Name of Sponsor/Company: Astellas Pharma Europe B.V.		
Name of Finished Product: YM150		
Name of Active Ingredient: YM150		

SYNOPSIS

Title of Study:

A Randomized, Double-Blind, Double-Dummy, Parallel Group Study to Compare YM150 bid and qd Doses and Enoxaparin for Prevention of Venous Thromboembolism in Patients Undergoing Elective Hip Replacement Surgery.

Responsible Medical Officer/Investigators:

Responsible Medical Officer: [redacted], MD, Astellas Pharma Global Development Inc.

Coordinating Investigator: [redacted] Sweden

Study Centers:

A total of 169 sites were initiated in 29 countries - Australia, Bosnia*, Brazil, Canada, Colombia, India, Israel, Norway, Russian Federation, South Africa, the Ukraine, and the United States; and the following countries in the EU: Austria, Czech Republic, Denmark, Estonia, Finland, Germany, Hungary, Italy, Latvia, Lithuania, The Netherlands, Poland, Peru*, Romania, Slovakia, Spain, Sweden and United Kingdom (UK).). *Note: sites in Bosnia and Peru were initiated, but no patients were recruited.

Publication (reference):

None.

Study Period:

The treatment period was 35 days. Patients were followed up for approximately one month after the end of treatment.

Date of first enrollment (Study initiation date):

29 Apr 2009

Date of last evaluation (Study completion date):

04 Jun 2010

Phase of Development:

Phase IIb

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Objectives:

The primary objective was to evaluate the efficacy and safety of oral doses of YM150 15 mg twice daily, 30 mg once daily, 30 mg twice daily and 60 mg once daily and to compare efficacy and safety with enoxaparin 40 mg once daily sc, in patients undergoing elective hip replacement surgery. In particular, the study was designed to compare efficacy and safety in patients undergoing elective hip replacement surgery for:

- Dose frequency (qd or bid) of YM150
- Total daily dose (30 mg or 60 mg) of YM150
- Doses of YM150 compared to enoxaparin 40 mg once daily

The secondary objectives were as follows:

- To characterize the pharmacokinetics of the active metabolite YM-222714, in patients undergoing elective hip replacement surgery.
- To characterize pharmacokinetic (PK)/coagulation parameters relationship, in patients undergoing elective hip replacement surgery.
- To evaluate the effects of YM150 and enoxaparin on:
  - The health status of patients undergoing elective hip replacement surgery.
  - The health care resource use associated with both treatment options.
  - The cost-effectiveness associated with both treatment options.

Methodology:

This was a multi-center, double-blind, double-dummy, randomized, parallel group study in patients undergoing elective hip replacement surgery.

Patients were randomized equally to one of five treatment groups (oral YM150 15 mg bid, 30 mg qd, 30 mg bid or 60 mg qd, or sc enoxaparin 40 mg qd). Patients in the YM150 groups received enoxaparin placebo injections and patients in the enoxaparin group received YM150 placebo tablets.

Enoxaparin (or placebo) daily administration was started 12 (± 2) hours before the planned surgery, while YM150 (or placebo) administration was started 6 to 10 hours after the end of surgery (i.e., after wound closure). All patients were to be treated for 35 days; a mandatory bilateral lower extremity venography was performed on day 10 ± 2 days. A follow-up visit was scheduled for approximately one month after the end of treatment.

Number of Patients (planned, enrolled and analyzed):

It was planned that 2000 patients would be randomized in order to yield 280 evaluable patients in the full analysis set (FAS) per treatment group (total 1400 patients). Patients

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included in the FAS were all randomized patients who underwent the scheduled surgery and who took at least one dose of study drug or placebo, and who had a primary event (venous thromboembolism [VTE] or death) or a fully evaluable venogram up to day 12 of treatment. By definition the FAS was also the "Modified Intention-To-Treat (mITT) Set". In total 1992 patients were randomized, of whom, 1959 took study drug, and 1937 took study drug and had the scheduled surgery. Of the 1992 patients who were randomized, 1922 were included in the safety (SAF) and intent-to-treat (ITT) analysis sets, 1446 were included in the FAS, and 1402 were included in the per protocol set (PPS).

Diagnosis and Main Criteria for Inclusion:

Male or female patients aged 18 years or older who were scheduled for elective hip replacement surgery, who had provided written informed consent for study participation, and who fulfilled none of the study exclusion criteria were eligible for inclusion in this study.

Test Product, Dose and Mode of Administration, Batch Numbers:

YM150 was administered as oral tablets containing 15, 30 or 60 mg of YM150 free base equivalent as monomaleate salt.

YM150 batch numbers are listed in [Appendix 13.1.6].

Reference Product, Dose and Mode of Administration, Batch Numbers:

Enoxaparin sodium was administered using prefilled single-dose syringes containing 40 mg enoxaparin sodium 0.4 mL solution for sc injection.

Placebo to match (PTM) YM150 tablets and enoxaparin syringes were also used.

Enoxaparin and placebo batch numbers are listed in [Appendix 13.1.6].

The timing of study drug administration is shown in Table 1.

Table 1: Timing of study drug administration

Group	Tablet type			Syringe type
	Morning		Evening	
YM150				
15 mg bid	15 mg	60 mg PTM	15 mg	Enoxaparin PTM
30 mg qd	30 mg	60 mg PTM	15 or 30 mg PTM	Enoxaparin PTM
30 mg bid	30 mg	60 mg PTM	30 mg	Enoxaparin PTM
60 mg qd	15 or 30 mg PTM	60 mg	15 or 30 mg PTM	Enoxaparin PTM
Enoxaparin	15 or 30 mg PTM	60 mg PTM	15 or 30 mg PTM	Enoxaparin 40 mg
PTM: placebo to match				

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Duration of Treatment:

Patients were to be administered YM150 or enoxaparin (or matching PTMs) for 35 days as follows:

- The first dose of enoxaparin or enoxaparin PTM was administered 12 ± 2 hours before the planned surgery.
- The first dose of YM150 or YM150 PTM was administered 6 to 10 hours after the end of surgery, i.e., wound closure. The tablets could be taken with or without food.
- Continuous doses of enoxaparin or enoxaparin PTM 24 ± 2 hours were administered after the previous dose.
- The last dose of YM150 or YM150 PTM and the last dose of enoxaparin or enoxaparin PTM were to be administered on the day before visit 8/ end of treatment.

