %)
BMI (kg/m^2)	Mean ± SD	25.6 ± 5.2	25.8 ± 5.9
[n (%)]	< 30	253 (80.3 %)	247 (77.9 %)
	≥ 30	62 (19.7 %)	70 (22.1 %)
	Missing	6	6
Creatinine clearance [a]	< 30	22 (6.9 %)	21 (6.6 %)
(ml/min) [n (%)]	≥ 30 - < 50	105 (33.0 %)	107 (33.8 %)
	≥ 50 - < 80	144 (45.3 %)	140 (44.2 %)
	≥ 80	47 (14.8 %)	49 (15.5 %)
	Missing	3	6
Gender	Male	129 (40.2 %)	144 (44.6 %)
[n (%)]	Female	192 (59.8 %)	179 (55.4 %)
Risk factors for VTE		55 (17.1 %)	70 (21.7 %)
History of DVT		7 (2.2 %)	15 (4.6 %)
History of PE		2 (0.6 %)	10 (3.1 %)
History of VTE (DVT and/or PE)		8 (2.5 %)	20 (6.2 %)
Cancer [b]		47 (14.6 %)	51 (15.8 %)

BMI: body mass index

[a] Last value available before first study drug injection, using the equation of Cockroft & Gault

Note: A patient could have more than one risk factor for VTE

[b] History of cancer or active cancer

The two treatment groups were similar with respect to reason for hospitalisation.

Reason for hospitalisation	Fondaparinux (N=321)	Placebo (N=323)
Congestive heart failure NYHA class III/IV only [a]	78 (24.3 %)	82 (25.4 %)
Acute respiratory illness only [a]	63 (19.6 %)	73 (22.6 %)
Acute infectious or inflammatory disease only [a]	77 (24.0 %)	88 (27.2 %)
More than one reason for hospitalization	103 (32.1 %)	80 (24.8 %)

[a] With no other reason for hospitalisation-

The study drug exposure was also similar in both treatment groups, with a median number of 7 dosing days in both groups and means (SD) of 7.7 (1.9) and 7.6 (1.7) in the fondaparinux and placebo groups, respectively.

Efficacy

Fondaparinux was superior to placebo for prevention of VTE since the rate of VTE was statistically significantly lower in the fondaparinux group than in the placebo group; 5.6% versus 10.5%, p=0.029. The VTE incidence in the placebo group was in line with the anticipated VTE rate (i.e. 10-14%) in this population.

Regarding *secondary endpoints*, the table shows that the DVT rate in the fondaparinux group was lower than in the placebo group (5.6% vs. 9.1%) but failed to show statistical significance (p=0.097). The rates of proximal DVT and distal only DVT were also lower in the fondaparinux group than in the placebo group, but again were not statistically significant.

Main efficacy results: primary and secondary endpoints

		Fondaparinux	Placebo
Patients with VTE	n / N (%)	18/321 (5.6 %)	34 /323 (10.5 %)
(up to day 15)	95% CI	[3.4;8.7]	[7.4;14.4]
Secondary outcomes			
Any DVT			
Either side	n / N (%)	18/321 (5.6 %)	29/318 (9.1 %)
	95% CI	[3.4;8.7]	[6.2;12.8]
Both sides	n / N (%)	1/345 (0.3 %)	4/342 (1.2 %)
	95% CI	[0.0;1.6]	[0.3;3.0]
Any proximal DVT			
Either side	n / N (%)	5/324 (1.5 %)	7/324 (2.2 %)
	95% CI	[0.5;3.6]	[0.9;4.4]
Both sides	n / N (%)	0/346 (0.0 %)	0/348 (0.0 %)
	95% CI	[0.0;1.1]	[0.0;1.1]
Distal only DVT			
Either side [a]	n / N (%)	14/320 (4.4 %)	23/320 (7.2 %)
	95% CI	[2.4;7.2]	[4.6;10.6]
Both sides	n / N (%)	0/348 (0.0 %)	3/342 (0.9 %)
	95% CI	[0.0;1.1]	[0.2;2.5]

The primary efficacy outcome did not include “all-cause mortality”, contrary to the recommendations in the CHMP Points to Consider on prophylaxis of VTE (CPMP/EWP/707/98). The MAH claim that this was not prospectively defined as a component of the primary endpoint (VTE) and therefore ARTEMIS was not powered in this respect. However, a re-analysis of the primary endpoint with all cause mortality included carried out further to a request from CHMP, showed the relative risk reduction (RRR) still exhibited a trend in favour of fondaparinux during the primary efficacy period, which was significant at day 32.

