SYNOPSIS

Name of Sponsor/Company: Astellas Pharma Europe B.V. (Successor in interest to Yamanouchi Europe/Fujisawa GmbH)		
Name of Finished Product: NA		
Name of Active Ingredient: YM150		

Title of Study: Direct Factor Xa inhibitor YM150 for prevention of venous thromboembolism in patients undergoing elective total hip replacement - A double-blind, parallel, dose-finding study in comparison with open label enoxaparin (ONYX-2)

Coordinating Investigator: [redacted] Sweden.

Study Centers: 81 centers in 17 European countries participated in the study.

Publication (reference): Eriksson BI, Turpie AGG, Lassen ML, Prins MH, Agnelli G, Kälebo P, Wetherill G, Meems L. Once daily YM150, an oral direct Factor Xa inhibitor, for prevention of venous thromboembolism in patients undergoing elective primary hip replacement (Abstract ASH) Blood 2007; 110: 98a

Study Period: **Date of First Enrollment:** 29 June 2006 **Date of Last Evaluation:** 07 August 2007	**Phase of Development:** IIB

Objectives: The study objectives were to investigate the optimal therapeutic dose by:

- Evaluation of the efficacy of YM150 in subjects undergoing elective primary hip replacement surgery
- Evaluation of the safety of YM150 in the target population

Study Design: This was a multi-center, randomized, active-controlled, parallel-group study to investigate the efficacy and safety of double-blind treatment with YM150 (5 mg, 10 mg, 30 mg, 60 mg, and 120 mg) in subjects undergoing elective primary hip replacement surgery. Enoxaparin (40 mg) was used as an open-label control. YM150 tablets were given once daily, starting 6 to 10 hours after the end of surgery (i.e., wound closure). Enoxaparin was given subcutaneously once daily, starting approximately 12 (± 2) hours before the planned surgery. All subjects were treated with study medication for 33-38 days. Subject continued study treatment after discharge from hospital as an outpatient. Venography was performed 7 to 10 days after surgery. YM150 was given as double-blind treatment, whereas enoxaparin was given in an open label manner. The study ended with a 4- to 5-week follow-up period during which no study treatment was given. An extra laboratory control visit for liver function test was performed 4 weeks after end of study.

Diagnosis and Main Criteria for Inclusion: The study population consisted of men or women aged ≥18 years and scheduled for an elective total primary hip replacement in a general hospital.

Number of Subjects (planned and analyzed): In total 960 subjects were to be randomized in order to yield approximately 660 subjects with an evaluable venogram.

Test Product, Dose and Mode of Administration: Subjects were randomized to 1 of 6 treatment groups: once daily treatment per os with 5 mg, 10 mg, 30 mg, 60 mg (1 active tablet and 2 placebo tablets) or 120 mg YM150 (2 active tablets and 1 placebo tablet), or 40 mg enoxaparin once daily by subcutaneous injection. The medication was to be taken preferably in the morning.

Batch Numbers: YM150 tablets: 5 mg: [redacted] 10 mg: [redacted] 30 mg: [redacted] 60 mg: [redacted] YM150 placebo tablets: 5 mg: [redacted] 10 mg: [redacted] Enoxaparin (Clexane): [redacted]

Duration of Study and Treatment: All subjects were treated with study medication for 33-38 days. Subject continued study treatment after discharge from hospital as an outpatient. The treatment period was followed by a 4- to 5-week follow up period during which no study treatment was given. An extra laboratory control was performed after another 4 weeks. Total study duration was 89-96 days.