Criteria for Evaluation:

The primary efficacy variable was the composite of the following adjudicated events observed up to day 12:

- Proximal or Distal DVT
- Symptomatic DVT (proximal and / or distal)
- Nonfatal PE
- Death from all causes

Secondary efficacy variables included the incidence of the following adjudicated events until Day 12, until the end of treatment, and during the entire study (including the follow-up period):

- Major VTE and all deaths (proximal DVT, symptomatic DVT, PE and death from all causes)
- Major VTE and VTE-related death (proximal DVT, symptomatic DVT, PE and VTE-related death)
- Symptomatic VTEs. These were events (DVT or PE) reported by the investigator with symptoms according to the eCRF and confirmed as VTE events (PE or DVT) by the adjudication committee(s). A VTE related death was also classed as a symptomatic VTE.
- Patients with symptomatic events adjudicated as nonevaluable, without any other suspected symptomatic event adjudicated as a VTE, and without a VTE-related death, still had the outcome reported as missing.
- Adjudicated or suspected symptomatic events. These included all adjudicated symptomatic VTEs and VTE-related deaths, and also included any suspected symptomatic events adjudicated as non-evaluable, as if the patient had a symptomatic event.

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- Total VTE (DVT, PE and VTE-related death)
- Total DVT (proximal and / or distal, symptomatic and / or asymptomatic)
- Any proximal DVT (symptomatic and / or asymptomatic)
- Any distal DVT (symptomatic and / or asymptomatic)
- PE
- VTE-related death, classifying deaths according to the adjudicated data.

Note that a venogram was also evaluable for proximal DVT if it was fully evaluable.

Patient's health status (patient reported outcomes) was assessed using the EuroQol – 5 Dimension Questionnaire (EQ-5D) (including the EuroQol – Visual Analog Scale visual analogue scale [EQ-VAS]) and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36).

Health economic variables planned to be assessed were cost-utility analysis (CUA) and quality-adjusted life years (QALY). However, these were not analyzed in this clinical study report (CSR) and are to be presented in a separate report.

Safety variables consisted of physical examinations, vital signs, electrocardiograms (ECGs), adverse events (AEs), bleeding events (major bleeding, clinically relevant non-major bleeding [CRNM], or minor bleeding), and laboratory assessments (hematology, biochemistry and urinalysis assessments).

Pharmacokinetic variables derived for YM150 and its metabolite (YM-222714) were to include the following:

- AUC_{tau} = area under the curve between two consecutive doses
- CL/F = apparent clearance
- C_{max} = maximum concentration
- C_{trough} = trough concentration

Pharmacodynamic variables, derived in the determination of Factor X (FX) activity of YM150, were to include the following coagulation parameters: prothrombin time (PT) and activated partial thromboplastin time (aPTT).

The pharmacokinetic and pharmacokinetic variables were not analyzed for this CSR; they are to be presented in a separate report.

Statistical Methods:

The primary analysis analyzed the presence / absence of an event; it did not distinguish between types of events (i.e., it was a composite of all adjudicated VTEs and deaths, and patients who had an event were included even if their venogram was not fully evaluable).

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The primary analysis was based on the full analysis set (FAS), which defined evaluability for the primary analysis; all patients in the FAS were evaluable, and included in the primary analysis as having an event, or not having an event. By definition the FAS was also the "Modified Intention-To-Treat (mITT) Set".

Incidence was summarized by treatment group (5 arms) and pooled by YM150 daily doses (30 and 60 mg) and YM150 regimens (qd and bid). Exact confidence intervals (CIs) were produced. The treatment effect was analyzed using a logistic regression including factors for treatment, sex and country (or pooled site) as covariates.

Contrasts were used to estimate the difference between YM150 once daily and twice daily dosing, total YM150 daily dose (30 or 60 mg), and the difference between each YM150 dose and enoxaparin; odds ratios and 95% CIs were presented.

The YM150 total daily dose by frequency interaction was investigated by presenting the p-value in addition to the summary statistics for each dose group.

For the comparisons of the YM150 once and twice daily regimens, the study had approximately 80% power to detect a difference (with a 5% 2-sided significance level) of the effect of daily dosing frequency on total VTE and deaths if the true odds ratio for total VTE on day 10 ± 2 of twice versus once daily dosing was 0.6 (equivalent to an absolute risk difference of -5.4%); and the event rate of total VTE and deaths on day 10 ± 2 was 15% for patients in the YM150 once daily treatment groups. For the comparisons of the YM150 30 and 60 mg total daily doses, the study had approximately 70% power to detect a difference between 30 and 60 mg/day if the (combined) event rate of total VTE on day 10 ± 2 was 15% for 30 mg/day and the true odds ratio between 30 and 60 mg was 0.64 (equivalent to an absolute risk difference of 4.9%).

As secondary comparisons, YM150 twice versus once daily dosing was presented for each daily dose and comparisons of 60 versus 30 mg total daily dose were also carried out separately for each dose frequency. Comparisons of YM150 30 mg twice daily versus 30 mg once daily were also presented.

Secondary efficacy variables including the incidence of adjudicated events were analyzed for the following periods: until day 12, during the treatment period, and for the entire study period. An efficacy analysis was performed for each period. This was different from the analysis on the FAS population, as the ITT principle had not been applied. For the follow-up period, the numbers and percentage of patients were presented for the primary variable and for all secondary efficacy variables.

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Times to mobilization and discharge were summarized descriptively in the FAS and the ITT analysis sets. To assess whether there were any differences between countries, time to mobilization was analyzed in the logistic regression model adjusted or unadjusted for pooled site, and likewise pooled site was analyzed adjusted or unadjusted for time to mobilization. (Note: pooled sites were all sites within each country combined, except for the one site in The Netherlands that was combined with the sites in Germany).

EQ-5D, EQ-VAS and SF-36 scores were summarized descriptively overall and by treatment and country. An analysis of covariance (ANCOVA) was performed for change in EQ-VAS at end of treatment covariance including sex, age, country (or pooled site) and treatment as class variables and baseline EQ-VAS as a covariate. An ANCOVA was performed on the change from baseline to end of treatment in the overall score of the SF-36 including sex, age, country (or pooled site) and treatment group as class variables and baseline score as a covariate.

Summary of Results/Conclusions:

Population:

A total of 2235 patients were screened for this study, of which 243 were considered screening failures and 1992 were randomized to treatment. Of the 1992 randomized, 1959 received study drug (i.e., 33 no study drug), and 1937 received study drug and had the scheduled surgery (i.e., a further 22 received study drug but had no surgery). A total of 1674 (84.0%) patients completed the study and 318 (16.0%) discontinued. An additional 15 patients were excluded from the safety analysis set due to major irregularities at a single site. The safety analysis set included 1922 patients. The main reason for discontinuation from the study was due to AEs (132 [6.6%] patients).

Approximately half of the population (safety analysis set) was male (931 [48.4%] patients); 991 (51.6%) were female [Table 2]. The majority of patients were white (94.0%); 2.9% were Asian, 1.1% were black or African American, and 2.0% were of other race. The mean (SD) age was 60.0 (11.70) years and the median age was 61.0 years; 64.2% of patients were $\leq$ 65 years (minimum age 19 years), 28.7% were 65-75 years, and 7.1% were >75 years (maximum age 87 years). Mean body weight was 81.7 kg and mean BMI was 28.6 kg/m^2. Demographic characteristics were similar across the five treatment groups.

