Drug Name (Code) **YM758** 22 January 2008
Protocol Number **758-CL-010**
Report Number 51.18/70464 (clinical study report synopsis number: 08/2344)

SYNOPSIS

Name of Sponsor/Company:
Astellas Pharma Europe B.V. (Successor in interest to Yamanouchi Europe/Fujisawa GmbH)

Name of Finished Product:

Name of Active Ingredient:
YM758

Title of Study: A randomized, double blind, placebo controlled study to evaluate the safety, tolerability and preliminary efficacy of a four-week treatment with YM758 in subjects with stable angina.

Study acronym: IRIS International Randomized If-inhibitor Study

Responsible Medical Officer/Coordinating Investigator: [redacted], UK.

Investigator(s):

Study Center(s): 14 centres in Russia, 9 centres in the Ukraine, 5 centres in Slovakia and 4 centres in Serbia.

Publication (reference): None at time of writing

Study Period:	**Phase of Development:**
Date of First Enrollment: 22 MAY 2006 **Date of Last Evaluation:** 27 DEC 2006	IIa

Objectives:

Primary Objective

- To evaluate the safety and tolerability of different oral doses of YM758 in subjects with stable angina.

Secondary Objectives

- To evaluate the efficacy and pharmacodynamics of YM758.
- To explore the pharmacokinetics of YM758 in the target population.

Study Design:

This was a multicenter, randomized, double blind, placebo controlled, multiple dose study in subjects with stable angina. Overall 32 centers in Russia, Ukraine, Slovakia and Serbia took part in the recruitment of subjects.
The study was composed of 2 parts. In the first part 3 parallel groups, groups A, B and C, were treated with 3 different dosages of YM758, i.e: 5, 10 and 20 mg YM758 q.d, respectively or matching placebo. Results from part 1 were reviewed by the DSMB, who then recommended on continuation and doses to be used in part 2. The second part consisted of 2 parallel groups, groups D and E. Group D received 40 mg q.d. or matching placebo. For optimization of the safety and efficacy profile a twice daily dose was decided upon for group E, this group received 20 mg b.i.d. or matching placebo.

Randomization was performed within each dose group. Sites were manually allocated to each dose group by the Project Manager. Within each country an equal number of sites was allocated to each of the 3

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groups for part 1 and into 2 groups for part 2, wherever possible. The sites were allocated based on their predicted recruitment to try and ensure recruitment was equal between the groups.

Diagnosis and Main Criteria for Inclusion:

1. Male or female of ≥ 18 years and ≤ 75 years.
2. At least 3 months chronic, stable, effort-induced angina relieved by rest or nitroglycerin, functional class I, II or III according to Canadian Cardiovascular Society Functional classification.
3. Analyzable ST segment on 12-lead ECG: morphology of ST segment within normal limits.
4. Two positive reproducible exercise tolerance tests (ETTs) at Day –7 (visit 1) and Day 0 (visit 2) with total duration of exercise ≥3 min: terminated due to limiting angina (moderate/severe pain ordinarily causing the patient to stop exercise during normal daytime activity) and ST-segment horizontal or downsloping depression ≥ 1 mm (measured 0.08 s after the J-point on ≥3 consecutive complexes) compared with rest, where the parameter "time to 1 mm ST segment depression" was within ±20% or ± 1 min in both ETTs. If reproducibility could not be demonstrated on the second ETT, a third pre-treatment ETT could be performed at least 24 h and not later than 7 days after Day 0. The patient continued to take placebo until the third ETT was completed. Reproducibility criteria were to be confirmed between any two of the three ETTs.

Number of Subjects (planned and analyzed):

A maximum of 5 groups (A to E) receiving different dosages of YM758 were to be studied. For each dose group, 42 subjects were to be recruited to enter the run-in period. Per group, 28 subjects were to be randomly assigned to receive YM758 or placebo in a 3:1 ratio, expecting that at least 20 subjects had an evaluable ETT on Day 28. In total, this study consisted of 5 groups, of which approximately 210 subjects were to enter the run-in period, 140 subjects were to be randomized and 100 subjects were to complete the study.

Overall 223 subjects were enrolled in this study and 195 subjects started the placebo run-in phase, 18 of whom dropped out during the run-in phase, i.e. 177 subjects started the double-blind treatment.

The number of subjects starting the different double-blind treatments, withdrawn during double-blind treatment (including the reason) and completing the study are given below.