Criteria for Evaluation: Primary efficacy endpoint was the rate of total venous thromboembolism (VTE) during hospitalization phase (up to Day 7-10) defined as the composite of deep vein thrombosis (DVT) proven by bilateral venography and/or symptomatic DVT and/or symptomatic pulmonary embolism (PE) and/or death due to any cause during treatment. Primary safety endpoint was the incidence of clinically relevant bleedings during 7-10 days hospitalization treatment rated as major bleeding.
Secondary efficacy endpoints were proximal or distal DVT, symptomatic VTE up to end of study treatment and up to end of study, rate of total VTE up to end of study, and death. Secondary safety endpoint was the incidence of individual and combined bleeding types. Other (safety) assessments were adverse events, vital signs, physical examination, ECG and laboratory assessments.
PK assessments comprised bioanalysis of YM150 and metabolites, FXa and anti-FXa activity.
PD assessments comprised coagulation parameters including prothrombin time (PT) and activated partial thromboplastin time (aPTT).

Statistical Methods: The primary efficacy analysis used the AS_Composite. The AS_Composite (originally called FAS in protocol) was the combination of all subjects who had (up to Day 10) an evaluable venogram, a DVT, symptomatic VTE, or death. The primary efficacy analysis used logistic regression to test for a linear trend with YM150 dose in the rate of events. The primary efficacy analysis only included the YM150 doses and did not include enoxaparin. The primary efficacy analysis included a step-down procedure to test for the effects of YM150 doses in descending order. As a secondary comparison the YM150 doses were compared to enoxaparin with respect to the same primary efficacy endpoint. All statistical comparisons were made using 2-sided tests at the α=0.05 significance level. All null hypotheses were of no treatment difference. All alternative hypotheses were 2-sided. Bleeding events were analyzed using the same methods as the primary efficacy analysis, using the SAF. Other safety variables were descriptively reported (SAF).

RESULTS:

Analysis Sets and Subject Disposition: The number and percentage of subjects randomized, treated, and completing the study, and the study populations are provided in the following table:

	YM150 daily dose						
Number (%) of subjects:	**5 mg**	**10 mg#**	**30 mg**	**60 mg**	**120 mg**	**Enoxaparin**	**Total**
Enrolled							1141
Randomized	169 (100)	171 (100)	170 (100)	171 (100)	168 (100)	168 (100)	1017 (100)
Pre-surgery medication	0	1 (0.6)[#]	0	0	0	164 (97.6)*	165 (16.2)
Received surgery	158 (93.5)	164 (95.9)	157 (92.4)	163 (95.3)	156 (92.9)	165 (98.2)	963 (94.7)
Post-surgery medication	158 (93.5)	162 (94.7)	156 (91.8)	163 (95.3)	156 (92.9)	164 (97.6)*	959 (94.3)
Any study medication	158 (93.5)	162 (94.7)	156 (91.8)	163 (95.3)	156 (92.9)	166 (98.8)*	961 (94.5)
Completed study	123 (72.8)	123 (71.9)	129 (75.9)	131 (76.6)	127 (75.6)	134 (79.8)	767 (75.4)
Randomized	169	171	170	171	168	168	1017
FAS	158	161	156	163	156	166	960
AS_Composite	117	120	114	120	110	127	708
PPS	114	116	111	119	108	120	688
SAF	158	161	156	163	156	166	960

Subject [redacted] was randomized to YM150 10 mg, but took enoxaparin in the hospital, and YM150 10 mg at home. This subject is under enoxaparin for all populations except the randomized population

*Enoxaparin group: Two subjects had first study treatment after surgery; two subjects had pre-surgery treatment, but one withdraw before surgery and one after surgery.

FAS, all randomized subjects with surgery and treated with at least one dose; AS_Composite, subject with evaluable venogram (including DVT), symptomatic VTE and death; PPS, AS_Composite subjects minus major protocol violations; SAF (safety analysis set): all randomized subjects with surgery and treated with at least one dose.

Demographics: Key demographic details for the SAF are provided in the following table. There were no consistent or clinically relevant differences between treatment groups.