ARTEMIS trial - Number (%) of patients with VTE plus all cause mortality during the primary efficacy period or up to Day 32

	Fondaparinux	**Placebo**	**RRR[*] [95%CI]**	**p-value (Fisher’s exact)**
During primary efficacy period	26/329 (7.9 %)	40/329 (12.2 %)	35.0% [-3.6%;59.3%]	0.091
Up to Day 32	32/429 (7.5 %)	57/420 (13.6 %)	45.0% [17.2%;63.6%]	0.0049

[*] : exact CI for RRR based on standardised statistic and inverting a 2-sided test

When examining the *symptomatic VTE*, the only statistically significant difference was regarding fatal PE. During the primary efficacy period (i.e. up to Day 15) there were no patients with a fatal PE in the fondaparinux group and 5 in the placebo group (p=0.029, 95% CI [-2.2; -0.2]). The number of patients with symptomatic VTE up to Day 32 was 4 in the fondaparinux group and 11 in the placebo group. Thus, the majority of the symptomatic VTE occurred after the primary efficacy period: 4/4 and 6/11 events in the fondaparinux and placebo groups, respectively. For the 5 additional events in the follow-up period adjudicated as fatal PE (3 in the fondaparinux group and 2 in the placebo group), death occurred suddenly without another plausible cause.

Number (%) of patients with symptomatic VTE up to Day 15 and 32 – All Randomised Patients

Patients With Symptomatic VTE up to day 15		**Fondaparinux (N=429)**	**Placebo (N=420)**
VTE	n (%)	0 (0.0 %)	5 (1.2 %)
DVT	n (%)	0 (0.0 %)	0 (0.0 %)
Non-fatal PE	n (%)	0 (0.0 %)	0 (0.0 %)
Fatal PE	n (%)	0 (0.0 %)	5 (1.2 %)
Patients With Symptomatic VTE up to day 32		**Fondaparinux (N=429)**	**Placebo (N=420)**
VTE	n (%)	4 (0.9 %)	11 (2.6 %)
DVT	n (%)	0 (0.0 %)	0 (0.0 %)
Non-fatal PE	n (%)	1 (0.2 %)	4 (1.0 %)
Fatal PE	n (%)	3 (0.7 %)	7 (1.7 %)
Patients With Symptomatic VTE + all deaths up to day 32 [1]		15/429 (3.5%)	29/420 (6.9%)
[1] *Post-hoc* analysis			

A secondary analysis performed further to a request from CHMP shows that, when mortality rates (irrespective of cause) at Day 32 were examined retrospectively, a non-significant RRR of 45% favouring fondaparinux was observed (14/429 and 25/420 in the fondaparinux and placebo groups, respectively). Importantly, when the combined endpoint of symptomatic VTE + all cause mortality at Day 32 was assessed, the beneficial effect of fondaparinux was clearly evident, with a statistically significant 49% RRR in symptomatic VTE + all deaths. Based on the point estimates the MAH has provided a number needed to treat analysis (NNT=60 for patients with symptomatic VTE up to day 32, and NNT=30 for patients with symptomatic VTE + all deaths up to day 32).

The percentage of patients who received *antithrombotic curative treatment* based on the investigator's decision after the qualifying VTE assessment used in the primary efficacy analysis was higher in the placebo group compared to the fondaparinux group (p=0.078), which is consistent with the -46.7% relative risk reduction observed for the primary efficacy outcome.

In order to put the main efficacy results of Artemis into clinical perspective, it is worth recalling the results of the pivotal trials carried out with enoxaparin and dalteparin to support a similar indication.

