3 SYNOPSIS

Name of Sponsor: **Astellas Pharma Europe B.V.**	Individual study table referring to part of the dossier	(For national authority use only)
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Title of study:	A randomized, double-blind, parallel group, proof-of-concept study of YM178 in comparison with placebo and tolterodine in patients with symptomatic overactive bladder.
(International) Study No:	178-CL-008
Principal or Coordinating Investigator:	[redacted] BSc, MD, FRCS [redacted] (UK)
Study site(s):	Multinational, multicenter.
Publication (reference):	Not applicable at the time of this report.
Study period:	Q2 2004 – Q1 2005
Clinical Phase:	Phase II
Objectives:	**Primary aim:** 1. To evaluate the efficacy of YM178 in patients with overactive bladder (OAB) in comparison with placebo. **Secondary aims:** 1. To evaluate the safety and tolerability of YM178 in patients with OAB in comparison with placebo. 2. To compare the efficacy of YM178 with tolterodine 4 mg once daily (od). 3. To compare the safety and tolerability of YM178 with tolterodine 4 mg od. 4. To collect population pharmacokinetics data in patients with OAB.
Methodology:	This was a multinational, multicenter, double-blind, double-dummy, randomized, parallel group, placebo and active controlled Phase II proof-of-concept study. Patients were enrolled into a single-blind, 2-week placebo run-in period after which they were randomized to 4 weeks of double-blind treatment with YM178 (100 mg twice daily [bid] and 150 mg bid), placebo or tolterodine 4 mg od. Subsequently, patients were followed for an additional 2 weeks with single-blind placebo treatment. There were 6 visits in total: Visit 1 at enrolment, Visit 2 (baseline) after the 2-week placebo run-in, Visits 3, 4 and 5 after 1, 2 and 4 weeks of double-blind treatment, respectively, and Visit 6 after a 2-week follow-up.
Number of subjects: (planned and analyzed)	It was planned to randomize 240 patients to have at least 200 evaluable patients (50 per treatment arm). Populations analyzed: Safety population (SAF) N=260; Full Analysis Set (FAS) N=256; Per-Protocol Set (PPS) N=209; Pharmacokinetic Set (PKS) N=123.

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Diagnosis and main criteria for inclusion:	At study entry: • Male or female patient aged ≥ 18 years with symptoms of OAB (urinary frequency and urgency with or without incontinence) for ≥ 3 months. Willing to give written informed consent. At randomization: • Patients had to have a micturition frequency of ≥ 8 times per 24-hours on average during the 3-day micturition diary period preceding Visit 2. Patients also had to have at least 3 episodes of urgency (grade 3 or 4), with or without incontinence, during the 3-day micturition diary period.
Test product **Doses:** **Mode of administration:** **Batch numbers:**	YM178 50 mg and 100 mg tablets 100 mg and 150 mg bid Oral, with food YM178 50 mg tablets: [redacted]; YM178 100 mg tablets: [redacted]
Duration of treatment:	2-week single-blind placebo run-in period, followed by a 4-week double-blind treatment, and a 2-week single-blind placebo follow-up period.
Reference therapy **Dose:** **Mode of administration:** **Batch numbers:**	Tolterodine 4 mg MR capsules (Detrusitol® 4 mg XL) Placebo Tolterodine: 4 mg od Oral, with food Placebo matching YM178 50 mg tablets: [redacted] and [redacted] Placebo matching YM178 100 mg tablets: [redacted] and [redacted] Placebo tolterodine capsules: [redacted] Tolterodine 4 mg MR capsules (Detrusitol® 4 mg XL): [redacted]
Criteria for evaluation **Efficacy:**	**Primary efficacy variable:** • Change from baseline in mean number of micturitions/24 hours **Secondary efficacy variables:** • Change from baseline in mean volume voided per micturition • Change from baseline in mean number of incontinence episodes/24 hours • Change from baseline in mean number of nocturia episodes/24 hours • Change from baseline in mean number of urge incontinence episodes/24 hours • Change from baseline in mean number of urgency episodes/24 hours • Change from baseline in severity of urgency • Change from baseline in patient perception of bladder condition • Patient perception of treatment benefit
Safety:	• Incidence and severity of adverse events (AEs). • Vital signs: sitting systolic and diastolic blood pressure and pulse rate. • Laboratory tests: hematology, biochemistry, urinalysis and urine culture. • 12-lead electrocardiogram (ECG) parameters. • Post-void residual volume (PVR), as measured by ultra-sonography or bladder scan.
Population pharmacokinetics:	Population pharmacokinetics data was generated from a timed blood sampling scheme at Visits 4 and 5.

