SYNOPSIS

Name of Sponsor/Company: Astellas Pharma Europe B.V		
Name of Finished Product:		
Name of Active Ingredient: YM178-OCAS		

Title of Study: A randomized, double-blind, parallel group, placebo and active controlled, multi-center dose ranging study with the beta-3 agonist YM178 in patients with symptomatic overactive bladder (DRAGON)

Coordinating Investigator: [redacted] BSc, MD, FRCS (Urol), FEBU, [redacted] U.K.

Study Centers: In 14 countries, a total of 97 centers participated in the study.

Publication (reference): Not applicable at the time of this report

Study Period: **Date of First Enrollment:** 12 April 2006 **Date of Last Evaluation:** 26 March 2007	**Phase of Development:** IIb

Objectives: The primary objective of the study was to evaluate the dose-response relationship of YM178 OCAS on efficacy in patients with OAB.
The secondary objectives of the study were:

- To evaluate the safety and tolerability of qd dosing with YM178 OCAS in patients with OAB.
- To compare the efficacy of YM178 OCAS with tolterodine 4 mg qd.
- To compare the safety and tolerability of YM178 OCAS with tolterodine 4 mg qd.
- To collect population PK data in patients with OAB.

Study Design: This was a multinational, multicenter, double-blind, double-dummy, randomized, parallel group, placebo- and active-controlled phase IIb study. Patients were enrolled into a single-blind, 2-week placebo run-in period followed by a randomized, double-blind, placebo-controlled, 12-week treatment period. There were 6 visits in total: Visit 1 at enrollment, Visit 2 (baseline) after the placebo run-in period, and Visits 3, 4, 5 and 6 after 1, 4, 8 and 12 weeks of double-blind treatment respectively. At screening (Visit 1) patients received a micturition diary which had to be completed during the 3 days preceding Visit 2. Patients received medication for the placebo run-in period. In addition, the patient received an ABPM device for measuring pulse rate and blood pressure during the 3-day diary period. The patient was instructed on how the measurements and documentation in the diary had to be done. After the placebo run-in period, patients returned to the clinic (Visit 2). Micturition diary scores were checked against the inclusion criteria. Patients who met the inclusion criteria and did not meet the exclusion criteria were randomized to one of the treatments with YM178 OCAS 25 mg qd, 50 mg qd, 100 mg qd, 200 mg qd, placebo or tolterodine 4 mg qd. Micturition diaries had to be completed by the patient during the 3 days preceding Visits 3, 4, 5 and 6. During the diary period preceding each visit, patients measured vital signs (HR, SBP, DBP) 2 times per day in triplicate by means of ambulatory blood pressure monitoring. Nature, frequency and severity of reported or observed adverse events were recorded at all visits. Symptom and Quality of Life Questionnaires were completed at Visits 2, 3, 4, 5 and 6. Post-void residual volume was determined at Visits 1 and 6. Laboratory tests (including hematology, biochemistry and urinalysis) were done at Visits 1, 3, 4, 5 and 6 and ECGs were performed at Visits 1, 2, 3, 4, and 6.

Diagnosis and Main Criteria for Inclusion: Men or women aged ≥18 years who had experienced symptoms of OAB (including urinary frequency, and urgency with/without urge incontinence) for at least 3 months prior to screening

Number of Subjects (planned and analyzed): A total of 1070 patients were to be enrolled in order to randomize 856 patients to obtain 770 evaluable patients. A total of 1108 subjects were screened and 927 were treated.

Test Product, Dose and Mode of Administration: Patients who met the inclusion criteria and did not meet the exclusion criteria were randomized to 12 weeks of double-blind treatment with YM178 OCAS 25 mg qd, 50 mg qd, 100 mg qd, 200 mg qd, placebo or tolterodine 4 mg qd. Each patient randomized to any group took 3 tablets and 1 capsule each morning after breakfast throughout the study. All treatments were taken orally with a glass of water and swallowed intact. YM178 tablets, tolterodine capsules and the corresponding placebo tablets and capsules were indistinguishable (double-dummy technique).

Lot Numbers: [redacted]

Duration of Study and Treatment: A single-blind, 2-week placebo run-in period followed by a randomized, double-blind, placebo-controlled, 12-week treatment period.