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Table 2 Demographic Characteristics – Safety Analysis Set

	YM150 15 mg bid N=374	YM150 30 mg qd N=383	YM150 30 mg bid N=387	YM150 60 mg qd N=385	Enoxaparin 40 mg qd N=393	Total N=1922
Sex: n (%)						
Male	188 (50.3)	191 (49.9)	204 (52.7)	182 (47.3)	166 (42.2)	931 (48.4)
Female	186 (49.7)	192 (50.1)	183 (47.3)	203 (52.7)	227 (57.8)	991 (51.6)
Race: n (%)						
White	357 (95.5)	357 (93.2)	361 (93.3)	362 (94.0)	370 (94.1)	1807 (94.0)
Asian	9 (2.4)	12 (3.1)	14 (3.6)	10 (2.6)	10 (2.5)	55 (2.9)
Black or African American	2 (0.5)	6 (1.6)	4 (1.0)	4 (1.0)	5 (1.3)	21 (1.1)
Other[c]	6 (1.6)	8 (2.1)	8 (2.1)	9 (2.3)	8 (2.0)	39 (2.0)
Ethnicity: n (%)						
Not Hispanic or Latino	364 (97.3)	364 (95.0)	377 (97.4)	374 (97.1)	380 (96.7)	1859 (96.7)
Hispanic or Latino	10 (2.7)	19 (5.0)	10 (2.6)	11 (2.9)	13 (3.3)	63 (3.3)
Age (years)						
Mean	60.4	59.5	59.8	59.5	61.1	60.0
(SD)	(10.95)	(11.73)	(12.13)	(11.82)	(11.79)	(11.70)
Median	61.0	61.0	61.0	61.0	62.0	61.0
Min, Max	19, 85	19, 85	24, 86	23, 84	19, 87	19, 87
Age group (years): n (%)						
≤ 65	243 (65.0)	255 (66.6)	248 (64.1)	251 (65.2)	236 (60.1)	1233 (64.2)
65 to 75	106 (28.3)	106 (27.7)	109 (28.2)	112 (29.1)	119 (30.3)	552 (28.7)
> 75	25 (6.7)	22 (5.7)	30 (7.8)	22 (5.7)	38 (9.7)	137 (7.1)
Weight (kg)						
Mean	81.4	82.2	82.0	82.8	80.3	81.7
(SD)	(16.54)	(16.54)	(17.67)	(17.13)	(15.42)	(16.68)
Median	80.0	80.5	80.0	82.0	79.0	80.0
Min, Max	50, 138	38, 140	38, 140	43, 173	43, 146	38, 173
Height (cm)						
Mean	169.0	168.6	169.2	168.9	167.9	168.7
(SD)	(9.02)	(9.28)	(9.66)	(9.70)	(9.29)	(9.40)
Median	168.3	168.0	170.0	168.0	168.0	168.0
Min, Max	143, 193	142, 191	138, 200	145, 198	140, 191	138, 200
BMI (kg/m^2)						
Mean (SD)	28.4 (4.97)	28.8 (5.14)	28.5 (5.22)	28.9 (5.00)	28.4 (4.66)	28.6 (5.00)
Median	27.9	28.2	28.3	28.7	28.0	28.1
Min, Max	19, 46	16, 55	17, 47	18, 50	18, 48	16, 55

Source: Table 12.1.2.1
BMI: body mass index (weight (kg)/height [m^2])

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Efficacy Results:

Primary Efficacy Variable

YM150 twice daily vs once daily

The results of the FAS for the primary efficacy variable (composite of all adjudicated VTEs and deaths up to day 12) showed that, 13.3% of patients who received a twice daily dose of YM150 (combined 15 and 30 mg bid), and 13.2% who received a once daily dose (combined 30 and 60 mg qd) had an event [Table 3]. Distal DVT was the most frequent event (11.2% bid and 12.0% qd) followed by proximal DVT (2.5% bid and 1.9% qd). There were no VTE-related deaths in the study; the one death that occurred was adjudicated as not VTE-related. The results of the logistic regression analysis showed the risk of incidence of a VTE to be similar for YM150 twice and once daily regimens, and it was not possible to demonstrate a statistically significant difference between the two dosing frequencies (odds ratio = 1.00 [95% CI: 0.71 to 1.42])

YM150 60 vs 30 mg/day

Up to day 12, 12.1% of patients who received a total daily dose of YM150 60 mg (combined 30 mg bid and 60 mg qd) had an event compared with 14.4% who received a total daily dose of 30 mg (combined 15 mg bid and 30 mg qd) [Table 3]. Distal DVT was the most frequent event (60 mg daily dose 10.5% and 30 mg 12.6%) followed by proximal DVT (60 mg 2.1% and 30 mg 2.3%). The results indicated that a YM150 60 mg total daily dose may be associated with a lower risk of incidence of the primary efficacy endpoint than a 30 mg total daily dose; the odds ratio on the difference between the doses was 0.81 (95% CI: 0.57 to 1.15). It was not possible to demonstrate that the difference between total daily doses of YM150 60 and 30 mg was statistically significant.

Frequency of dosing and total daily dose interaction was tested in order to check that the hypothesis that the relative difference between twice and once daily dosing was the same as total daily dose (60 vs 30 mg). No evidence of an interaction was shown (P = 0.347), hence the overall tests (bid vs qd and 60 vs 30 mg/day) were valid.

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Table 3 **Primary Analysis - Logistic Regression of Venous Thromboembolisms and Deaths up to Day 12 – Full Analysis Set - YM150 Treatment Group Combinations**

Number (%) of Patients	**YM150 bid N=565**	**YM150 qd N=567**	**YM150 30 mg/day^ N=562**	**YM150 60 mg/day^ N=570**	**YM150 Total N=1132**
Deaths due to any cause	1 (0.2)	0	0	1 (0.2)	1 (0.1)
Pulmonary embolism	2 (0.4)	1 (0.2)	2 (0.4)	1 (0.2)	3 (0.3)
Symptomatic DVT	3 (0.5)	0	0	3 (0.5)	3 (0.3)
Any proximal DVT	14 (2.5)	11 (1.9)	13 (2.3)	12 (2.1)	25 (2.2)
Any distal DVT	63 (11.2)	68 (12.0)	73 (12.6)	60 (10.5)	131 (11.6)
Both proximal and distal DVT	5 (0.9)	4 (0.7)	4 (0.79)	5 (0.9)	9 (0.8)
Patients with events	75 (13.3)	75 (13.2)	81 (14.4)	69 (12.1)	150 (13.3)
95% CI	(10.6, 16.4)	(10.5, 16.3)	(11.6, 17.6)	(9.5, 15.1)	(11.3, 15.4)
Comparison	bid vs qd		60 mg/day vs 30 mg/day		
Odds ratio	1.00		0.81		
95% CI	(0.71, 1.42)		(0.57, 1.15)		
p-value	0.988		0.244		
Secondary comparison	15 mg bid vs 30 mg qd	30 mg bid vs 60 mg qd	30 mg bid vs 15 mg bid	60 mg qd vs 30 mg qd	YM150 total daily dose by frequency interaction
Odds ratio	1.19	0.85	0.69	0.96	
95% CI	(0.73, 1.92)	(0.51, 1.41)	(0.42, 1.13)	(0.59, 1.58)	
p-value	0.485	0.525	0.136	0.874	0.347

Source: Table 12.3.2.1
This table displays the number of patients with events based on adjudicated results. Patients may appear in more than 1 row.
Only events and venograms up to day 12 are included.
Odds ratio < 1 represents having less risk of primary endpoint events. The opposite applies for odds ratios > 1.