Primary endpoint

Clinical trial	**Active (No. Of events/No. of patients)**	**Placebo (No. Of events/No. of patients)**	**RR [nominal 95% CI], p value**
ARTEMIS[1] (fondaparinux 2.5mg)	18/321(5.6%)	34/323 (10.5%)	0.53 [0.31, 0.92], p=0.029
MEDENOX[1] (enoxaparin 40mg)	16/291(5.5%)	43/288 (14.9%)	0.37 [0.22, 0.63], p=0.002
PREVENT[1] (dalteparin, 5000IU)	42/1518 (2.8%)	73/1473 (5%)	0.55, [0.38, 0.80] p=0.0015

[1] In ARTEMIS and MEDENOX, the primary efficacy endpoint was a composite of the incidence of VTE (including venogram positive for DVT, symptomatic DVT, non-fatal PE and fatal PE), whereas in PREVENT, the primary endpoint was a composite of symptomatic DVT, fatal or non-fatal PE, sudden death and asymptomatic proximal DVT detected by venous Doppler ultrasonography. The primary endpoint was assessed up to Day 15, Day 14, or Day 21, or up to the first venogram (which ever came first) in ARTEMIS, MEDENOX and PREVENT, respectively.

Proximal asymptomatic DVT

Clinical trial	Active (No. Of events/No. of patients)	Placebo (No. Of events/No. of patients)	RR
ARTEMIS[1] (fondaparinux 2.5mg)	5/324 (1.5%)	7/324 (2.2%)	0.71, p=0.77
MEDENOX[1] (enoxaparin 40mg)	5/291(1.7%)	14/288 (4.9%)	0.35, p=0.037
PREVENT[1] (dalteparin, 5000IU)	27/1507(1.8%)	53/1453(3.7%)	0.48, p=0.002

[1] In PREVENT, DVT was assessed by venous Doppler ultrasonography, whereas bilateral venography was used in ARTEMIS and MEDENOX. The endpoint was assessed up to Day 15, Day 14, or Day 21, or up to the first venogram (which ever came first) in ARTEMIS, MEDENOX and PREVENT, respectively.

Regarding ancillary analyses carried out to test for *heterogeneity*, the primary efficacy outcome was analysed using a number of baseline covariates and the reason for hospitalisation to examine if treatment effect varied with subgroups or covariates between the 2 groups (Table 6).

	Fondaparinux (N=321)				Placebo (N=323)			
Covariate[a]		VTE				VTE		
Subgroup	**N**	**n**	**%**	**95% CI**	**N**	**n**	**%**	**95% CI**
Gender								
Male	129	8	6.2	[2.7;11.9]	144	10	6.9	[3.4;12.4]
Female	192	10	5.2	[2.5;9.4]	179	24	13.4	[8.8;19.3]
Weight (kg)								
< 50	25	2	8.0	[1.0;26.0]	33	3	9.1	[1.9;24.3]
≥ 50 - <100	284	15	5.3	[3.0;8.6]	272	30	11.0	[7.6;15.4]
≥ 100	9	1	11.1	[0.3;48.2]	15	1	6.7	[0.2;31.9]
History of VTE								
Yes	8	0	0.0	[0.0;36.9]	20	3	15.0	[3.2;37.9]
No	313	18	5.8	[3.4;8.9]	303	31	10.2	[7.1;14.2]
Creatinine clearance at baseline (ml/min)								
< 30	22	2	9.1	[1.1;29.2]	21	1	4.8	[0.1;23.8]
≥ 30 - <50	105	8	7.6	[3.3;14.5]	107	13	12.1	[6.6;19.9]
≥ 50 - <80	144	5	3.5	[1.1;7.9]	140	15	10.7	[6.1;17.1]
≥ 80	47	3	6.4	[1.3;17.5]	49	4	8.2	[2.3;19.6]
Cancer								
Yes	47	8	17.0	[7.6;30.8]	51	2	3.9	[0.5;13.5]
No	274	10	3.6	[1.8;6.6]	272	32	11.8	[8.2;16.2]

No statistically significant heterogeneity of treatment effect was demonstrated for any covariate analysed except for cancer (p=0.0003). No medical reasons were found for this imbalance. The difference in number of patients with VTE was less pronounced in favour of fondaparinux in males as compared to females. However, no statistically significant interaction of gender and treatment was found (Breslow-Day: p=0.14), and the treatment effect in males is not inconsistent with the gender variation observed in the 5 previous MOSLL studies. The VTE outcome per subgroup of renal function, as expressed by creatinine clearance, is consistent with previous fondaparinux studies.