		Treatment Group						
		5 mg q.d.	**10 mg q.d**	**20 mg q.d**	**40 mg q.d**	**20 mg b i.d.**	**Combined placebo**	**Overall**
Subjects entered double-blind treatment	N	26	25	25	27	29	45	177
Withdrawals during double-blind treatment	N(%)	3 (11.5%)	4 (16.0%)	5 (20.0%)	2 (7.4%)	6 (20.7%)	3 (6.7%)	23 (13.0%)
- adverse events	N(%)	1 (3.8%)	1 (4.0%)	3 (12.0%)	2 (7.4%)	3 (10.3%)	-	10 (5.6%)
- protocol violation	N(%)	1 (3.8%)	1 (4.0%)	-	-	-	1 (2.2%)	3 (1.7%)
- lost to follow-up	N(%)	1 (3.8%)	-	-	-	-	-	1 (0.6%)
- withdrawal consent	N(%)	-	1 (4.0%)	1 (4.0%)	-	2 (6.9%)	2 (4.4%)	6 (3.4%)
- other	N(%)	-	1 (4.0%)	1 (4.0%)	-	1 (3.4%)	-	3 (1.7%)
Subjects completing the study	N(%)	22 (84.6%)	21 (84.0%)	20 (80.0%)	26 (96.3%)	23 (79.3%)	42 (93.3%)	154 (87.0%)

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Test Product, Dose And Mode of Administration:

Part 1

Test Drug
YM758
Dose: 5, 10 or 20 mg YM758 q.d.
Tablets used: YM758 5 mg tablet, YM758 10 mg tablet, YM758 20 mg tablet
Mode of administration: one dose per day taken with a glass of water within 30 minutes after breakfast

Comparative Drug
Matching placebo tablets
Dose: not applicable
Mode of administration: one dose per day taken with a glass of water within 30 minutes after breakfast

Drug for Run-in Period

Matching placebo tablets were supplied to assess protocol compliance during the run-in period.

Part 2

Test Drug
YM758
Dose: 40 mg YM758 q.d. (group D) and 20 mg YM758 b.i.d (group E).
Tablets used: YM758 20 mg tablet
Mode of administration: one (group D) or two (group E) doses per day taken with a glass of water within 30 minutes after breakfast and dinner (for the b.i.d. group E).

Comparative Drug
Matching placebo tablets
Dose: not applicable
Mode of administration: one (group D) or two (group E) doses per day taken with a glass of water within 30 minutes after breakfast and dinner (for the b.i.d. group E).

Drug for Run-in Period

Matching placebo tablets were supplied to assess protocol compliance during the run-in period.

Lot Numbers

Tablets	Batch number	Expiry date
YM758 5 mg tablet	[redacted]	February 2007
YM758 10 mg tablet	[redacted]	February 2007
YM758 20 mg tablet	[redacted]	February 2007
placebo matching to YM758 5 mg tablet	[redacted]	August 2007
placebo matching to YM758 10 mg tablet	[redacted]	August 2007
placebo matching to YM758 20 mg tablet	[redacted]	August 2007

Duration of Study and Treatment:

Run-in period (visit 1-visit 2): 7 days with treatment of 1 to 2 placebo tablets q.d. (groups A-D) and b.i.d. (group E), with the possibility to expand this period by maximally 7 days in case of no reproducible ETTs at visits 1.

Treatment period (visit 3-visit 4): 28 days. Groups A, B and C received 5 mg q.d, 10 mg q.d or 20 mg q.d., respectively. Group D received 40 mg YM758 q.d. and Group E was assigned to 20 mg b.i.d.

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Study duration per subject: approximately 35 to 42 days

Criteria for Evaluation:

Efficacy and Pharmacodynamics:

- **ETT variables:**
  - Change in time to 1-mm horizontal or down-sloping ST-segment depression 0.08 seconds after the J point during ETT compared to baseline.
  - Change from baseline of time to angina onset
  - Change from baseline of total exercise duration
  - Change from baseline in maximum level of MET achieved
  - Change from baseline of maximum workload achieved
  - Change from baseline of maximum heart rate achieved
  - Change from baseline of maximum double product
- Change from baseline of heart rate (at rest and during ETT)
- Use of short acting nitrate (rescue medication)
- Angina attack frequency

Safety:

Nature, frequency and severity of adverse events

- Medical history, physical examination and vital signs
- Routine safety laboratory test: hematology, biochemistry and urinalysis
- Pregnancy test in females
- 12-lead ECG
- Visual acuity and color discrimination tests
- Fundoscopy

Pharmacokinetics:

- Population pharmacokinetic model parameters at least comprised k_a, CL/F and V/F. Derived (secondary) parameters were: t_{max}, C_{max}, $AUC_{0\text{-}tau}$, $t_{1/2}$.