		YM150 daily dose					Enoxaparin (N=166)
		5 mg (N=158)	10 mg (N=161)	30 mg (N=156)	60 mg (N=163)	120 mg (N=156)	
Age (years)	Mean (SD)	60.2 (10.8)	60.3 (11.8)	57.9 (12.1)	61.3 (11.8)	60.2 (11.2)	58.1 (12.5)
Sex	Female, n (%)	89 (56.3)	88 (54.7)	79 (50.6)	90 (55.2)	79 (50.6)	86 (51.8)
	Male, n (%)	69 (43.7)	73 (45.3)	77 (49.4)	73 (44.8)	77 (49.4)	80 (48.2)
Weight (kg)	Mean (SD)	77.8 (14.9)	77.0 (14.1)	80.4 (14.2)	80.1 (12.9)	79.9 (14.8)	78.1 (14.0)
BMI (kg/m^2)	Mean (SD)	27.2 (3.9)	27.5 (4.2)	28.0 (4.8)	28.5 (4.2)	28.1 (4.6)	27.3 (4.3)

The mean duration of surgery in each group was approximately 1.5 h (range: 0.4 to 4.7 h), and time to first day out of bed varied between 1 and 9 days, with no clear difference between treatment groups. The overall median duration of hospitalization was 11-12 days, but there were considerable differences between countries and regions.

Study Drug Exposure: Duration of exposure to study medication is summarized in the following table (SAF).

		YM150 daily dose					Enoxaparin (N=166)
		5 mg (N=158)	10 mg (N=161)	30 mg (N=156)	60 mg (N=163)	120 mg (N=156)	
Day of last dose	Mean (SD)	31.2 (10.7)	30.7 (11.5)	31.9 (10.6)	31.5 (10.9)	31.3 (11.1)	31.3 (10.2)
	Median	35	35	35	35	35	35
	Min-Max	1-45	1-45	1-48	2-45	1-46	0-43
Subjects (n, %) dosed until	Day 7+	153 (96.8)	156 (96.9)	148 (94.9)	153 (93.9)	145 (92.9)	157 (94.6)
	Day 10+	140 (88.6)	135 (83.9)	139 (89.1)	146 (89.6)	136 (87.2)	148 (89.2)
	Day 19+	132 (83.5)	131 (81.4)	133 (85.3)	137 (84.0)	130 (83.3)	142 (85.5)
	Day 33+	120 (75.9)	117 (72.7)	123 (78.8)	125 (76.7)	116 (74.4)	128 (77.1)

Efficacy Results: The primary efficacy endpoint (the rate of total VTE during hospitalization phase up to Day 7-10 is summarized in the following table (AS_Composite).

		YM150 daily dose					Enoxaparin (N=127)
Characteristic	Statistic/category	5 mg (N=117)	10 mg (N=120)	30 mg (N=114)	60 mg (N=120)	120 mg (N=110)	
Deaths due to any cause	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
PE	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Symptomatic DVT	n (%)	1 (0.9)	1 (0.8)*	0 (0.0)	1 (0.8)*	1 (0.9)	0 (0.0)
Proximal DVT only	n (%)	2 (1.7)	2 (1.7)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Distal DVT only	n (%)	25 (21.4)	31 (25.8)	17 (14.9)	14 (11.7)	14 (12.7)	19 (15.0)
Proximal and distal DVT	n (%)	4 (3.4)	5 (4.2)	4 (3.5)	2 (1.7)	1 (0.9)	5 (3.9)
Total VTE	n (%)	32 (27.4)	38 (31.7)*	22 (19.3)	16 (13.3)*	16 (14.5)	24 (18.9)
	95% CI	(20.0,36.1)	(23.5,40.7)	(12.9,27.2)	(7.8, 20.5)	(8.5, 22.4)	(12.5, 26.4)

* Two subjects with symptomatic DVT had also a venographic DVT: only one event counts in the total VTE.