Further to a request from CHMP, the MAH has further analysed the consequences on the overall results of the imbalance in the proportion of patients with a history of VTE in the primary efficacy population. Importantly, the subgroup of patients with no history of VTE showed a comparable RRR

with fondaparinux to the overall population (see table below). Therefore, the treatment imbalance in patients with a history of VTE did not make a major contribution to the primary efficacy result.

Number (%) of patients with VTE during the primary efficacy period according to history of VTE - Primary efficacy population

	Fondaparinux (N=321)	**Placebo (N=323)**	**RRR* [95%CI]**
Overall population	18/321 (5.6%)	34/323 (10.5%)	46.7% [7.7%;69%]
History of VTE	0/8 (0.0%)	3/20 (15.0%)	100.0% [-175.9%;100.0%]
No history of VTE	18/313 (5.8%)	31/303 (10.2%)	43.8% [2.5%;67.7%]

* *: exact CI for RRR based on standardised statistic and inverting a 2-sided test*

However, a markedly heterogeneous efficacy response across various countries was observed i.e. positive response in the UK (n=87), Czech Republic (n=221) and Denmark (n=42); negative in Poland (n=232) and Australia (n=37). Most notably, the results in the UK are surprising as compared to the other countries: 2.5% of patients in the fondaparinux group experienced VTE events versus 23.4% for placebo. Of note, 4 out of the 5 fatal PE occurred in the UK. In Poland there results are unfavourable despite the largest patient enrolment.

Countries	**Fondaparinux**	**Placebo**	**Difference, IC 95 %**
Poland	8/117 (6.8 %)	7/115 (6.1 %)	0.8 %, [-5.6 % ; 7.1 %]
Czech Republic	6/106 (5.7 %)	14/115 (12.2 %)	-6.5 %, [-13.9 % ; 0.9 %]
UK	1/40 (2.5 %)	11/47 (23.4 %)	-20.9 %, [-33.9 % ; -7.9 %]
Denmark	0/23 (0 %)	1/19 (5.3 %)	-5.3 %, [-15.3 % ; 4.8 %]
Australia	2/22 (9.1 %)	1/15 (6.7 %)	2.4 %, [-15 % ; 19.8 %]
Sweden	0/7 (0 %)	0/10 (0 %)	0 %
Mexico	1/5 (20 %)	0/2 (0 %)	20 %, [-15.1 % ; 55.1 %]
Netherlands	0/1 (0 %)	0/0 (0 %)	

However, the sensitivity analyses performed by the MAH further to a request from CHMP would appear to show that the overall results are valid. e.g. after exclusion of the 2 centres with the most positive and negative results, respectively, the results are still significant.

When analysing the results based on the reason for hospitalisation, the VTE rate was lower in the fondaparinux group than in the placebo group for each of the reasons for hospitalisation and also for patients admitted for more than one reason, although none of the differences was statistically significant.

Safety results

The extent of exposure to study drug for the "as treated" patients population was similar to that observed for the primary efficacy population.

Serious adverse events and deaths

Up to two days after the last injection, 4 (0.9%) patients had died in the fondaparinux group and 7 (1.7%) in the placebo group. By Day 32, the incidences were 14 (3.3%) and 25 (6.0%), respectively.