Statistical Methods:

The efficacy results were evaluated on exploratory basis.

All endpoints were listed and summarized in tabular or graphical form, as appropriate. The efficacy and pharmacodynamic endpoints were subjected to appropriate statistical analyses to evaluate efficacy and to assess dose response. For ECG reporting purposes the results of the central independent review prevailed over the interpretation of local investigators. Thus, only the results for time to ST-segment depression of the independent reading were used for the statistical analysis. Analyses were based on the FAS and PPS.

The changes from baseline for the quantitative efficacy endpoints were analyzed by visit and time point by means of an analysis of covariance (ANCOVA) including gender, baseline, treatment and country as factors. The treatment-by-country interaction also was investigated in a pre-test but was found not to be significant and therefore was removed from the final model. Due to the relatively low number of subjects per treatment in some of the countries, the statistical analysis recognized only two categories for the countries: Russia and "others". The least square means (LS-means) for each treatment and the corresponding 95% confidence intervals were presented. Due to the hierarchical testing principle, results for comparisons of active doses to pooled placebo were presented only if the overall F-test gave indication of a difference between the means.

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RESULTS:

Analysis Sets and Subject Disposition:

Safety population: 177 subjects
Full analysis set (FAS): 167 subjects (10 subjects provided no post-dose efficacy data)
Per protocol set (PPS): 147 subjects (reason for exclusion from PPS:11 subjects withdrew prior to visit 4, seven subjects had major time deviations, one subject took forbidden medication and for one subject the post-dose ETT was not performed according to the protocol).

The number of subjects in each analysis set by treatment groups is given below.

		Treatment Group						
		5 mg q.d.	**10 mg q.d.**	**20 mg q.d.**	**40 mg q.d.**	**20 mg b i.d.**	**Combined placebo**	**Overall**
Subjects randomized	N	26	25	25	27	29	45	177
Full Analysis Set	N(%)	25 (96.2%)	24 (96.0%)	22 (88.0%)	27 (100.0%)	25 (86.2%)	44 (97.8%)	167 (94.4%)
Per Protocol Set	N(%)	21 (80.8%)	21 (84.0%)	18 (72.0%)	24 (88.9%)	23 (79.3%)	40 (88.9%)	147 (83.1%)
Safety Population	N(%)	26 (100.0%)	25 (100.0%)	25 (100.0%)	27 (100.0%)	29 (100.0%)	45 (100.0%)	177 (100.0%)
Pharmacokinetic Population	N(%)	24 (92.3%)	21 (84.0%)	20 (80.0%)	25 (92.6%)	24 (82.8%)	Not applicable	114 (86.4% of 132)

Percentages are based on the number of subjects randomized within each treatment group
Source: Table 13.1.3

Demographics:

There were no substantial differences between the treatment groups: mean age ranged from 57.0 to 61.2 years (SAF), 56.7 to 60.8 years (FAS) and 57.2 to 60.8 years (PPS); mean weight ranged from 77.7 to 84.9 kg (SAF), 77.8 to 85.6 kg (FAS) and 78.2 to 85.1 (PPS) and mean height ranged from 167.5 to 173.1 cm (SAF), 167.4 to 173.9 cm (FAS) and 169.0 to 173.8 (PPS). For the BMI the ranges of the mean were 26.53 to 28.86 kg/m^2 (SAF), 26.53 to 28.36 kg/m^2 and 26.43 to 28.85 kg/m^2. These results also show that the differences between the different analysis sets were marginal.

More male than female subjects were included in this study: overall 140 (79.1%) men and 37 (20.9%) women entered the double-blind treatment phase. Within the different treatment groups the proportion of male subjects ranged from 69.2% to 86.2% and consequently the proportion of female subjects ranged from 13.8% to 30.8%. All subjects were Caucasians.

All subjects had a chronic, stable, effort-induced angina for at least 3 months (range 3 months to 29 years), mainly of functional class II according to Canadian Cardiovascular Society Functional classification (overall 66.7%, range from 48.3% - 20 mg b.i.d. – to 88.0% - 10 mg q.d.). The number of subjects with grade III was highest in the 20 mg b.i.d. group (27.6%) and lowest in the 10 mg q.d. group (8.0%). About half of the subjects had a myocardial infarction in the past (overall 49.7%, range 42.4% in the placebo group and 62.1% in the 20 mg b.i.d. group).