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Statistical methods:	Continuous variables were summarized using descriptive statistics (mean, standard deviation [SD], minimum, median, maximum). Categorical variables were described using absolute and relative frequency.
Primary efficacy analysis	The primary analysis was performed on the change from baseline to endpoint in mean number of micturitions per 24 hours as derived from the micturition diary for the FAS. Changes from baseline to endpoint in mean number of micturitions per 24 hours were subjected to Analysis of Covariance (ANCOVA) with treatment as a fixed factor, and center as a random factor. Baseline was included in the model as covariate. Comparison of any of the active doses to placebo as well as YM178 versus tolterodine was tested at the two-sided significance level 0.05 by means of the corresponding contrast.
Secondary efficacy analysis	The analysis as described for the primary efficacy variable was also performed on the PPS. A repeated measure analysis was performed to evaluate the data over time. A mixed models approach for repeated measures data was performed. Furthermore, the same analyses as described above (ANCOVA, endpoint and repeated measures) were applied to the secondary efficacy variables urgency, incontinence and nocturia episodes and mean volume voided per micturition. PBC and patient perception of treatment benefit were subjected to a logistic regression analysis.
Safety	Safety was analyzed descriptively.
Summary of Results	
Efficacy results:	The primary efficacy analysis showed a statistically significant reduction of micturition frequency following treatment with 100 mg and 150 mg YM178 bid compared to placebo. The estimated active-placebo difference was 1.0 for both treatment groups. The estimated treatment difference from placebo in the tolterodine 4 mg od treatment group was 0.4 micturitions per 24 hours. Treatment with YM178 was statistically significantly superior to placebo with respect to the secondary efficacy variables mean volume voided per micturition (YM178 150 mg bid), and the mean number of (urge) incontinence episodes (YM178 100 mg bid), nocturia episodes (YM178 100 mg bid), and urgency episodes per 24 hours. An early onset of efficacy was visible with approximately two-thirds of the efficacy obtained after 4 weeks already achieved after 2 weeks. Overall, YM178-treated patients showed larger changes versus baseline than patients treated with tolterodine. No consistent differences and dose-response relationship were found between the 100 mg and 150 mg YM178 bid dose groups. For most variables the de-challenge in the placebo follow-up period confirmed the existence of a YM178 treatment effect in the double-blind treatment period. The results from the primary efficacy analysis were confirmed in the PPS, and in sensitivity analyses, which shows the robustness of the results.

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Efficacy results (cont'd): The estimated differences to placebo and the corresponding p-values for the change from baseline for the primary and secondary efficacy variables at endpoint are shown below for the FAS. Statistically significant p-values ($p \leq 0.05$) are marked with an asterisk (*).

	Placebo	**YM178 100 mg bid**	**YM178 150 mg bid**	**Pooled YM178 group**	**Tolterodine 4 mg od**
Micturitions/24 h					
FAS	**N=64**	**N=65**	**N=63**	**N=128**	**N=63**
Baseline mean (SD)	12.34 (3.51)	11.30 (2.65)	12.25 (3.62)	11.77 (3.19)	11.00 (3.06)
Change from baseline[a]	-1.32 (2.49)	-2.00 (1.76)	-2.30 (2.12)	-2.15 (1.95)	-1.27 (1.99)
Estimated difference[b] (p-value)		-1.016 0.0047*	-1.031 0.0047*	-1.022 0.0004*	-0.399 0.2332
Mean volume voided/micturition (mL)					
FAS	**N=64**	**N=65**	**N=63**	**N=128**	**N=63**
Baseline mean (SD)	151.79 (58.34)	164.65 (62.86)	150.67 (53.49)	157.77 (58.63)	179.85 (65.21)
Change from baseline[a]	10.86 (35.99)	26.71 (51.20)	32.44 (47.67)	29.53 (49.38)	23.24 (42.18)
Estimated difference[b] (p-value)		15.56 0.052	22.25 0.012*	18.81 0.0063*	13.10 0.1038
Incontinence episodes/24 h					
FAS	**N=41**	**N=37**	**N=41**	**N=78**	**N=41**
Baseline mean (SD)	2.41 (1.69)	2.50 (2.53)	3.57 (3.47)	3.06 (3.08)	2.95 (2.52)
Change from baseline[a]	-0.80 (1.47)	-2.01 (2.30)	-1.96 (2.64)	-1.98 (2.47)	-1.70 (2.26)
Estimated difference[b] (p-value)		-1.156 0.0081*	-0.568 0.1460	-0.806 0.0133*	-0.612 0.1004
Nocturia episodes/24h					
FAS	**N=57**	**N=58**	**N=54**	**N=112**	**N=58**
Baseline mean (SD)	1.88 (1.16)	1.84 (0.97)	1.92 (1.08)	1.88 (1.02)	1.84 (1.08)
Change from baseline[a]	-0.25 (0.93)	-0.59 (0.73)	-0.42 (0.83)	-0.51 (0.78)	-0.37 (0.87)
Estimated difference[b] (p-value)		-0.388 0.0086*	-0.171 0.2124	-0.274 0.0218*	-0.196 0.1547
Urge incontinence episodes/24 h					
FAS	**N=40**	**N=37**	**N=39**	**N=76**	**N=39**
Baseline mean (SD)	2.10 (1.54)	2.41 (2.50)	3.47 (3.39)	2.95 (3.02)	2.70 (2.11)
Change from baseline[a]	-0.78 (1.43)	-1.92 (2.28)	-1.89 (2.70)	-1.90 (2.49)	-1.55 (1.89)
Estimated difference[b] (p-value)		-0.968 0.0267*	-0.353 0.3634	-0.646 0.0445*	-0.44 0.2312