Number (%) of deaths from first injection up to Day 32

Patients With:	Artemis	
	Fondaparinux (N=425)	Placebo (N=414)
SAE starting during the randomised treatment period		
Leading to death during the treatment period	4 (0.9 %)	7 (1.7 %)
Leading to death after the treatment period up to Day 32	3 (0.7 %)	4 (1.0 %)
Leading to death after Day 32	1 (0.2 %)	0 (0.0 %)
SAE starting after the randomised treatment period up to Day 32		
Leading to death after the treatment period up to Day 32	7 (1.6 %)	14 (3.4 %)
Leading to death after Day 32	3 (0.7 %)	0 (0.0 %)
Total deaths during the randomised treatment period	4 (0.9 %)	7 (1.7 %)
Total deaths between first injection and Day 32	14 (3.3 %)	25 (6.0 %)
Total deaths reported [a]	18 (4.2 %)	25 (6.0 %)

[a] Deaths due to AEs which started after Day 32 were not counted in this table.

The overall percentage of patients with SAEs during the treatment period was similar between treatment groups (4.7% for fondaparinux and 5.1% for placebo). There was also no apparent difference in the SAE incidence for any WHO organ-class.

Incidence of bleeding

There were numerical differences in any bleeding occurring up to 2 days after the last injection (Table 8). However, the number of minor bleedings only drove this difference. The main safety outcome, incidence of major bleeding between first injection and 2 calendar days after the last injection, was low and identical (n=1, 0.2%) in each group. Both major bleeding cases were associated with a haemoglobin fall, one due to hemoptysis (fondaparinux group), and one due to rectal bleeding related to radiation induced colitis (placebo group). By Day 32, the incidences of major or minor bleeding became similar between the 2 treatment groups, suggesting an absence of a relationship to the study treatment but rather to the underlying diseases of the patients.

Table 8 Number (%) of patients with bleeding events - As Treated Patients population

Patients With		Fondaparinux (N=425)	Placebo (N=414)
Up to two days after last injection			
Major bleeding event	n (%)	1 (0.2 %)	1 (0.2 %)
	95% CI	[0.0;1.3]	[0.0;1.3]
Minor bleeding event only	n (%)	11 (2.6 %)	4 (1.0 %)
	95% CI	[1.3;4.6]	[0.3;2.5]
Any bleeding event	n (%)	12 (2.8 %)	5 (1.2 %)
	95% CI	[1.5;4.9]	[0.4;2.8]
Up to day 32			
Major bleeding event	n (%)	2 (0.5 %)	4 (1.0 %)
	95% CI	[0.1;1.7]	[0.3;2.5]
Minor bleeding event only	n (%)	13 (3.1 %)	12 (2.9 %)
	95% CI	[1.6;5.2]	[1.5;5.0]
Any bleeding event	n (%)	15 (3.5 %)	16 (3.9 %)
	95% CI	[2.0;5.8]	[2.2;6.2]

The number of patients transfused as well as the number of transfusions given during study treatment was low and similar between treatment groups. Paradoxically, there was a higher percentage of patients with a haemoglobin value < 8 g/dl after the first study drug injection in the placebo group

compared to the fondaparinux group, while there were no statistically significant differences between treatment groups in the change from baseline to last value on treatment.

Due to the very low incidence of events, covariate analysis on major bleeding alone was not meaningful. Consistent with historical observations, the risk of any (major or minor) bleeding increases with decreasing renal function across treatment groups. The difference between treatment groups in any bleeding was consistent across the four categories of renal function.

For events other than those related to bleeding, overall there was no evidence for any differences between patients who received fondaparinux and those who received placebo. Consequently, no other adverse reactions were identified.

Laboratory findings
There was no difference in platelet count drops between the 2 treatment groups. There was no statistically significant difference between the treatment groups in the change from baseline to last value on treatment for either creatinine concentration or creatinine clearance. Liver enzymes were not assayed. No cases of heparin-induced thrombocytopenia (HIT) were observed after fondaparinux treatment.