Study Drug Exposure:

The total drug exposure ranged from a mean of 137.4 mg for the 5 mg q.d. treatment group to 1120.7 mg and 1071.2 mg for the 40 mg q.d. and 20 mg b.i.d. treatment group, respectively (FAS). No subject was excluded from any analysis set due to bad compliance. During the double blind treatment mean compliance ranged from 97.51% (visit 4, 20 mg b.i.d.) to 102.4% (visit 4, 5 mg q.d.) for the FAS.

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Efficacy Results:
Baseline results varied somewhat between the treatment groups but also showed a fairly large variability between the subjects. There were no remarkable differences between the FAS and the PPS, except that in the PPS the total exercise duration in the 20 mg q.d. group was similar to that of the 10 and 40 mg q.d. groups, whereas the mean value was lower in the FAS. For each parameter the treatment effect during the statistical analysis of baseline results was always insignificant, in fact, the confidence intervals for any two treatment means always were overlapping each other. Imbalance is probably due to the study design as treatment groups were not randomized, but, with the exception of placebo, were conducted at independent sites.

ETT variables
Time to 1-mm ST-depression:

After the start of study treatment the mean time to 1-mm ST-depression increased in all treatment groups compared to baseline. The highest increases were observed for the 20 mg q.d. and the 20 mg b.i.d groups (mean change from baseline by 150.89 and 132.16 sec at visit 4 post-dose, respectively, FAS, see Figure below - means calculated from data of subjects who developed 1-mm ST-depression on both occasions). The mean time to 1-mm ST-depression at baseline varied between treatment groups from 444.9 to 604.7 sec.

Time to angina:

After the start of study treatment the time to angina increased in all treatment groups compared to baseline. The highest increases were observed for the 20 mg q.d. and the 40 mg q.d. groups (increase of 152.76 and 141.25 sec at visit 4 post-dose, respectively, FAS, see Figure below – means calculated from data of subjects who developed angina on both occasions). The mean time to angina at baseline varied between treatment groups from 505.0 to 599.9 sec.

Total exercise duration:

After the start of study treatment the exercise duration increased in all treatment groups compared to baseline, showing the most pronounced increase in the 20 mg q.d. and 20 mg b.i.d group. The prolongation of the exercise duration was less pronounced in the 40 mg q.d. group. No relevant differences compared to placebo were observed for the 5 and 10 mg q.d. groups (see Figure below). The mean total exercise duration at baseline varied between treatment groups from 570.6 to 698.6 sec.

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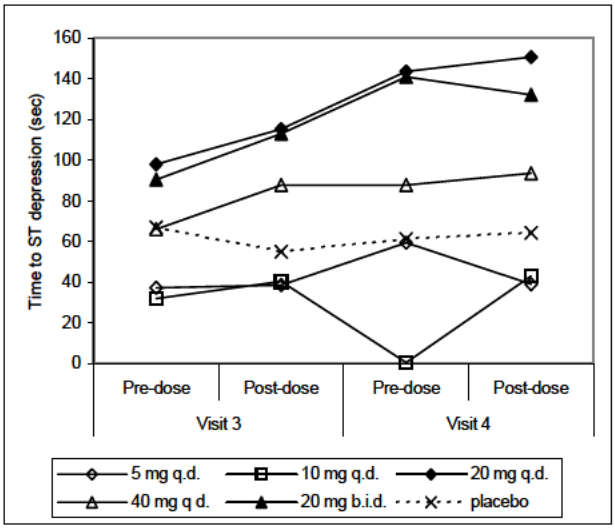
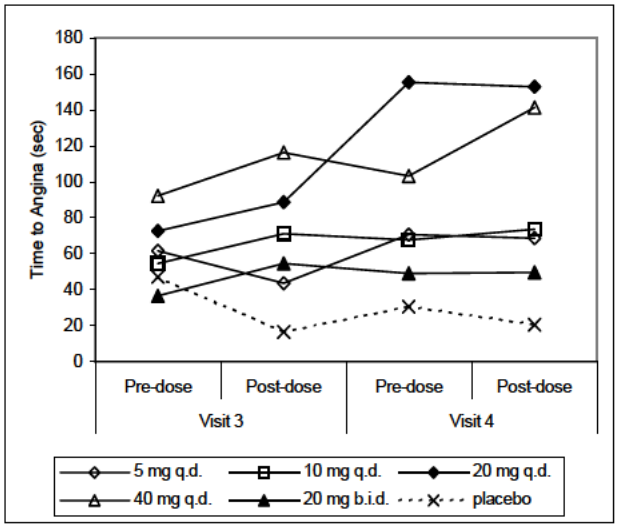
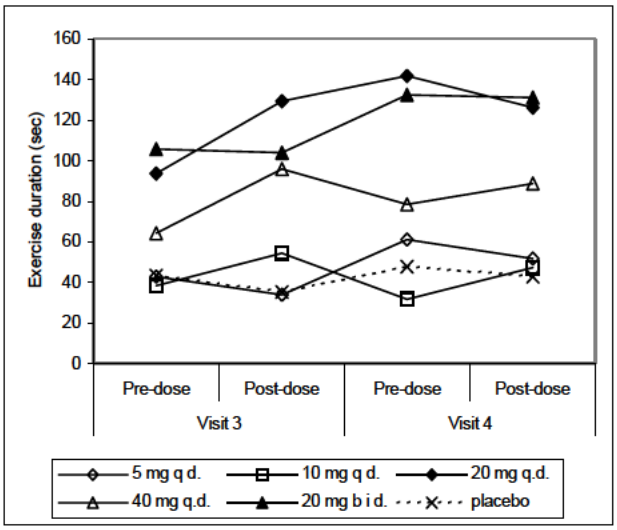
Changes from Baseline for Time to 1-mm ST-Depression, Time to Angina and Total Exercise Duration by Treatment Group (Full Analysis Set)