YM150 vs enoxaparin

In the original treatment groups, the primary efficacy endpoint was observed in 15.6% of patients in the YM150 15 mg twice daily group, 13.3% in the 30 mg once daily group, 11.1% in the 30 mg twice daily group, 13.1% in the 60 mg once daily group, and 15.3% for enoxaparin [Table 4]. The overall incidence across the five treatment groups was 13.7%.

The results of the logistic regression showed that the risk of incidence of a VTE in the YM150 15 mg twice daily group was similar to enoxaparin (odd ratio on the difference = 1.04), whereas the risk of incidence in the other YM150 groups was lower than for enoxaparin (odds ratios = 0.71 to 0.87). It was not possible to demonstrate a statistically significant difference between the two drugs.

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Table 4 **Logistic Regression of Venous Thromboembolisms and Deaths up to Day 12 – Full Analysis Set – All Treatment Groups**

Number (%) of Patients	**YM150 15 mg bid N=269**	**YM150 30 mg qd N=293**	**YM150 30 mg bid N=296**	**YM150 60 mg qd N=274**	**Enoxaparin 40 mg qd N=314**	**Total N=1446**
Deaths due to any cause	0	0	1 (0.3)	0	0	1 (0.1)
Pulmonary embolism	1 (0.4)	1 (0.3)	1 (0.3)	0	1 (0.3)	4 (0.3)
Symptomatic DVT	0	0	3 (1.0)	0	0	3 (0.2)
Any proximal DVT	6 (2.2)	7 (2.4)	8 (2.7)	4 (1.5)	9 (2.9)	34 (2.4)
Any distal DVT	38 (14.1)	33 (11.3)	25 (8.4)	35 (12.8)	45 (14.3)	176 (12.2)
Both proximal and distal DVT	3 (1.1)	1 (0.3)	2 (0.7)	3 (1.1)	6 (1.9)	15 (1.0)
Patients with events	42 (15.6)	39 (13.3)	33 (11.1)	36 (13.1)	48 (15.3)	198 (13.7)
95% CI	(11.5, 20.5)	(9.6, 17.7)	(7.8, 15.3)	(9.4, 17.7)	11.5, 19.8)	(12.0, 15.6)
Comparison vs enoxaparin						
Odds ratio	1.04	0.87	0.71	0.84		
95% CI	(0.65, 1.64)	(0.55, 1.39)	(0.44, 1.15)	(0.52, 1.35)		
p-value	0.879	0.567	0.165	0.466		
Secondary comparison: 30 mg bid vs 30 mg qd						
Odds ratio		0.81				
95% CI		(0.49, 1.35)				
p-value		0.422				

Source: Table 12.3.2.1
This table displays the number of patients with events based on adjudicated results. Patients may appear in more than 1 row. Only events and venograms up to day 12 are included.
Odds ratio < 1 represents having less risk of primary endpoint events. The opposite applies for odds ratios > 1.

Secondary analysis of the primary efficacy variable

When the primary efficacy variable was analyzed for the entire treatment period (FAS-trt) and the entire study (FAS-stdy), the results were similar to those up to day 12 (FAS).

VTEs were also analyzed by sex (male vs female patients) and age (≤ 61 years and ≥ 62 years) in the FAS-stdy. The odds ratios indicated that YM150 twice daily dosing had a similar risk of VTE and deaths as the once daily dosing for both age groups. However, regarding sex, the results for female patients indicated less risk of VTE and deaths with twice dosing (12.5% of patients) compared to once daily dosing (16.3% of patients) (odds ratio = 0.74 [95% CI: 0.46, 1.20]). For male patients the results indicated more risk with twice daily dosing (13.7% of patients) compared with once daily dosing (10.8% of patients) (odds ratio = 1.29 [95% CI: 0.77, 2.14]). For both sex and age the YM150 60 mg/day dose was associated with a lower incidence of VTEs and deaths than the 30 mg/day dose. In the comparisons of YM150 with enoxaparin, the incidence of VTEs with 15 mg twice daily was higher for

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male patients than observed with enoxaparin, and in the other YM150 dosing groups the incidence of VTEs was generally lower than seen with enoxaparin.

In the analysis of the effects of covariates on the primary efficacy variable (BMI, surgery technique, type of anesthesia, type of prosthesis, surgery duration, baseline systolic pressure, concomitant treatment for thrombosis [prior to a VTE], and time to mobilization [first day walking more than 2 steps]) a similar trend to the overall primary efficacy was observed. This was consistent across treatment groups and covariates. The exception was for BMI > 30 kg/m^2, where the incidence of VTEs was higher in the 15 mg twice daily group (23.0%) compared with enoxaparin (11.1%), which was similar or higher than the other YM150 groups (30 mg qd 9.5%, 30 mg bid 11.4% and 60 mg qd 12.0%), although it was not possible to demonstrate any statistically significant differences. There was little or no evidence of a treatment by pooled site interaction. Due to some local variation in time to mobilization, this variable was also analyzed in the logistic regression model adjusted or unadjusted for pooled site, and likewise pooled site was analyzed adjusted or unadjusted for time to mobilization. The results show that mobilization unadjusted for pooled site was statistically significant (P = 0.038); mobilization adjusted for pooled site, pooled site adjusted for mobilization and pooled site unadjusted for mobilization were not statistically significant.

Logistic regression analysis of the primary endpoint in the PPS was consistent with results for the FAS. Results of other sensitivity analyses were also similar to the FAS results.