Discussion

Efficacy
The ARTEMIS study, pivotal to this application, has demonstrated a reduction of the composite primary end-point in medical patients who are 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. The study is of limited size; it demonstrates that fondaparinux is moderately superior to placebo for the prevention of VTE in medical patients under the premises of the protocol but there is no difference for overall symptomatic VTE during the primary efficacy period. In addition, some weaknesses of the ARTEMIS study have been noted by CHMP with respect to the CHMP Points to Consider (PtC) on applications with one pivotal study (CPMP/EWP/2330/99):

- The robustness of the study results is questionable. CPMP/EWP/2330/99 states that the single pivotal trial should show a statistically convincing benefit (i.e. substantially higher than the usual significance level of $p<0.05$) of clinical relevance and that none of the study centres should dominate the overall result, neither in terms of number of subjects nor in terms of magnitude of effect. These requirements are not fulfilled in the present application, where the demonstrated effect is of less convincing statistical significance ($p=0.027$) and clinical relevance. In addition, the results show heterogeneity in efficacy across different countries (positive effect in the UK, where the magnitude of the positive response is surprisingly strong despite a low recruitment, and unfavourable results in Poland, despite a very high recruitment).
- An important objective [in the efficacy evaluation in VTE prophylaxis studies] is to demonstrate that the medicinal product decreases the number of patients developing DVT's during the prophylactic treatment period". The DVT rate in the fondaparinux group was lower than in the placebo group (5.6% vs. 9.1%) but was not statistically significant ($p=0.097$), thus failing to meet one of the major clinically relevant efficacy criteria.
- The unusual treatment response in cancer patients and the apparent lack of treatment effect in male patients would appear to reflect an internal inconsistency in the study results, thus constituting another deviation from CPMP/EWP/2330/99.
- When put into clinical perspective, the results of the Artemis trial appear less robust and convincing than the corresponding results for enoxaparin and dalteparin in the Medenox and Prevent trials, respectively.

The efficacy results of Artemis are thus not fully reassuring regarding either statistical significance or clinical relevance. Nonetheless, the outcome is consistent and in line with what could be expected considering its limited size and the expected magnitude of risk for clinical VTE in the target population. Different sensitivity analyses provide some support for the validity of the primary end-point results. Given the limited size of the study it cannot be expected that significant effects on the

individual components of the composite end-point be demonstrated. Indeed, demonstrating in this medical setting a convincing reduction in clinical events is probably almost impossible due to the expected low event rates, since high-risk patients would have to be excluded in a placebo-controlled trial for ethical reasons. The design and evaluation of an actively controlled non-inferiority study would also offer major difficulties. In addition, it should be reminded that the efficacy of fondaparinux with regard to antithrombotic activity has been convincingly demonstrated, with experience of fondaparinux in over 4000 patients in orthopaedic surgery demonstrating superior efficacy over enoxaparin in prevention of VTE in this population. Thus, the CHMP PtC on applications with one pivotal study (CPMP/EWP/2330/99) may may not be fully applicable in the context of this variation.

The variability in efficacy results in the different countries is not easily explained by chance alone and, as proposed by the MAH, other factors may have contributed (e.g. a population with a higher VTE risk in the UK patients). The sensivity analyses performed seem to provide support for the conclusion that the overall results are valid.

Active malignant disease is an important risk factor for VTE during immobilisation; therefore the results for this subgroup appear surprising. However, the low event rates, and low numbers of patients with active malignant disease could explain the findings of an apparent lack of effect in this subgroup. External support for the efficacy of fondaparinux in patients with malignant disease may be derived not only from the MOSLL studies, but also from the abdominal surgery prophylaxis study where fondaparinux appeared effective also in the large subpopulation with malignant disease.

In ARTEMIS, the difference in number of patients with VTE was less pronounced in favour of fondaparinux in males as compared to females. The apparent lower efficacy in males observed for primary efficacy outcome was not observed across the key secondary efficacy endpoints - symptomatic VTEs and all deaths were slightly lower in men than in women. The treatment effect in males on the primary efficacy endpoint is not inconsistent with the gender variation observed in the 5 previously reviewed MOSLL studies, most notably in the PENTIFHRA Plus study (a study in extended prophylaxis with key similarities in terms of dosage, patient population and comparator), where fondaparinux was efficacious in both males and females. The gender results in ARTEMIS are thus most likely to be chance findings.