Criteria for Evaluation: The primary efficacy variable was the change from baseline to endpoint in mean number of micturitions per 24 hours.
Secondary efficacy variables were:

- Change from baseline in mean volume voided per micturition
- Change from baseline in mean number of urgency episodes (grade 3 and/or 4) per 24 hours
- Change from baseline in level of urgency
- Change from baseline in mean number of urge incontinence episodes per 24 hours
- Change from baseline in mean number of incontinence episodes per 24 hours
- Change from baseline in mean number of nocturia episodes per 24 hours
- Change from baseline in symptom scores as assessed by International Consultation on Incontinence Questionnaire-Overactive Bladder (ICIQ-OAB)
- Change from baseline in quality of life scores as assessed by International Consultation on Incontinence Questionnaire-Overactive Bladder-Quality of Life (ICIQ-OABqol)
- Change from baseline in patient's perception of treatment benefit.

Safety was assessed by monitoring of incidence and severity of adverse events (AEs), vital signs, laboratory tests, 12-lead-electrocardiogram (ECG), and post-void residual volume (PVR), as measured by ultrasonography or bladder scan.

Statistical Methods: The full analysis set (FAS) was the primary population for the efficacy analyses and comprised all patients who were randomized, who took at least 1 dose of double-blind study medication, and who provided primary efficacy data from the diary at baseline and endpoint.
The following statistical hypotheses were applied:
H_0 : The change in mean number of micturitions per 24 hours from baseline to endpoint is the same for all doses of YM178 OCAS and for placebo;
H_a: The change in mean number of micturitions per 24 hours from baseline to endpoint is not the same for all doses of YM178 OCAS and for placebo.
The hypothesis was evaluated using a 2-sided test with a significance level of 0.05.
The primary analysis was performed on the change from baseline (Visit 2) to endpoint in the mean number of micturitions per 24 hours as derived from the micturition diary.
Changes from baseline to endpoint in mean number of micturitions per 24 hours were subjected to a model including YM178 OCAS dose as a fixed factor taking on the values 0 mg (placebo), 25 mg, 50 mg, 100 mg and 200 mg. The tolterodine group was not part of this analysis. The baseline value of mean number of micturitions per 24 hours was included in the model as a covariate. Safety variables were reported descriptively.

RESULTS:

Analysis Sets and Subject Disposition: The SAF comprised 927 patients who received at least 1 dose of double-blind study medication. The FAS comprised 919 randomized patients who received at least 1 dose of study medication and for whom primary efficacy data at the baseline visit and at least 1 on-treatment visit were available. The PPS consisted of a subset of 793 FAS patients who complied with the major protocol requirements through all applicable visits, i.e., those patients who had no major protocol violations. A total of 1108 patients were enrolled (screened) in the study of whom 928 were randomized of whom 927 received at least one dose of double-blind study medication.
Of these 927 subjects (SAF population), 169 patients received placebo, 169 patients were treated with YM178 OCAS 25 mg qd, 169 patients were treated with YM178 OCAS 50 mg qd, 168 patients were treated with YM178 OCAS 100 mg qd, 167 patients were treated with YM178 OCAS 200 mg qd, and 85 patients were treated with tolterodine 4 mg qd. Seventy subjects prematurely discontinued and 857 subjects completed the study.

Demographics: Patients were predominantly female (89.3%) and Caucasian (98.2%), between 18 and 91 years of age; the mean age was 57.2 years. Approximately half of the patients (42.2%) had urgency with incontinence. The mean time since the start of symptoms was 3.9 years. Overall, 45.5% of patients had had previous drug therapy for symptoms of OAB.

Study Drug Exposure: The mean treatment duration ranged between 79.8 and 84.4 days. The majority of the patients (60.9 to 68.9%) were treated between 84 and 90 days. The target exposure was 12 weeks (84 days).

Efficacy Results: Primary variable: The mean number of micturitions per 24 hours at endpoint and changes from baseline are presented below.