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Urgency episodes/24 h (severity ≥3)					
FAS	**N=63**	**N=65**	**N=62**	**N=127**	**N=63**
Baseline mean (SD)	5.83 (3.39)	5.52 (3.47)	6.58 (4.34)	6.03 (3.94)	5.55 (3.64)
Change from baseline[a]	-1.01 (3.03)	-2.19 (3.01)	-2.55 (3.80)	-2.37 (3.41)	-1.98 (2.84)
Estimated difference[b] (p-value)		-1.268 0.0363*	-1.271 0.0363*	-1.278 0.0048*	-1.087 0.038*

[a] Changes expressed as mean (SD) change at endpoint [b] Estimated difference versus placebo

	The percentage of patients classified as responder with respect to patients' assessment of treatment benefit and patient's perception of bladder condition were statistically significantly higher compared to placebo for both YM178 groups and the YM178 150 mg bid group, respectively.
Safety results:	The incidence of patients with treatment emergent AEs was 36.4% in the placebo treatment group, 40.0% and 38.5% with 100 mg and 150 mg YM178 bid, respectively, and 48.4% in the tolterodine 4 mg od treatment group. There were no deaths during the study. Four patients had a treatment-emergent SAE. These SAEs were mild rash during double-blind treatment with 4 mg tolterodine od (probably related to treatment with the study medication); moderate angina pectoris (possibly related) during the double-blind treatment with placebo; moderate tiredness during the placebo follow-up period following double-blind treatment with YM178 100 mg bid (not related); and moderate rotator cuff syndrome (not related) during the placebo follow-up period following double-blind treatment with placebo. The proportion of patients that discontinued because of treatment-emergent AEs was 1 (1.5%) in the placebo group, 3 (4.6%) and 5 (7.7%) in the 100 mg and 150 mg YM178 bid treatment group, respectively, and 2 (3.1%) in the tolterodine 4 mg od treatment group. No single AE preferred term led to discontinuation from the double-blind treatment period of more than 1 patient in any treatment group. However, 3 patients in the YM178 mg bid group discontinued prematurely due to a mild or moderate skin reaction (i.e., urticaria, rash, and allergic exanthem). The most commonly reported AEs during the double-blind treatment period were gastrointestinal AEs (dry mouth, nausea, vomiting, and diarrhea) and headache. The incidence of gastrointestinal AEs and headache was highest in the tolterodine treatment group (23.4% and 9.4%, respectively), intermediate in the YM178 treatment group (13.8% and 6.9%, respectively), and lowest in the placebo treatment group (3.0% both). Dizziness and palpitations tended to be more commonly reported with YM178 treatment compared with placebo or tolterodine (i.e., reported by 3.1% of the patients in the pooled YM178 group). Most of these AEs were considered treatment-related by the investigator.

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	Two patients had a treatment-emergent AE of severe intensity, both judged as possibly related to the study medication. These AEs were headache during double-blind placebo treatment, and increased hepatic enzymes during treatment with 150 mg YM178 bid. All other AEs were of mild or moderate intensity. The YM178 150 mg bid dose appeared to cause a small (approximately 5 bpm) mean increase from baseline in pulse rate. This was however not associated with a clinically significant increase in AEs such as tachycardia and palpitations. There were no clinically relevant effects on systolic and diastolic blood pressure, ECG, laboratory safety parameters, physical examination findings, or PVR.
Population pharmacokinetics:	The population pharmacokinetic analysis and results are described in a separate report.
Overall Conclusion:	The consistent positive effects of YM178 treatment on the various symptoms of OAB, along with more YM178-treated patients becoming continent, provides evidence that treatment with 100 mg and 150 mg YM178 bid results in a clinically meaningful benefit to patients. This is confirmed by the patients' assessment of treatment benefit and patients' perception of bladder condition. Treatment with YM178 was well tolerated, with no clinically relevant difference between 100 mg and 150 mg YM178 bid in AE profile. The incidence of AEs with YM178 treatment (39.2%) was intermediate between the placebo (36.4%) and the 4 mg tolterodine od treatment group (48.4%). There were no SAEs related to YM178 treatment. The discontinuation rate because of AEs during treatment with YM178 was low (6.2%). The most common AEs reported during the double-blind treatment period were gastrointestinal AEs (dry mouth, nausea, vomiting, and diarrhea) and headache. Dizziness and palpitations tended to be somewhat more commonly reported during treatment with YM178 compared with placebo or tolterodine. The vast majority of AEs was of mild or moderate intensity. There appeared to be a small (approximately 5 bpm) mean increase from baseline in pulse rate in the YM178 150 mg bid group when compared to the other treatment groups. This was however not associated with a significant increase in AEs such as tachycardia and palpitations. There was no clinically relevant effect of treatment on blood pressure, ECG, laboratory safety parameters, physical examination findings, or on PVR. Taken together, these results clearly indicate that proof-of-concept is achieved and suggest that YM178 is a highly effective and well-tolerated treatment for the symptoms of overactive bladder.
Date of the report:	Final Version, 14 December 2006 Reissued Version, 18 July 2011