The MAH has proposed a broad indication; ARTEMIS was designed to show a clinically relevant and statistically significant effect of fondaparinux in the overall medical patient population where the common characteristic of the patients enrolled was immobilisation. The efficacy and safety of fondaparinux has been confirmed across patient groups reflecting the spectrum of VTE risk; indeed, significant effects in all medical subgroups cannot be requested or expected from such a study. However, it is acknowledged that prophylaxis is not appropriate in all acutely ill patients. Whilst there is no generally accepted consensus regarding the criteria for selecting patients for prophylaxis, the need for an individual risk assessment is widely recognised in international treatment guidelines. The details of such criteria obviously have to be determined by treating physicians taking local and general clinical guidelines into account. Therefore, the CHMP believe the indication should be restricted to the treatment of high-risk medical patients based on an individual risk assessment. This has been reflected in sections 4.1 and 4.2 of the SPC and is in line with current treatment guidelines.

Finally, the current submission does not provide any separate data on the 1.5 mg dose regimen in medical patients as it is bridged to previous studies in MOSLL patients. Based on past population pharmacokinetic modelling, the MAH proposes to maintain the same dosing recommendations for medical and surgical patients with renal impairment, namely to recommend 1.5mg for patients with severe renal impairment (Clcr 20- 30 ml/min) and its possible use as an alternative in patients with moderate renal impairment (Clcr 30-50 ml). Whilst the CHMP agree with this proposal, it should be emphasised that the posology currently provided for MOSLL patients with Clcr 30-50 ml/min, recommending 2 different doses for the same patient population, gives poor guidance to the prescriber. Bearing in mind that this point cannot be resolved within this variation procedure the MAH should commit to provide an overview of the clinical experience in these patients, including experience from clinical studies and from spontaneous reporting, as part of the next PSUR.

Safety
The safety observations made in the present study in medical patients are similar to those in the previously submitted MOSLL studies. As expected in this medical setting, fondaparinux was well tolerated with only an excess of minor bleedings compared to placebo. The rates of major bleedings were low in the two groups and comparable. The effect of renal function was consistent with the previous fondaparinux experience in MOSLL patients; the risk of bleeding is higher in patients with impaired renal function. However, there are insufficient patients with severe renal impairment (Clcr <30 ml/min) to draw any final conclusion on the benefit/risk ratio for this patient sub-group in the medical indication. The overall bleeding rate is also higher in patients over 75 years old compared to patients under the age of 65 years old.

It is agreed that the overall risk for bleedings probably is lower during short-time prophylaxis in medical patients than in patients with recent orthopaedic surgery. However, the risks associated with prolonged treatment in this heterogeneous target population, which can be expected to include a large proportion of elderly patients with multiple diseases and physiologically impaired renal function, have not been assessed in the current clinical trial. This is reflected in section 4.2 of the SPC, which mentions that experience from prophylactic treatment in medical patients is restricted to 14 days and that the target population should be identified based on an individual risk assessment.

Finally, the Applicant is requesting a label change allowing the use of fondaparinux in patients with heparin-induced thrombocytopaenia (HIT), quoting 4 publications on the successful clinical use of fondaparinux in HIT patients. These publications correspond to anecdotal reports of limited experience in a total of 7 patients with HIT. These data and the post-marketing surveillance data are insufficient to support the requested change.

Conclusions and Benefit/Risk Assessment
Several weaknesses of the ARTEMIS study have been identified, as detailed in the efficacy discussion. However, extensive clinical evidence for the efficacy and safety of fondaparinux for prophylaxis in connection with orthopaedic surgery is available, including data on the prolonged prophylaxis up to an additional 24 days documented in the Pentifhra plus study. There are no scientific indications that VTE in medical patients should be prevented or treated differently from VTE in surgical patients. Further experience can be derived from prophylactic treatment in abdominal surgery (on-going procedure) and the approved indication for treatment of VTE. In addition, the pharmacodynamic and pharmacokinetic properties of fondaparinux have been well characterised. Thus, for fondaparinux and for the dose regimen proposed, extensive external evidence is available supporting efficacy and safety in the currently targeted population.

Therefore, the results of the pivotal Artemis trial, despite its obvious shortcomings, together with the the overall experience with fondaparinux in similar clinical settings, are deemed sufficient for a prophylaxis indication in high VTE risk medical patients based on an assessment of the individual VTE risk.