There was a statistically significant trend towards a lower incidence of VTE endpoint with increasing YM150 dose between 5 and 120 mg YM150 (p=0.0002) and between 5 and 60 mg YM150 (p=0.0005). The primary analysis (trend test) over the dose range 5 – 30 mg was close to statistically significance (p=0.0668), which suggests that 30 mg YM150 may also be effective in reducing incidence of the VTE endpoint. The incidence of VTE was highest in the 5 mg and 10 mg YM150 dose group (27.4% and 31.7%, respectively), and lowest in the 60 mg and 120 mg YM150 dose group (13.3% and 14.5%, respectively). The incidence in the enoxaparin group (18.9%) was similar to the incidence in the 30 mg YM150 dose group (19.3%), and higher than in the 60 mg and 120 mg YM150 group, but the comparisons with enoxaparin were not statistically significant (p=0.1907 and p=0.2825 for 60 mg and 120 mg YM150, respectively).

The primary analysis provides evidence that YM150 30 mg, 60 mg and 120 mg are effective in reducing the incidence of the VTE endpoint (p=0.0668, p=0.0005 and p=0.0002 respectively). The robustness of the results was confirmed by the secondary analysis using the Peto method, and the outcome of the sensitivity analyses. 26 venograms have been performed after day 10, resulting in one additional distal DVT in the YM150 5 mg group, and 2 additional distal DVTs in the enoxaparin group. These 3 DVTs are not included in the primary and secondary analyses, but are included in the sensitivity analysis.
A similar trend as for the VTE endpoint was observed for the secondary endpoints distal and proximal DVT, i.e., the highest incidence was observed in the low (5 mg and 10 mg) YM150 dose groups (25.0% and 30.0%, respectively, for distal DVT, and 4.8% and 5.1%, respectively, for proximal DVT) and the lowest incidence in the highest (60 mg and 120 mg) YM150 dose groups (13.3% and 13.8%, respectively, and 1.5% and 0.8%, respectively). The incidence in the 30 mg YM150 group was intermediate (18.4% and 4.1% for distal and proximal DVT, respectively) and comparable to the enoxaparin group (18.9% and 3.7%, respectively).
The incidence of total VTE and deaths up to the end of the study was between 13.1% and 30.6% in the YM150 dose groups. The incidence in the enoxaparin group was comparable to the incidence in the 30 mg YM150 group (20.0% and 18.5%, respectively). The incidence of major VTE endpoint (composite of proximal DVT, symptomatic DVT, non-fatal PE and all cause mortality) tended to decrease with increasing dose of YM150 (5.5%, 5.1%, 4.1%, 2.2%, 2.5% for 5, 10, 30, 60 and 120 mg YM150, respectively; 3.7% for enoxaparin) but the effect was not statistically significant (p= 0.1358), as the study was not powered for this comparison.
One subject in the 120 mg YM150 group died. The cause of death was myocardial infarction.
There were no PEs during the study. Four subjects (1 subject in the 5, 10, 60 and 120 mg YM150 dose groups each) had a confirmed adjudicated symptomatic DVT. All confirmed symptomatic DVTs emerged during the first 10 days of treatment.

Pharmacokinetic Results: The steady state pharmacokinetics of the main YM150 metabolite YM-222714 was adequately described by a 2-compartment model with sequential zero and first order absorption. Influential covariates were creatinine clearance on clearance (CL), body weight on central volume of distribution (V2), race on peripheral volume of distribution (V3) and inter-compartmental clearance (Q), gender on Q, dose on the first order absorption rate constant (Ka), subject status on Ka and relative bioavailability (F1), and age on F1. As a result, clearance decreased with creatinine clearance, the central volume of distribution increased with body weight, the peripheral volume of distribution was lower in Asians and slightly lower in blacks compared to Caucasians. The bioavailability increased with age, especially above the age of 60 years. Rate of absorption was slower at the highest dose of 120 mg. Within the dose range investigated, AUC_{tau}, C_{av}, and C_{trough} increased in proportion to the dose. Between 5 and 60 mg YM150, C_{max} increased dose proportionally. However, when going to the highest dose (120 mg YM150) a slightly less than proportional increase was observed. A similar observation could be made for the inter subject variability (SD).