Secondary Efficacy Variables

With respect to the secondary efficacy endpoints, the results were similar to the primary endpoint, in that no statistically significant differences in the effect of YM150 dosing frequency (bid vs qd), or total daily dose (30 vs 60 mg) were observed, although there was a general trend of a lower incidence of VTEs with a 60 mg daily dose. Regarding comparisons of YM150 with enoxaparin, incidence of major events for YM150 60 mg once daily were numerically lower (1.4%) than those in the enoxaparin group (3.0%). YM150 30 mg twice daily (3.5%) was similar to enoxaparin, and the other two groups, YM150 15 mg twice daily (2.4%) and 30 mg once daily (2.3%) were lower than enoxaparin. It is also noted that there were no symptomatic VTEs observed in the YM150 60 mg once daily group (ITT analysis set to day 12), compared with 15 mg twice daily (1 event, 0.3%), 30 mg once daily (1 event, 0.3%), 30 mg twice daily (4 events, 1.0%), and enoxaparin (1 event, 0.3%). The results were similar to those for the entire treatment period and those for the entire study, and none demonstrated any statistically significant differences.

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Most VTEs occurred during the first 12 days of treatment (198/1446 patients [13.7%]). Very few VTEs started after day 12: entire treatment period 201/1478 (13.6%) and entire study 207/1495 (13.8%).

It is noted that although the incidence of distal DVT in the 60 mg once daily dosing group was similar or higher to the other YM150 groups, the incidence of major events, such as proximal DVT were consistently lower in the 60 mg once daily group.

Summary of Efficacy Results

In summary, the efficacy findings generally showed that the risk of an incidence of observed VTEs with the YM150 twice daily regimens were similar to the once daily regimens, but total daily doses of YM150 60 mg were associated with a lower risk of VTEs than total daily doses of 30 mg, although a statistically significant difference could not be demonstrated. Compared with enoxaparin, the findings demonstrated that a total daily dose of YM150 30 mg was associated with a risk of VTE comparable to that for enoxaparin, whereas a total daily dose of YM150 60 mg was associated with a trend towards a reduced VTE risk.

Time to Mobilization and Discharge:

Over three quarters (76.8%) of patients had started walking 2 or more steps by day 3 after surgery: 7.3% on day 1, 36.0% on day 2, and 33.5% on day 3. A further 4.1% of patients started walking 2 or more steps on day 5, 1.6% on day 6 and 4.2% from day 7 onwards. The mean (SD) time to mobilization was 3.0 (1.79) days (median 3.0 days, range [minimum, maximum] 1 to 33 days). The mean (SD) time to discharge was 10.4 (5.10) days (median 10.0 days, range 2 to 65 days). Time to mobilization and discharge were similar across the 5 treatment groups, with no observable differences between the YM150 dosing regimens and no observed difference from enoxaparin.

Patient Reported Outcomes:

The changes from baseline to end of treatment (day 35) in responses to EQ-5D were consistent with the expected recovery period following major surgery, and were similar across the 5 treatment groups.

The change from baseline to end of treatment in EQ-VAS score showed no effect of either dosing frequency (YM150 bid vs qd: difference = -0.2 [95% CI: -1.7, 1.4]) or total daily dose (YM150 60 vs 30 mg/day: difference = 0.6; [95% CI: 1.0, 2.1]), and no differences between the four YM150 dosing regimens and enoxaparin were observed (treatment differences ranging from -1.1 to -0.2).

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Mean (SD) overall SF-36 scores were 49.7 (16.91) at baseline and 57.9 (15.61) at end of treatment; the mean (SD) change from baseline was 8.0 (17.18). The scores were similar across the 5 treatment groups. No effect of either dosing frequency (YM150 bid vs qd: -0.9 [95% CI: -2.3, 0.5]) or total daily dose (YM150 60 and 30 mg/day: 0.3; [1.7, 1.2]), on SF-36 scores was observed, and there were no differences between the four YM150 dosing regimens and enoxaparin (differences in score ranging from -0.9 to 0.2).

Mean (SD) Physical Health Composite Summary (PCS) scores of the SF-36 were 41.2 (16.26) at baseline and 50.5 (15.99) at end of treatment; the mean (SD) change from baseline was 9.3 (17.72). Mean (SD) Mental Health Composite Summary (MCS) ST-36 scores were 58.3 (20.01) at baseline and 65.2 (17.75) at end of treatment; the mean (SD) change from baseline was 6.7 (19.62). All scores were similar across the 5 treatment groups

Mean (SD) changes from baseline in the 8 dimensions of the SF-36 scale showed that patients' greatest perception of improvement was in bodily pain (22.7 [25.67]). Improvements were also seen in vitality (10.9 [21.30]), general mental health (10.2 [19.10]), general health perceptions 8.2 [16.26]), and physical functioning (7.8 [26.34]). Small improvements in role limitations due to emotional problems (2.6 [31.39]) and social functioning (3.1 [30.17] were observed. The least improvement was observed for role limitations due to physical health problems, with an overall mean (SD) decrease from baseline of -1.6 (28.63).

Health Economic Results:

These data are not included in this CSR, and will be described in a separate report.

Pharmacokinetic and Pharmacodynamic Results:

It is planned that the pharmacokinetic and pharmacodynamic results (including FXa activity) are to be reported in a separate bioanalytical report and are not part of this CSR.

Safety Results:

Adverse Events

In this study TEAEs were reported in 68.7% of patients [Table 5]. Gastrointestinal disorders were the most frequently reported TEAEs, of which the most common was nausea (10.5% of patients).

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Table 5 Summary of Treatment-Emergent Adverse Events Experienced by ≥ 5% of Patients in Any Treatment Group – Safety Analysis Set

Number (%) Patients **MedDRA (v9.1) SOC** Preferred term	**YM150 15 mg bid N=374**	**YM150 30 mg qd N=383**	**YM150 30 mg bid N=387**	**YM150 60 mg qd N=385**	**Enoxaparin 40 mg qd N=393**	**Total N=1922**
Overall	260 (69.5)	270 (70.5)	257 (66.4)	261 (67.8)	272 (69.2)	1320 (68.7)
Gastrointestinal disorders	**88 (23.5)**	**97 (25.3)**	**89 (23.0)**	**92 (23.9)**	**98 (24.9)**	**464 (24.1)**
Nausea	47 (12.6)	38 (9.9)	40 (10.3)	37 (9.6)	39 (9.9)	201 (10.5)
Constipation	25 (6.7)	30 (7.8)	34 (8.8)	32 (8.3)	33 (8.4)	154 (8.0)
Vomiting	22 (5.9)	23 (6.0)	17 (4.4)	23 (6.0)	26 (6.6)	111 (5.8)
Investigations	**65 (17.4)**	**58 (15.1)**	**77 (19.9)**	**69 (17.9)**	**73 (18.6)**	**342 (17.8)**
ALT increased	18 (4.8)	7 (1.8)	20 (5.2)	13 (3.4)	15 (3.8)	73 (3.8)
Injury, poisoning & procedural complications	**59 (15.8)**	**63 (16.4)**	**64 (16.5)**	**67 (17.4)**	**68 (17.3)**	**321 (16.7)**
Anemia postoperative	22 (5.9)	22 (5.7)	19 (4.9)	23 (6.0)	19 (4.8)	105 (5.5)
General disorders & administration site conditions	**56 (15.0)**	**69 (18.0)**	**61 (15.8)**	**53 (13.8)**	**59 (15.0)**	**298 (15.5)**
Pyrexia	27 (7.2)	35 (9.1)	28 (7.2)	25 (6.5)	30 (7.6)	145 (7.5)
Vascular disorders	**47 (12.6)**	**49 (12.8)**	**46 (11.9)**	**48 (12.5)**	**54 (13.7)**	**244 (12.7)**
Hypotension	19 (5.1)	17 (4.4)	15 (3.9)	17 (4.4)	26 (6.6)	94 (4.9)
Blood & lymphatic system disorders	**15 (4.0)**	**23 (6.0)**	**23 (5.9)**	**21 (5.5)**	**25 (6.4)**	**107 (5.6)**
Anemia	11 (2.9)	18 (4.7)	19 (4.9)	14 (3.6)	21 (5.3)	83 (4.3)