The statistical analysis of these parameters compared with placebo revealed an overall $p<0.05$ at single time points (visit 4 post-dose for time to onset of angina) and visit 3 post-dose for total exercise duration (the table below summarizes the results for the FAS, results for the PPS were similar).

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Statistical analysis: p-values for the overall difference between treatments of changes from baseline in ETT parameters

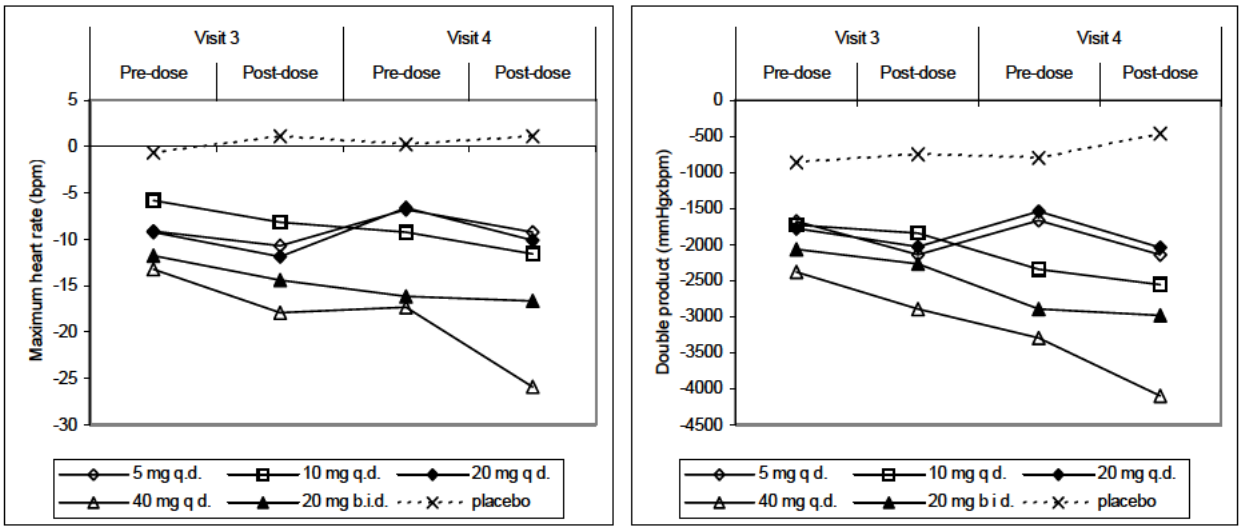
	Visit 3		Visit 4	
	pre-dose	post-dose	pre-dose	post-dose
Time to onset of 1-mm ST-depression	0.5131	0.3801	0.1996	0.0691
Time to onset of angina	0.4869	0.1523	0.3700	0.0432
Total exercise duration	0.4404	0.0451	0.0895	0.1199

Maximum heart rate:

The means for the maximum heart rate at baseline varied between treatment groups from 122.2 to 129.3 bpm. After the start of study treatment the mean maximum heart rate decreased in all groups treated with YM758, for the placebo group the mean maximum heart rate remained rather constant during the study. No clinically relevant differences were observed between the 5, 10 and 20 mg q.d. treatment groups, during the course of the study the mean changes from baseline varied between –5.83 bpm (20 mg q.d., visit 4 pre-dose) and –11.89 bpm (20 mg q.d., visit 3 post-dose, FAS). Larger decreases were observed for the highest dose groups: after treatment with 20 mg b.i.d.. The mean maximum heart rate decreased by -11.80 bpm at visit 3 pre-dose to –16.60 bpm at visit 4 post-dose; after 40 mg q.d. a decrease of –13.24 bpm was observed at visit 3 pre-dose increasing to – 25.87 bpm at visit 4 post-dose.