Micturitions/24 hrs	**Placebo** N = 166 Mean (SD)	**YM178 OCAS 25 mg qd** N = 167 Mean (SD)	**YM178 OCAS 50 mg qd** N = 167 Mean (SD)	**YM178 OCAS 100 mg qd** N = 168 Mean (SD)	**YM178 OCAS 200 mg qd** N = 166 Mean (SD)	**Tolterodine 4 mg qd** N = 85 Mean (SD)
Baseline	11.67 (3.39)	11.87 (2.88)	11.85 (3.30)	11.81 (3.51)	11.34 (2.41)	12.31 (3.68)
Endpoint	10.25 (2.82)	9.84 (2.97)	9.71 (3.33)	9.67 (3.53)	9.27 (2.90)	10.07 (3.47)
CFB	-1.43 (3.24)	-2.03 (2.59)	-2.14 (2.47)	-2.14 (3.23)	-2.08 (2.67)	-2.23 (3.03)
% CFB	-9.79 (22.46)	-16.04 (19.90)	-17.45 (19.19)	-16.82 (22.37)	-17.34 (22.31)	-16.49 (20.04)
median	-11.11	-16.67	-17.50	-18.35	-20.00	-19.15

CFB = change from baseline

The results from the inferential analysis (FAS) are summarized in the following table.

	Placebo	**YM178 OCAS 25 mg qd**	**YM178 OCAS 50 mg qd**	**YM178 OCAS 100 mg qd**	**YM178 OCAS 200 mg qd**
Adjusted mean CFB	-1.44	-1.88	-2.08	-2.12	-2.24
Estimated difference to placebo		-0.45	-0.64	-0.68	-0.80
95% CI		-0.99; 0.10	-1.19; -0.10	-1.22; -0.13	-1.34; -0.25
P-value		0.1083	0.0205	0.0152	0.0041

The effect of YM178 OCAS on the mean number of micturitions per 24 hours increased with dose when compared to placebo. It was estimated from the model that at the endpoint there were 0.45, 0.64, 0.68 and 0.80 fewer micturitions per 24 hours in the YM178 OCAS 25 mg, 50 mg, 100 mg and 200 mg groups, respectively, compared to placebo. The YM178 OCAS 50 mg, 100 mg and 200 mg groups all had statistically significant larger increases when compared to placebo at endpoint. The overall comparison to placebo was statistically significant, indicating that YM178 OCAS is efficacious with respect to the mean number of micturitions per 24 hours ; the study met its primary objective.

The results of the inferential statistical analysis for the secondary variables are presented below. There was a statistically significant effect of YM178 over placebo for all secondary efficacy variables except 'mean number of nocturia episodes per 24 hours', 'mean number of incontinence episodes per 24 hours' and 'the sum of QoL questions 3 until 27 scores as assessed by ICIQ-OABqol questionnaire'. For the latter two, a statistically significant dose trend with YM178 was found in a secondary analysis. In general, differences versus placebo tended to become larger with increasing YM178 dose

Change in mean volume voided per micturition at endpoint (FAS)

	Placebo	YM178 OCAS 25 mg qd	YM178 OCAS 50 mg qd	YM178 OCAS 100 mg qd	YM178 OCAS 200 mg qd
Adjusted mean CFB	7.29	15.32	27.34	25.56	33.34
Estimated difference to placebo		8.03	20.05	18.28	26.06
95% CI		-1.54; 17.60	10.48; 29.63	8.66; 27.89	16.49; 35.62
P-value		0.0998	< 0.0001	0.0002	< 0.0001
Change in mean number of incontinence episodes per 24 hours at endpoint (FAS)					
Adjusted mean CFB	-0.53	-1.36	-1.15	-1.06	-1.10
Estimated difference to placebo		-0.84	-0.62	-0.53	-0.58
95% CI		-1.45; -0.23	-1.22; -0.02	-1.12; 0.06	-1.16; 0.01
P-value		0.0072	0.0416	0.0758	0.0551
Change in mean number of nocturia episodes per 24 hours at endpoint (FAS)					
Adjusted mean CFB	-0.38	-0.52	-0.60	-0.42	-0.59
Estimated difference to placebo		-0.15	-0.22	-0.04	-0.21
95% CI		-0.36; 0.07	-0.44; -0.01	-0.26; 0.17	-0.43; 0.00
P-value		0.1753	0.0426	0.6984	0.0523
Change in mean number of urge incontinence episodes per 24 hours at endpoint (FAS)					
Adjusted mean CFB	-0.44	-1.31	-1.13	-1.18	-1.24
Estimated difference to placebo		-0.86	-0.69	-0.74	-0.80
95% CI		-1.38; -0.35	-1.18; -0.19	-1.23; -0.25	-1.29; -0.31
P-value		0.0011	0.0068	0.0033	0.0014
Change in mean number of urgency episodes (graded ≥3) at endpoint (FAS)					
Adjusted mean CFB	-1.07	-1.77	-1.67	-2.28	-2.48
Estimated difference to placebo		-0.70	-0.60	-1.21	-1.42
95% CI		-1.38; -0.01	-1.29; 0.08	-1.90; -0.52	-2.10; -0.73
P-value		0.0456	0.0845	0.0006	0.0001
Change in mean level of urgency per 24 hours at endpoint (FAS)					
Adjusted mean CFB	-0.10	-0.21	-0.18	-0.29	-0.38
Estimated difference to placebo		-0.12	-0.08	-0.19	-0.28
95% CI		-0.25; 0.02	-0.22; 0.05	-0.33; -0.06	-0.41; -0.15
P-value		0.0922	0.2189	0.0047	< 0.0001
Change in sum of quality of life scores as assessed by ICIQ-OAB questionnaire (questions 3a, 4a, 5a, 6a) at endpoint (FAS)					
Adjusted mean CFB	-1.82	-2.40	-2.51	-2.72	-3.02
Estimated difference to placebo		-0.58	-0.69	-0.90	-1.20
95% CI		-1.13; -0.02	-1.24; -0.13	-1.45; -0.34	-1.76; -0.65
P-value		0.0410	0.0150	0.0016	< 0.0001