Source: Table 12.6.1.2

The majority of patients experienced mild (40.6%) or moderate TEAEs (23.2%); 4.9% patients experienced severe TEAEs. A total of 153 (8.0%) patients discontinued the study due to TEAES, and the numbers of patients discontinuing were similar across treatment groups. The most common TEAE leading to discontinuation was DVT (32 [1.7%] patients).

Drug-related TEAEs were reported for 420 (21.9%) patients. Abnormal liver function test results accounted for the most frequently reported drug-related events, including ALT increased (2.7%) and AST increased (2.5%).

Serious TEAEs were reported for 140 (7.3%) patients. The incidence of serious TEAEs was similar across the five treatment groups (% patients: YM150 15 mg bid 7.0%, YM150 30 mg qd 8.1%, YM150 30 mg bid 8.8%, YM150 60 mg qd 6.2%, and enoxaparin 40 mg qd 6.4%). The most common serious TEAE was DVT, and was reported in 0.9% of patients. Drug related serious TEAES were reported for 50 (2.6%) patients. The most common drug-related serious TEAE was DVT, which was reported in 9 (0.5%) patients (YM150 15 mg bid no patients; YM150 30 mg qd 3 [0.8%]; YM150 30 mg bid 2 [0.5%]; YM150 60 mg qd 1 [0.3%]; and enoxaparin 40 mg qd 3 [0.8%]).

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One patient (YM150 30 mg bid group) died in the study. This patient discontinued study drug on day 3 after feeling ill, was diagnosed with aspiration pneumonia and ileus on day 4, and died on day 5. The investigator did not consider the death to be related to study drug, and the death was adjudicated as not VTE-related. Autopsy revealed no PE and confirmed that aspiration pneumonia was the cause of death.

Bleeding Adverse Events

The results show that most BAEs occurred within the first 12 days of treatment (160 patients [8.3%]: entire treatment period 176 patients (9.2%), and the entire study 178 patients (9.3%). Major and/or CRNM (clinically relevant non-major) bleeding events were observed in 4.5% of patients during the first 12 days, and 4.9% of patients over the entire study [Table 6].
A total of 33 patients (1.7%) had major BAEs within the first 12 days of treatment. Of all 33 patients that had reported a major bleeding event, 29 were reported on the day of surgery. More specifically, 21 of 25 patients assigned to YM150, reported a major bleeding event in the perioperative period before they received the first dose of active YM150 tablets.

A trend indicating a higher incidence of BAEs was observed in the YM150 30 mg twice daily dosing group (10.9% of patients for any BAE up to 12 days, compared with 5.3% for 15 mg bid, 8.1% 30 mg qd, 8.3% 60 mg qd, and 8.9% for enoxaparin). Likewise the incidence of major and/or CRNM BAEs up to day 12 was also greatest in the YM150 30 mg twice daily dosing group (6.7% of patients, compared with 3.5% 15 mg bid, 3.9% 30 mg qd, 3.6% 60 mg qd, and 4.6% for enoxaparin). The incidence of minor BAEs was also greater in the YM150 30 mg twice daily group than the other treatment groups.

Major adjudicated BAEs were due to an overt BAE leading to transfusion of > 2 units of blood (31 patients [1.6%]), or an overt BAE with a decrease in hemoglobin of > 20 g/L (11 patients [0.6%]). The main categories of clinically relevant non-major BAEs were epistaxis (> 5 minutes, repetitive or leading to intervention) (9 patients [0.5%]), wound hematoma > 100 cm^2 (7 patients [0.4%]), macroscopic hematuria (7 patients [0.4%]), and spontaneous rectal bleeding (6 patients [0.3%]).

No retroperitoneal, intracranial, intraspinal, intraocular or pericardial bleeding events were reported during the study.

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Table 6 **Overview of Bleeding Adverse Events (Adjudicated Results) – Safety Analysis Set – All Treatment Groups**

Period Endpoint	**YM150 15 mg bid N=374**	**YM150 30 mg qd N=383**	**YM150 30 mg bid N=387**	**YM150 60 mg qd N=385**	**Enoxaparin 40 mg qd N=393**	**Total N=1922**
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with BAEs up to Day 12						
Major BAEs	5 (1.3)	4 (1.0)	9 (2.3)	7 (1.8)	8 (2.0)	33 (1.7)
CRNM	8 (2.1)	11 (2.9)	17 (4.4)	7 (1.8)	10 (2.5)	53 (2.8)
Minor	7 (1.9)	17 (4.4)	20 (5.2)	19 (4.9)	18 (4.6)	81 (4.2)
Major and/or CRNM	13 (3.5)	15 (3.9)	26 (6.7)	14 (3.6)	18 (4.6)	86 (4.5)
Any BAE	20 (5.3)	31 (8.1)	42 (10.9)	32 (8.3)	34 (8.9)	160 (8.3)
Patients with BAEs in the treatment period (up to and including day after last dose)						
Major BAEs	5 (1.3)	4 (1.0)	9 (2.3)	7 (1.8)	8 (2.0)	33 (1.7)
CRNM	10 (2.7)	14 (3.7)	18 (4.7)	9 (2.3)	11 (2.8)	62 (3.2)
Minor	10 (2.7)	20 (5.2)	19 (4.9)	21 (5.5)	21 (5.3)	91 (4.7)
Major and/or CRNM	15 (4.0)	18 (4.7)	27 (7.0)	16 (4.2)	19 (4.8)	95 (4.9)
Any BAE	24 (6.4)	36 (9.4)	42 (10.9)	35 (9.1)	39 (9.9)	176 (9.2)
Patients with BAEs in the study						
Major BAEs	5 (1.3)	4 (1.0)	9 (2.3)	7 (1.8)	8 (2.0)	33 (1.7)
CRNM	10 (2.7)	14 (3.7)	18 (4.7)	9 (2.3)	11 (2.8)	62 (3.2)
Minor	10 (2.7)	20 (5.2)	21 (5.4)	21 (5.5)	21 (5.3)	93 (4.8)
Major and/or CRNM	15 (4.0)	18 (4.7)	27 (7.0)	16 (4.2)	19 (4.8)	95 (4.9)
Any BAE	24 (6.4)	36 (9.4)	44 (11.4)	35 (9.1)	39 (9.9)	178 (9.3)
Patients with BAEs in the follow-up period						
Major BAEs	0	0	0	0	0	0
CRNM	0	0	0	0	0	0
Minor	0	0	2 (0.5)	0	1 (0.3)	3 (0.2)
Major and/or CRNM	0	0	0	0	0	0
Any BAE	0	0	2 (0.5)	0	1 (0.3)	3 (0.2)