Maximum double product:
The means for the maximum double product at baseline varied between treatment groups from 20444.8 to 22114.7 mmHg*bpm. After the start of study treatment double product decreased in all treatment groups, but more pronounced after treatment with YM758 than after placebo. Corresponding to the decrease in heart rate a considerable decrease was observed after 40 mg q.d.: at visit 3 pre-dose the double product decreased by -2376.94 mmHg*bpm compared to baseline and further decreased during the course of the study to –4093.20 mmHg*bpm at visit 4 post-dose. A less pronounced decrease was observed for the 20 mg b.i.d. group (-2977.98 mmHg*bpm at visit 4 post-dose).

Changes from Baseline for Maximum Heart Rate and Maximum Double Product (Full Analysis Set)



The statistical analysis revealed a significant decrease in maximum heart rate compared to placebo after all treatments with YM758, which was already present after 14 days of treatment. For the double product overall statistical significance was gained for visit 4 (pre- and post-dose). Comparison of the different doses showed a clear difference to placebo for the 40 mg q.d. and the 20 mg b.i.d. groups at both time

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points (the table below summarizes the results for the FAS, results for the PPS were similar).

Statistical analysis: p-values for changes from baseline in maximum heart rate and maximum double product during ETT (FAS)

Maximum heart rate

	Visit 3						Visit 4					
	pre-dose			post-dose			pre-dose			post-dose		
	est. diff.	95% CI	p-value	est. diff.	95% CI	p-value	est. diff.	95% CI	p-value	est. diff.	95% CI	p-value
Overall			<0.0001	-	-	<0.0001	-	-	<0.0001	-	-	<0.0001
5 mg q.d. -placebo	-8.1	[-13.11, -3.09]	0.0017	-10.24	[-15.78, -4.70]	0.0004	-5.99	[-12.43, 0.44]	NS	-8.98	[-15.55, -2.42]	0.0077
10 mg q.d. -placebo	-6.05	[-11.31, -0.78]	0.0247	-9.29	[-15.19, -3.40]	0.0022	-11.17	[-18.14, -4.20]	NS	-13.51	[-20.62, -6.40]	0.0002
20 mg q.d. -placebo	-8.48	[-13.82, -3.14]	0.0020	-11.37	[-17.27, -5.46]	0.0002	-6.46	[-13.50, 0.58]	0.0719	-9.74	[-16.93, -2.55]	0.0082
20 mg b.i.d.- placebo	-12.01	[-16.99, -7.03]	<0.0001	-16.71	[-22.22, -11.21]	<0.0001	-17.49	[-23.93, -11.05]	<0.0001	-18.76	[-25.33, -12.19]	<0.0001
40 mg q.d. -placebo	-11.98	[-16.85, -7.11]	<0.0001	-17.68	[-23.06, -12.30]	<0.0001	-16.18	[-22.45, -9.91]	<0.0001	-26.29	[-32.77, -19.81]	<0.0001

Maximum double product

	Visit 3						Visit 4					
	pre-dose			post-dose			pre-dose			post-dose		
	esti. diff.	95% CI	p-value	esti. diff.	95% CI	p-value	esti. diff.	95% CI	p-value	esti. diff.	95% CI	p-value
Overall			0.2823			0.0649			0.0135			0.001
5 mg q.d. -placebo	Not evaluated due to overall p-value > 0.05			Not evaluated due to overall p-value > 0.05			-532	[-1922, 858]	NS	-1256	[-2827, 315]	
10 mg q.d. -placebo							-1294	[-2803, 215]	NS	-1739	[-3445, -33]	
20 mg q.d. -placebo							-292	[-1817, 1233]	0.7058	-915	[-2639, 808]	0.2957
20 mg b.i.d.- placebo							-2080	[-3464, -695]	0.0035	-2535	[-4099, -970]	0.0017
40 mg q.d. -placebo							-1987	[-3347, -627]	0.0045	-3280	[-4835, -1725]	<0.0001

NS : Not statistically significant due to hierarchical testing.