Change in sum of quality of life scores as assessed by ICIQ-OAB questionnaire (questions 3b, 4b, 5b, 6b) at endpoint (FAS)					
Adjusted mean CFB	-6.01	-7.83	-8.38	-8.47	-10.02
Estimated difference to placebo		-1.82	-2.37	-2.46	-4.01
95% CI		-4.15; 0.52	-4.70; -0.03	-4.80; -0.12	-6.34; -1.68
P-value		0.1273	0.0474	0.0396	0.0008
Change in sum of quality of life scores as assessed by ICIQ-OABqol questionnaire (questions 3 to 27) at endpoint (FAS)					
Adjusted mean CFB	-16.11	-17.09	-20.36	-20.57	-22.19
Estimated difference to placebo		-0.98	-4.25	-4.46	-6.08
95% CI		-5.88; 3.92	-9.13; 0.62	-9.37; 0.46	-11.0; -1.19
P-value		0.6943	0.0872	0.0754	0.0149
Change in sum of quality of life scores as assessed by ICIQ-OABqol questionnaire (question 28) at endpoint (FAS)					
Adjusted mean CFB	-1.50	-1.85	-2.12	-2.17	-2.52
Estimated difference to placebo		-0.35	-0.61	-0.67	-1.02
95% CI		-0.96; 0.27	-1.23; 0.00	-1.29; -0.05	-1.63; -0.40
P-value		0.2709	0.0518	0.0330	0.0012

CFB = change from baseline

The efficacy of YM178 OCAS and tolterodine 4 mg qd were in the same range.

Pharmacokinetic Results: The summary statistics of the individual values of the PK parameters are provided in the table below.

Dose (mg)		**YM178 OCAS 25 mg qd**	**YM178 OCAS 50 mg qd**	**YM178 OCAS 100 mg qd**	**YM178 OCAS 200 mg qd**
Statistic					
C_{max} (ng/mL)	Mean	6.8	16.6	47.6	137.8
	SD,CV (%)	2.7, 40.0	5.0, 30.3	16.9, 35.5	40.2, 29.2
	Min - max	3.3-22.1	7.4-35.0	10.0-121.3	43.2-273.4
	Median	6.0	15.9	46.1	135.7
	N	135	138	146	146
C_{trough} (ng/mL)	Mean	1.8	4.5	12.9	34.8
	SD,CV (%)	0.7, 37.1	1.7, 37.0	4.6, 36.0	9.6, 27.6
	Min - max	0.8-4.8	1.7-14.2	2.5-29.2	12.0-71.5
	Median	1.7	4.3	12.7	34.7
	N	135	138	146	146
AUC_{tau} (ng.h/mL)	Mean	77.9	191.8	548.0	1547.4
	SD,CV (%)	29.8, 38.2	63.5, 33.1	194.8, 35.5	426.7, 27.6
	Min - max	34.9-203.2	77.6-498.2	110.0-1319.8	508.1-2778.5
	Median	69.8	184.0	524.0	1543.3
	N	135	138	146	146

Increasing the dose from 25 to 200 mg qd (an 8-fold increase) resulted in a more than dose-proportional increase in each of the parameters. The mean values of C_{max}, C_{trough} and AUC_{tau} increased approximately 21, 19, and 20-fold, respectively.