Pharmacodynamic Results: A population PK/PD model was developed that related FXa activity and PT(INR) to YM-222714 plasma concentration. The inhibition of FXa activity increased in a dose and concentration dependent fashion. The change in FXa activity followed the PK profile of YM-222714. Surgery resulted in an additional decrease in FXa activity by approximately 26% which was maximal on the day following surgery, and then rebounded back in about 2 weeks time to a 12% increase compared to baseline. On top of this, a slow decline in baseline activity with time was observed. Due to the combined effect of YM150 and surgery, FXa activity was decreased by approximately 25% to 56% at doses between 5 and 120 mg, respectively, after the second dose. When the surgery was maximally rebounced, doses of 5 and 10 mg YM150 did not result in a decrease in FXa activity below the baseline value anymore. At the highest dose of 120 mg, the minimum FXa activity was around 63%, but at trough no noticeable effect on FXa activity was present. Relevant covariates of FXa activity, other than surgery, were body weight, the FXa baseline increased by 0.2% per kg, and sex, the FXa baseline was 4% higher in females.

PT(INR) increased in a dose and concentration dependent fashion. The change in PT(INR) followed the PK profile of YM-222714. An effect of surgery was observed as well, but this effect was small in comparison to the effect of YM-222714 itself, and small in comparison with the effect on FXa. The baseline PT(INR) decreased slightly with decreasing creatinine clearance. Females had a 4% lower baseline than males. Furthermore a slight decrease in baseline with time was observed. At a dose of 5 mg YM150 the PT(INR) increased to approximately 1.5, while at 120 mg YM150 the PT(INR) varied between approximately 2 at trough and 5.5 at maximum, with little change during the days after surgery.
No clear profile of anti-FXa activity of enoxaparin *vs.* time was observed.

Safety Results: Bleeding: The incidence of treatment emergent bleeding events up to Day 10 is summarized below (SAF).

		YM150 daily dose					
Characteristic	Statistic/category	**5 mg (N=158)**	**10 mg (N=161)**	**30 mg (N=156)**	**60 mg (N=163)**	**120 mg (N=156)**	**Enoxaparin (N=166)**
Major bleeding event	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)
	95% CI	(0.0, 2.2)	(0.0, 2.2)	(0.0, 2.2)	(0.0, 3.1)	(0.0, 2.2)	(0.0, 3.0)
Any bleeding	n (%)	4 (2.5)	5 (3.1)	10 (6.4)	14 (8.6)	15 (9.6)	9 (5.4)
	95% CI	(0.9, 6.1)	(1.2, 6.8)	(3.2, 11.2)	(5.1, 13.8)	(5.5, 15.0)	(2.7, 10.0)
Major or clinically relevant non-major bleeding	n (%)	3 (1.9)	0 (0.0)	4 (2.6)	8 (4.9)	3 (1.9)	5 (3.0)
	95% CI	(0.5, 5.4)	(0.0, 2.2)	(0.9, 6.1)	(2.1, 9.2)	(0.5, 5.5)	(1.2, 6.6)
Clinically relevant non-major bleeding	n (%)	3 (1.9)	0 (0.0)	4 (2.6)	7 (4.3)	3 (1.9)	4 (2.4)
	95% CI	(0.5, 5.4)	(0.0, 2.2)	(0.9, 6.1)	(2.0, 8.4)	(0.5, 5.5)	(0.8, 5.8)
Minor bleeding	n (%)	1 (0.6)	5 (3.1)	6 (3.8)	8 (4.9)	14 (9.0)	5 (3.0)
	95% CI	(0.0, 3.2)	(1.2, 6.8)	(1.7, 8.0)	(2.1, 9.2)	(5.3, 14.5)	(1.2, 6.6)