Corresponding to the decrease in maximum heart rate, heart rate at rest and during ETT decreased after treatment with YM758 compared to baseline, whereas no decrease compared to baseline was observed after placebo dosing. For the three highest doses of YM758 the decrease in heart rate was greater during the course of the study. The highest decrease was observed after 40 mg q.d. (-21.07 bpm at visit 4 post-dose at rest, FAS). Systolic or diastolic blood pressure, measured every minute during the ETT, showed no clinically relevant differences between baseline and all other visits in any treatment group.

No clear time- or dose-related differences were observed for the frequency of angina attacks or for the use of rescue medication. At visit 4 the number of subjects with angina attacks was highest in the 5 mg q.d. group (64.0%), similar in the 10 mg q.d., 40 mg q.d. and placebo groups (between 52.4% and 59.5%), slightly lower in the 20 mg q.d. group (45.0%) and lowest in the 20 mg b.i.d. group (29.2%, statistically significant difference to placebo, p=0.0144).

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Safety Results:
Overall 91 of 177 subjects (51.4%) reported adverse events after the start of the double-blind treatment. The incidence after placebo dosing was 22.2% (10/45 subjects) and slightly higher after 5 mg YM758 q.d. (30.8%, 8/26 subjects). After 10 mg q.d. 56.0% (14/25 subjects) reported adverse events. A similar incidence of adverse events was observed after 20 mg q.d. and b.i.d. (76.0% - 19/25 subjects after 20 mg q.d. and 75.9% - 22/29 subjects after 20 mg b.i.d.). After 40 mg q.d. adverse events were less frequently reported (by 66.7%, 18/27 subjects).

No deaths or serious adverse events were reported during the double-blind treatment phase. One SAE occurred during the placebo run-in (syndrome of dyspepsia, which required hospitalization, the event resolved and the subject continued the study). Most adverse events were of mild to moderate intensity; there was one subject with a severe adverse event (photopsia, Subject [redacted] 20 mg b.i.d.).

Eye disorders (mainly photopsia) were the most frequently reported adverse events, the incidence of eye disorders increased dose-dependently. All other adverse events were less frequently reported and the incidence showed no dose related pattern.

Summary of Treatment Emergent Adverse Events (Safety Population)

System organ class Preferred term	**YM758**					**Combined placebo**	**Overall**
	5 mg q.d.	**10 mg q.d.**	**20 mg q.d.**	**40 mg q.d.**	**20 mg b.i.d.**		
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
No. of subjects in safety population	26	25	25	27	29	45	177
No. of subjects with any treatment emergent AE	8 (30.8%)	14 (56.0%)	19 (76.0%)	18 (66.7%)	22 (75.9%)	10 (22.2%)	91 (51.4%)
Cardiac disorders							
Bradycardia	-	-	-	-	4 (13.8%)	-	4 (2.3%)
Sinus bradycardia	-	1 (4.0%)	4 (16.0%)	1 (3.7%)	-	-	6 (3.4%)
Supraventricular extrasystoles	-	2 (8.0%)	-	1 (3.7%)	-	2 (4.4%)	5 (2.8%)
Ventricular extrasystoles	-	2 (8.0%)	-	2 (7.4%)	-	1 (2.2%)	5 (2.8%)
Eye disorders							
Diplopia	-	-	2 (8.0%)	2 (7.4%)	-	-	4 (2.3%)
Photopsia	3 (11.5%)	4 (16.0%)	8 (32.0%)	12 (44.4%)	9 (31.0%)	-	36 (20.3%)
Vision blurred	-	-	-	-	3 (10.3%)	2 (4.4%)	5 (2.8%)
Visual disturbance	1 (3.8%)	5 (20.0%)	3 (12.0%)	1 (3.7%)	9 (31.0%)	-	19 (10.7%)
General disorders and administration site conditions							
Fatigue	-	1 (4.0%)	-	3 (11.1%)	2 (6.9%)	1 (2.2%)	7 (4.0%)

Only adverse events with an overall incidence of >2% are included in this summary

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Mean biochemistry and hematology data showed no clinically relevant time or dose-related changes in any of the parameters. The changes from baseline reveal that mean decreases as well as increases were observed for most parameters without showing any dose-related pattern.