Source: Table 12.6.6.1
BAE: bleeding adverse event; CRNM: Clinically-relevant nonmajor

The logistic regression of major and/or CRNM BAEs up to day 12 is shown in [Table 7] and [Table 8]. In the logistic regression analysis of major and/or CRNM BAEs up to day 12, the YM150 total daily dose by frequency interaction was statistically significant (P = 0.039), and in the comparison of individual doses, 30 mg twice daily vs 60 mg once daily was statistically significant (P = 0.033; odds ratio = 2.22 [1.07, 4.61]), and likewise 30 mg twice daily vs 15 mg twice daily (P = 0.017; odds ratio = 2.52 [1.18, 5.41]). This trend was also shown in the analysis of major and/or CRNM BAEs in the entire treatment period and in the entire study, as well as for any BAE.

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Table 7 Logistic Regression of Major and/or Clinically Relevant Non-Major Bleeding Adverse Events (Adjudicated Results) Up to Day 12 – Safety Analysis Set – All Treatment Groups

Number (%) of Patients - SAF	YM150 15 mg bid N = 374	YM150 30 mg qd N = 383	YM150 30 mg bid N = 387	YM150 60 mg qd N = 385	Enoxaparin 40 mg qd N = 393	Total N = 1922
Major and/or CRNM BAE up to day 12						
Patients with events	13 (3.5)	15 (3.9)	26 (6.7)	14 (3.6)	18 (4.6)	86 (4.5)
95% CI	(1.9, 5.9)	(2.2, 6.4)	(4.4, 9.7)	(2.0, 6.0)	(2.7, 7.1)	(3.6, 5.5)
Comparison vs enoxaparin						
Odds ratio	0.62	0.90	1.57	0.71		
95% CI	(0.28, 1.39)	(0.43, 1.88)	(0.81, 3.05)	(0.33, 1.52)		
P-value	0.245	0.772	0.187	0.374		
Secondary comparison: 30 mg bid vs 30 mg qd						
Odds ratio		1.75				
95% CI		(0.87, 3.51)				
P-value		0.116				

Source: Table 12.6.6.4
BAE: bleeding adverse event, CI: confidence interval, CRNM: clinically relevant non-major. This table displays the number of patients with events based on adjudicated results. Patients may appear in more than 1 row. Only events up to day 12 are included

Table 8 Logistic Regression of Major and/or Clinically Relevant Non-Major Bleeding Adverse Events (Adjudicated Results) Up to Day 12 – Safety Analysis Set – YM150 Treatment Group Combinations

Number (%) of Patients - SAF	YM150 bid N = 761	YM150 qd N = 768	YM150 30 mg/day † N = 757	YM150 60 mg/day † N = 772	YM150 Total N = 1529
Major and/or CRNM BAE up to day 12					
Patients with events	39 (5.1)	29 (3.8)	28 (3.7)	40 (5.2)	68 (4.4)
95% CI	(3.7, 6.9)	(2.5, 5.4)	(2.5, 5.3)	(3.7, 7.0)	(3.5, 5.6)
Comparison	bid vs qd ‡		60 mg/day vs 30 mg/day §		
Odds ratio	1.24		1.41		
95% CI	(0.71, 2.16)		(0.81, 2.45)		
P-value	0.446		0.222		
Secondary comparison	15 mg bid vs 30 mg qd	30 mg bid vs 60 mg qd	30 mg bid vs 15 mg bid	60 mg qd vs 30 mg qd	YM150 total daily dose by frequency interaction
Odds ratio	0.69	2.22	2.52	0.79	
95% CI	(0.30, 1.59)	(1.07, 4.61)	(1.18, 5.41)	(0.36, 1.75)	
P-value	0.386	0.033	0.017	0.559	0.039

Source: Table 12.6.6.4
BAE: bleeding adverse event, CI: confidence interval, CRNM: clinically relevant non-major. † Includes both qd and bid dosing with total daily dose as specified, ‡ Odds ratio < 1 represents bid having less risk of primary endpoint events (i.e., bid better than qd), § Odds ratio < 1 represents 60 mg/day having less risk of primary endpoint events (i.e., YM150 60 better than 30 mg/day); the opposite applies for odds ratios > 1. This table displays the number of patients with events based on adjudicated results. Patients may appear in more than 1 row. Only events up to day 12 are included

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There were clinically significant laboratory test findings of transitional elevations in liver function tests, of ALT, AST and bilirubin [Table 9]. Four patients (0.2%) had concurrent elevations (combined abnormality) of total bilirubin > 2 x ULN and ALT or AST > 3 x ULN between days 2 and 4 of the study. Three of these patients were in the enoxaparin group and one was in the YM150 30 mg twice daily group. In all four patients the abnormalities were reported as TEAEs, for which the patients discontinued the study, and all were considered possibly drug-related apart for one patient in the enoxaparin group. For 2 of the 3 patients in the enoxaparin group the TEAEs were also reported as serious. Overall the elevations of laboratory hepatic markers were numerically lower in the YM150 groups than in the enoxaparin group.

Table 9 Clinically Significant Values in Liver Function Laboratory Tests – Safety Analysis Set – All Treatment Groups