The primary safety endpoint was the incidence of treatment emergent clinically relevant bleedings during 7-10 days hospitalization treatment rated as major bleeding. There was 1 treatment emergent major bleed in a subject in the YM150 60 mg group and 1 in a subject in the enoxaparin group. Both bleedings were wound bleedings. There was no statistically significant dose trend for YM150 ($p=0.8065$), and none of the treatment comparisons between YM150 dose groups and enoxaparin were statistically significant (all $p>0.9$).
Analysis of secondary bleeding parameters showed a statistically significant dose trend for the incidence of any treatment emergent bleeding up to Day 10 ($p=0.0025$, $p=0.0081$ and $p=0.0662$ for the YM150 dose ranges of 5 - 120 mg, 5 - 60 mg, and 5-30 mg YM150, respectively.
Treatment emergent clinically relevant non-major bleeds until the end of the study occurred in 2.5% to 5.5% of subjects in the YM150 groups compared with 2.4% of subjects in the enoxaparin group and were more frequent in the YM150 60 mg group (5.5%) and YM150 120 mg group (5.1%).
Most bleeding events occurred during the hospitalization phase. The rate of treatment emergent minor bleeding events in the study increased with YM150 dose (1.3% to 9.0%) compared with 3.0% in the enoxaparin group up to the end of the study. Wound bleeding was the most frequently reported minor bleed.
Other safety parameters: The adverse events reported most frequently were nausea, vomiting, pyrexia, hyperthermia, and DVT. Generally, the constellation of commonly occurring adverse events was consistent with the post-operative environment following major surgery, with no clear dose-related trends in adverse events apparent in the YM150 treatment groups. Generally, no patterns in the incidence or types of adverse events in the YM150 groups as compared to the enoxaparin group were observed.
Serious adverse events related mostly to thrombosis and to surgical complications: e.g., wound infection, post-procedural complication, seroma, and pyrexia.
The overall rate of cardiac disorders appears to be similar among subjects receiving YM150 and enoxaparin. The most common renal adverse event in all treatment groups was hematuria and was primarily reported by one investigator. Increased creatinine occurred in all treatment groups and was the most common abnormal renal laboratory finding.

Most changes in biochemical laboratory values were considered related to surgery (i.e., either surgery itself or medications related to surgery).
In each treatment group, mean values for AST, ALT, and gamma-GT increased after surgery, reaching maximum values 5 to 9 days after surgery. Values returned to baseline and were unremarkable at the last study visit (4-5 weeks after last dose)) and/or the extra laboratory control visit (4 weeks after last study visit). Mean ALT and AST values remained higher for a longer period in the enoxaparin group.
The mean of total bilirubin showed an increase up to 6-9 days after surgery in the YM150 groups and returned to below baseline after this period of 6-9 days despite continued dosing. The increase was more pronounced in the higher dose groups. No increase was observed during enoxaparin treatment. Differences between YM150 and the enoxaparin group occurred throughout the whole treatment period.
Six subjects in the YM150 treatment groups had ALT elevations >3x the ULN and concurrent bilirubin elevations >2x the ULN. No cases were reported in the enoxaparin comparator group. A definite cause of gallstones at day 17 was found in one subject. The remaining five cases had an event latency of 7 to 10 days. Several confounding factors were postulated but an alternative diagnosis could not be confirmed in these six cases. There was spontaneous resolution of abnormal hepatic function with continuation of study drug in two subjects. The resolution of liver function tests in three subjects occurred after withdrawal of YM150, with improvement towards resolution at the time of withdrawal.