Main changes in ECG parameters were related to the decrease of heart rate and correspondent prolongation of uncorrected QT interval. Mean QTc interval did not show any prolongation when corrected according to Bazett's formula. A prolongation of QTc interval (according to Fridericia's formula) of 5 to 10 msec was seen in the 20 mg q.d., these changes did not show a clear dose-relationship, and the increased of doses in part 2 did not cause similar prolongation of mean QTc interval in 40 mg q.d and 20 mg b.i.d, which stayed within the range of 1 msec to 7 msec, compared with baseline. Changes of mean PR interval were small and did not induce the occurrence of AV blockade of 2nd and/or 3rd degree.

There were no clinically significant changes of vital signs.

The number of subjects with sinus bradycardia (defined as ECG heart rate <50 bpm) increased dose-dependently from 15.4% and 8.0% after 5 mg and 10 mg q.d., respectively, to 31.0% and 44.8% after 20 mg q.d. and b.i.d., respectively, to 70.4% of the subjects after 40 mg q.d..

There were no clinically relevant changes after dosing in any ophthalmological examination.

Pharmacokinetic Results

The steady state pharmacokinetics of YM758 was described by a 1-compartment model with first order absorption and lag time. Influential covariates were α_1-AGP serum concentration, age and dose; CL/F and V/F decreased with increasing α_1-AGP and dose, while CL/F also decreased with increasing age. These effects on CL/F and V/F resulted in an increase in C_{max}, C_{trough} and AUC_{tau} with increasing α_1-AGP and age, while an increase in age also resulted in an increase in $t_{1/2}$. The dose dependency resulted in a slightly more than dose proportional increase in C_{max}, C_{trough} and AUC_{tau}. Mean (SD) values of the derived pharmacokinetic parameters are shown in the table below.

Mean (SD) Values of the Derived Pharmacokinetic Parameters

Dose (mg)	t_{max} (h)	C_{max} (ng/ml)	AUC_{tau} (ng.h/ml)	$t_{1/2}$ (h)	C_{trough} (ng/ml)
5 (q.d.)	1.92 (0.91)	15.2 (3.8)	136 (31)	5.39 (0.58)	0.931 (0.378)
10 (q.d.)	1.66 (1.30)	36.0 (11.1)	313 (91)	5.44 (0.64)	2.25 (1.02)
20 (q.d.)	2.33 (1.00)	68.1 (15.4)	619 (124)	5.12 (0.62)	4.01 (1.74)
20 (b.i.d.)	1.98 (0.96)	85.1 (18.5)	619 (141)	5.09 (0.65)	23.7 (10.2)
40 (q.d.)	1.94 (0.94)	160 (31)	1361 (270)	4.96 (0.55)	7.95 (3.48)

CONCLUSIONS:

Safety and Tolerability:

Repeated doses of 5 to 40 mg YM758 q.d and 20 mg YM758 b.i.d. were generally well tolerated. Eye disorders, mainly photopsia, were the most frequently reported adverse events.

There was a 5-10 msec prolongation of mean QTc interval (Fridericia formula) in 20 mg q.d. dose. No clinically significant changes from baseline were observed for the other ECG parameters or vital signs, for laboratory parameters or any ophthalmological examination.

Efficacy and Pharmacodynamics:

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YM758 caused a decrease in maximum heart rate, heart rate at rest and during ETT at all doses (compared to baseline and to placebo), which was most pronounced at 20 and 40 mg q.d. and 20 mg b.i.d.

There was a trend to an improvement in ETT parameters (time to 1-mm ST-depression, time to onset of angina, total exercise duration during ETT, double product and maximum level of MET) after dosing of 20 mg q.d., 40 mg q.d. and 20 mg b.i.d. compared to placebo. Treatment effects of doses 5 mg q.d. and 10 mg q.d. were similar to placebo.

Systolic or diastolic blood pressure, measured during the ETT, showed no clinically relevant differences between baseline and all other visits in any treatment group.

No clear time- or dose-related differences were observed for the frequency of angina attacks and for the use of rescue medication.

Pharmacokinetics:

A 1-compartment model with first order absorption and lag time could be used to model the absorption and disposition of YM758 in steady state. Influential covariates were α_1-AGP serum concentration, age and dose; CL/F and V/F decreased with increasing α_1-AGP serum concentration, while CL/F also decreased with increasing age. As a result C_{max}, C_{trough} and AUC_{tau} increased with increasing α_1-AGP serum concentration, while C_{max}, C_{trough}, AUC_{tau} and $t_{1/2}$ increased with age. The dose dependent CL/F and V/F resulted in a slightly more than dose-proportional increase in C_{max}, C_{trough} and AUC_{tau}.

Date of Report: 29 August 2007