Number (%) Patients Laboratory test/ Abnormality name	YM150 15 mg bid N=374	YM150 30 mg qd N=383	YM150 30 mg bid N=387	YM150 60 mg qd N=385	Enoxaparin 40 mg qd N=393	Total N=1922
ALT > 3 x ULN	18 (4.9)	15 (4.0)	23 (6.0)	12 (3.2)	27 (7.0)	95 (5.0)
ALT > 5 x ULN	10 (2.1)	8 (2.2)	8 (2.1)	3 (0.8)	14 (3.6)	43 (2.3)
ALT > 10 x ULN	3 (0.8)	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.5)	8 (0.4)
AST > 3 x ULN	22 (6.0)	14 (3.7)	13 (3.4)	17 (4.5)	24 (6.2)	90 (4.8)
AST > 5 x ULN	6 (1.6)	4 (1.1)	3 (0.8)	5 (1.3)	10 (2.6)	28 (1.5)
AST > 10 x ULN	2 (0.5)	1 (0.3)	0	0	1 (0.3)	4 (0.2)
ALT or AST > 3 x ULN	28 (7.6)	19 (5.1)	27 (7.0)	22 (5.8)	37 (9.6)	133 (7.0)
ALT or AST > 5 x ULN	11 (3.0)	8 (2.2)	9 (2.4)	6 (1.6)	16 (4.2)	50 (2.6)
ALT or AST > 10 x ULN	3 (0.8)	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.5)	8 (0.4)
Total bilirubin > 2 x ULN	1 (0.3)	2 (0.5)	2 (0.5)	2 (0.5)	6 (1.6)	13 (0.7)
Total bilirubin > 3 x ULN	0	0	0	0	2 (0.5)	2 (0.1)
Moderate and/or marked liver abnormality[a]	29 (7.9)	21 (5.7)	28 (7.3)	24 (6.4)	39 (10.2)	141 (7.5)
Marked liver abnormality[b]	11 (3.0)	8 (2.2)	10 (2.6)	6 (1.6)	16 (4.2)	51 (2.7)
Combined abnormality[c]	0	0	1 (0.3)	0	3 (0.8)	4 (0.2)

Source: Table 12.6.2.4
[a] Defined as total bilirubin > 2 x ULN, ALT > 3 x ULN and/or AST > 3 x ULN
[b] Defined as total bilirubin > 3 x ULN, ALT > 5 x ULN and/or AST > 5 x ULN; or total bilirubin >2 x ULN with ALT or AST >3 x ULN
[c] Defined as ALT or AST > 3 x ULN and total bilirubin >2 x ULN

Elevations of serum creatinine > 25% compared with baseline were lowest in the 60 mg once daily group (5.3% of patients) compared with the other YM150 groups (8.1% to 8.8%) and enoxaparin (8.8%) [Table 10]. Similarly, elevations of serum creatinine > 50% compared with baseline were lowest in the 60 mg once daily group (1.1% of patients) compared with the other YM150 groups (3.0% to 3.4%) and enoxaparin (3.6%).

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Table 10 Clinically Significant Values in Renal Function – Safety Analysis Set - All Treatment Groups

Number (%) Patients Laboratory test/ Abnormality name	YM150 15 mg bid N=374	YM150 30 mg qd N=383	YM150 30 mg bid N=387	YM150 60 mg qd N=385	Enoxaparin 40 mg qd N=393	Total N=1922
Serum creatinine increase:						
>25% compared to baseline	30 (8.1)	33 (8.8)	33 (8.6)	20 (5.3)	34 (8.8)	150 (7.9)
>50% compared to baseline	11 (3.0)	12 (3.2)	13 (3.4)	4 (1.1)	14 (3.6)	54 (2.8)

Source: Table 12.6.2.5

Of the 18 fractures reported during the study, 15 fractures (83.3%) were probably related to surgery on the basis of the fact that the event was reported on the day of surgery and/or was reported as being procedure-related by the investigator. For three events there was no obvious relation to the surgical procedure.

There were 8 events adjudicated as acute coronary syndrome (ACS) in this study, 2 in the YM150 15 mg twice daily group, 3 in the YM150 30 mg twice daily group, 1 in the YM150 60 mg once daily group, and 2 in the enoxaparin group.

No differences were observed between treatment groups regarding the incidence of cardiac, hepatic or renal TEAEs, or between treatment groups for vital signs measurements, ECGs or physical examination findings.

CONCLUSIONS:

Efficacy Conclusions:

- The incidence of the primary efficacy endpoint (composite of adjudicated VTEs and deaths observed up to day 12 in the FAS) with the YM150 twice daily regimens (15 mg bid and 30 mg bid, 13.3%) was similar to the once daily dosing regimens (30 mg qd and 60 mg qd, 13.2%). The odds ratio was 1.00 and the 95% CI ranged from 0.71 to 1.42, and there was no statistically significant difference between the 2 dosing frequencies.
- A total daily dose of YM150 60 mg (30 mg bid and 60 mg qd) was associated with a lower incidence (12.1% of patients) of the primary efficacy endpoint than a 30 mg total daily dose (15 mg bid and 30 mg qd) (14.4%), but despite an odds ratio of < 1 there was no statistically significant difference between the 2 doses (odds ratio = 0.81 [95% CI: 0.57 to 1.15])
- The observed incidence of the primary efficacy endpoint for YM150 15 mg twice daily (15.6% of patients) was similar to enoxaparin (15.3%), whereas the incidence for the other YM150 arms (11.1% to 13.3%) was lower than enoxaparin, although the differences between treatments were not statistically significant.

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- With respect to the secondary efficacy endpoints, the results were similar to the primary endpoint, in that no statistically significant differences between YM150 twice and once daily dosing, and between 30 and 60 mg total daily doses were observed, although there was a general trend of fewer VTEs with a 60 mg total daily dose. Moreover, the incidence of major events for YM150 60 mg once daily were generally numerically lower (1.4%) than those in the enoxaparin group (3.0%). Additionally, no symptomatic VTEs were observed with YM150 60 mg once daily.
- Most VTEs occurred during the first 12 days of treatment (13.7 % of patients). Very few VTEs started after day 12 (entire treatment period 13.6% and entire study [treatment and follow-up period] 13.8%).

Safety Conclusions

- The proportion of patients with adverse events was similar across the treatment groups.
- The results show that most BAEs occurred within the first 12 days of treatment (8.3% of patients: entire treatment period 9.1%, and entire study including follow-up 9.2%. In total, 4.9% of patients major and/or CRNM BAEs; 1.7% of patients had major BAEs.
- Of the 25 patients assigned to YM150 for whom a bleeding event adjudicated as major was reported, 21 patients reported a major bleeding event in the perioperative period before they received the first dose of active YM150 tablets.
- A trend indicating a higher incidence of BAEs with twice daily YM150 30 mg dosing was observed (10.9% of patients up to 12 days, compared with 5.3% for 15 mg bid, 8.1% 30 mg qd, 8.3% 60 mg qd, and 8.9% for enoxaparin). The interaction between YM150 total daily dose and dose frequency was statistically significant ($P = 0.039$ up to 12 days) as well as in the pairwise comparisons of 30 mg twice daily vs 60 mg once daily ($P = 0.033$), and 30 mg twice daily vs 15 mg twice daily ($P = 0.017$).
- A total of 4 patients had concurrent elevations of total bilirubin > 2 x ULN with ALT or AST > 3 x ULN. Three were randomized to enoxaparin and one to YM150 30 mg twice daily. Elevations of laboratory hepatic markers were numerically lower in the YM150 arms compared with enoxaparin.
- Elevations of serum creatinine in the YM150 arms were numerically lower (60 mg qd) or similar to those observed in the enoxaparin arm.
- There were no other clinically significant safety findings.

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