CONCLUSIONS:

- There was a statistically significant decreasing trend in the incidence of the primary efficacy endpoint rate of total VTE with increasing dose of YM150 for the dose ranges 5 - 120 mg (p=0.0002) and 5 - 60 mg (p=0.0005).
- The decrease in incidence of VTE with increasing dose of YM150 was close to statistical significance for the dose range 5 - 30 mg (p=0.0668), which suggests that 30 mg YM150 may also be effective in reducing incidence of the VTE endpoint.
- Symptomatic DVTs were infrequent (n=4), and occurred during the first 10 days of treatment.
- There were no PEs during the study.
- Almost all VTE events were observed in the first 10 days. Three additional distal DVTs were venographically detected between Day 11 and 14: one in the YM150 5 mg group and two in the enoxaparin group.
- The incidence of major VTE endpoint tended to decrease with increasing dose of YM150.
- Females had higher VTE rates than males (p=0.0008 for the primary efficacy parameter). Estimates of the linear trend were similar in males and females, with no evidence of an interaction – thus indicating that the effect of treatment was similar in both sexes.
- YM150 at doses of 30 - 120 mg appears to be at least as effective compared to enoxaparin for prevention of venous thromboembolism in subjects undergoing elective total hip replacement.
- The primary safety endpoint was the incidence of treatment-emergent clinically relevant bleedings up to Day 10 rated as major. There was one major bleed in the 60 mg YM150 dose group, and one in the enoxaparin group.
- The secondary safety endpoints were the incidences of major or clinically relevant non-major (CRNM) bleedings, CRNM, and all bleedings. Clinically relevant non-major bleeds were more frequent in the higher YM150 dose groups, but an analysis of all clinically relevant bleedings (major or CRNM) did not reveal any statically significant results, irrespective of evaluation period.
- There was a dose trend for the incidence of any bleeding with YM150, which was statistically significant in the dose ranges of 5 - 60 mg (p=0.0081) and 5 - 120 mg (p=0.0025) group up to Day 10, and close to statistical significance for 5-30 mg (p=0.0662). A similar dose trend is valid for up to 7 days after last dose or up to end of study.
- Females (24/425=5.6%) had similar bleeding rates to males (24/369=6.5%) over all five doses of YM150 combined (p=0.6460 for the any bleeding event up to Day 10). Estimates of the linear trend were similar in males and females, with no evidence of an interaction – thus indicating that the effect

of treatment on bleeding was similar in both sexes. There was a statistically significant linear trend for females (p=0.0498), and for males (p=0.0073 for the any bleeding event up to Day 10).

- YM150 was generally safe and well tolerated. The most common adverse events and serious adverse events were related to surgical procedures and not unexpected for this specific subject population.
- Most frequently reported adverse events were nausea, vomiting, pyrexia, hyperthermia, and DVT, with no clear YM150 dose-related trends and no patterns in the incidence or types of adverse events in the YM150 groups as compared to the enoxaparin group.
- The incidence of any cardiac disorder was similar across all treatment groups.
- In the YM150 dose groups, increases in ALT of >5 xULN were observed with a lower incidence than in the enoxaparin group.
- Concomitant increases of ALT and/or AST of >3 xULN and total bilirubin of > 2 xULN were seen in five subjects and there was one subject with increases measured two days apart, all treated with YM150.
- YM150 is associated with slight mean increases in bilirubin.
- A 2-compartment model with first order absorption and sequential zero order release and first order absorption adequately described the absorption and disposition of YM-222714. Exposure values AUC_{tau}, C_{av}, and C_{trough} increase in proportion to the dose. C_{max} increases in proportion to the dose up to a dose of 60 mg, but at 120 mg a slightly less then dose proportional increase was observed. Covariate analysis showed that clearance decreased with creatinine clearance and the central volume of distribution increased with body weight. The bioavailability increased with age, especially above the age of 60 years. Rate of absorption was slower at the highest dose of 120 mg YM150.
- Within the dose range of 5 – 120 mg, once daily treatment with YM150 resulted in a dose and YM-222714 concentration dependent decrease in FXa activity, and increase in PT(INR). The effects on FXa and PT(INR) varied over the day, following the concentration – time profile of YM-222714. Surgery itself resulted in a decrease in FXa activity, and in an increase in PT(INR), independently of the YM150 dose. The surgery effects on FXa activity and PT(INR) were of similar magnitude, while the drug effects on PT(INR) appeared relatively larger than those on FXa.

Date of Report: 8 January 2009