Safety Results: Overall, 45.2% of all patients had 1 or more treatment-emergent AEs during the study. Patients from placebo treatment had the lowest incidence of AEs (43.2%), and patients from 4 mg tolterodine qd had the highest incidence of AEs (48.2%). The incidence of AEs in the YM178 OCAS treatment groups slightly increased from 43.8% for the 25 mg qd YM178 OCAS group to 47.9% for the 200 mg qd YM178 OCAS treatment group.

There was no relevant difference in the type of AEs or the number of patients reporting AEs between YM178 OCAS treatment and placebo or tolterodine treatment and there was no dose relationship.

The majority of AEs were of mild or moderate intensity. There were no deaths during the study. A summary table of treatment-emergent AEs is presented.

Number (%) of patients		Placebo (N = 169)		YM178 OCAS 25 mg qd (N = 169)		YM178 OCAS 50 mg qd (N = 169)		YM178 OCAS 100 mg qd (N = 168)		YM178 OCAS 200 mg qd (N = 167)		Toltero-dine 4 mg qd (N = 85)		Total (N = 927)	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
With AEs[1]		73	(43.2)	74	(43.8)	74	(43.8)	77	(45.8)	80	(47.9)	41	(48.2)	419	(45.2)
Total number of AEs		132		148		171		148		164		78		841	
With SAEs[1]		1	(0.6)	1	(0.6)	1	(0.6)	2	(1.2)	3	(1.8)	1	(1.2)	9	(1.0)
Total number of SAEs		2		2		1		2		3		1		11	
With AEs by severity[1]	Mild	34	(20.1)	38	(22.5)	37	(21.9)	40	(23.8)	46	(27.5)	19	(22.4)	214	(23.1)
	Moderate	37	(21.9)	29	(17.2	33	(19.5)	32	(19.0)	30	(18.0)	19	(22.4)	180	(19.4)
	Severe	2	(1.2)	7	(4.1)	4	(2.4)	5	(3.0)	4	(2.4)	2	(2.4)	24	(2.6)
	Missing	0	-	0	-	0	-	0	-	0	-	1	(1.2)	1	(0.1)
Who discontinued because of AEs[1, 2]		5	(3.0)	9	(5.3)	4	(2.4)	4	(2.4)	7	(4.2)	1	(1.2)	30	(3.2)
With treatment-related AEs[1,3]		26	(15.4)	34	(20.1)	38	(22.5)	36	(21.4)	37	(22.2)	13	(15.3)	184	(19.8)
Who died		0	-	0	-	0	-	0	-	0	-	0	-	0	-

[1] Only treatment-emergent AEs are taken into account
[2] Only AEs that were the primary reason for discontinuation are taken into account
[3] AEs that are possibly or probably treatment-related, or for which the relationship is missing

The most commonly reported AEs during the treatment period were infections (bronchitis, influenza, nasopharyngitis, pharyngitis and urinary tract infection) in the class of infections and infestations, followed by gastrointestinal disorders (constipation, diarrhea, dry mouth, dyspepsia, nausea and vomiting). The majority of infection and infestation AEs were considered not treatment-related by the investigator. Approximately two-thirds of the gastrointestinal AEs were considered treatment-related by the investigator. The AEs dry mouth, constipation, dyspepsia and nausea were always (dry mouth) or mostly (constipation, dyspepsia and nausea) considered related to treatment by the investigator. The AEs diarrhea and vomiting were mostly considered unrelated to treatment by the investigator.
Nine (1.0%) patients had treatment-emergent serious adverse events (SAE). These SAEs were experienced by 3 patients in the 200 mg qd YM178 OCAS group, 2 patients in the 100 mg qd YM178 OCAS group and by 1 patient in each of the remaining groups. The SAEs reported were unstable angina and cardiac failure (both reported by the same patient), hypothyroidism, gastritis, pneumonia (reported by 3 patients), complex regional pain syndrome, multiple sclerosis and pulmonary edema and hypertensive crisis (also both reported by the same patient).
The proportion of patients that discontinued because of treatment-emergent AEs was 5 (3.0%) in the placebo group, 4-9 (2.4-5.3%) in the YM178 OCAS treatment groups and 1 (1.2%) in the tolterodine 4 mg treatment group. Within the YM178 OCAS treatment groups, there was no dose-relationship.
None of the changes in hematology parameters or serum chemistry parameters in YM178 OCAS-treated patients showed a dose related trend. The incidence of patients with abnormal values at the end of the 12-week treatment period was low and similar across treatment groups. An analysis of glucose levels in patients with diabetes revealed no tendency towards abnormalities in glucose levels.
The results of the inferential statistical analyses of the vital signs parameters are presented below:

	Placebo	YM178 OCAS 25 mg qd	YM178 OCAS 50 mg qd	YM178 OCAS 100 mg qd	YM178 OCAS 200 mg qd
Change from baseline to endpoint in mean systolic blood pressure (morning)					
Adjusted mean CFB	0.35	-0.70	-1.14	0.79	0.83
Estimated difference to placebo		-1.05	-1.49	0.43	0.47
95% CI		-3.00; 0.90	-3.44; 0.45	-1.52; 2.39	-1.48; 2.43
P-value		0.2911	0.1318	0.6628	0.6334
Change from baseline to endpoint in mean systolic blood pressure (afternoon)					
Adjusted mean CFB	0.38	0.57	0.39	0.65	2.24
Estimated difference to placebo		0.20	0.01	0.28	1.86
95% CI		-1.67; 2.06	-1.85; 1.87	-1.59; 2.15	-0.00; 3.73
P-value		0.8367	0.9907	0.7719	0.0502
Change from baseline to endpoint in mean diastolic blood pressure (morning)					
Adjusted mean CFB	0.24	-0.77	-0.22	1.06	0.90
Estimated difference to placebo		-1.01	-0.46	0.82	0.66
95% CI		-2.15; 0.13	-1.60; 0.68	-0.32; 1.97	-0.48; 1.80
P-value		0.0823	0.4281	0.1589	0.2550
Change from baseline to endpoint in mean diastolic blood pressure (afternoon)					
Adjusted mean CFB	0.67	0.07	0.50	1.32	0.94
Estimated difference to placebo		-0.60	-0.17	0.65	0.28
95% CI		-1.82; 0.61	-1.38; 1.05	-0.57; 1.87	-0.94; 1.49
P-value		0.3313	0.7889	0.2955	0.6569
Change from baseline to endpoint in mean pulse rate (morning)					
Adjusted mean CFB	0.51	0.34	1.64	2.15	4.66
Estimated difference to placebo		-0.17	1.13	1.64	4.14
95% CI		-1.42; 1.08	-0.11; 2.38	0.39; 2.89	2.90; 5.39
P-value		0.7901	0.0747	0.0103	< 0.0001
Change from baseline to endpoint in mean pulse rate (afternoon)					
Adjusted mean CFB	-0.04	0.44	1.12	2.71	4.63
Estimated difference to placebo		0.48	1.15	2.74	4.67
95% CI		-0.92; 1.87	-0.24; 2.55	1.34; 4.14	3.27; 6.06
P-value		0.5025	0.1044	0.0001	< 0.0001

CFB = change from baseline

The effect of YM178 OCAS on blood pressure was not statistically significant when compared to placebo at any dose level. The overall comparison for pulse rate was statistically significant, meaning that YM178 OCAS has an effect on morning and afternoon pulse rate.
Heart rate (HR) at baseline was comparable between treatment groups. No changes over time were observed, except for the 100 mg and 200 mg YM178 OCAS groups, where a small, dose-related, increase was observed. In the 100 mg YM178 OCAS group, mean HR increased by 1.7, 3.2, and 2.6 bpm at Visits 3, 4, and 6 (Weeks 1, 4 and 12), respectively. In the 200 mg YM178 OCAS group, mean HR increased by 4.5, 5.1, and 3.8 bpm at Visits 3, 4, and 6 (Weeks 1, 4 and 12), respectively.
QTcF at baseline was comparable between YM178 OCAS treatment groups. No consistent changes over time were observed.
There was a mean decrease in PVR in all treatment groups, except for the YM178 OCAS 100 mg group, where a small increase was observed. However, the mean changes were small, and the inter-patient variability was very high.

CONCLUSIONS:

Based on the results of this study, it is concluded that:

- YM178 was efficacious in the treatment of patients with OAB at doses of 50 mg, 100 mg, and 200 mg in a dose-dependent manner.
- YM178 was well tolerated in patients with OAB.
- A small dose-dependent increase in pulse rate was observed across the dose range studied (25-200mg YM178 OCAS once daily). This pulse rate change was not associated with an overt increased incidence of cardiovascular adverse events.

Date of Report: 26 April 2010