75

Chapple C. R. [1], Arano P. [2], Bosch J. H. R. [3], De Ridder D. [4], Kramer A. [5], Ridder A. M. [6]
1. Royal Hallamshire Hospital, 2. Fundacion Puigvert, 3. Erasmus Medical Center, 4. University Hospitals Leuven, 5. Berufsgenossenschaftliche Unfallklinik, 6. Yamanouchi Europe B.V.

YM905 APPEARS EFFECTIVE AND WELL TOLERATED IN PATIENTS WITH SYMPTOMATIC IDIOPATHIC DETRUSOR OVERACTIVITY IN A EUROPEAN PLACEBO- AND TOLTERODINE-CONTROLLED, PHASE-II, DOSE-FINDING STUDY

Aims of Study
YM905 is a bladder-selective, antimuscarinic agent being developed for the relief of symptoms of urinary frequency, urinary urgency, and urinary urge incontinence associated with idiopathic detrusor overactivity. The objectives of this European phase II study were to evaluate the dose-response relationship on efficacy, safety, and tolerability of once daily dosing of YM905 in patients with symptomatic idiopathic detrusor overactivity and to compare YM905 in terms of efficacy and tolerability with tolterodine 2 mg bid.

Methods
This was a multinational, multicenter, double-blind, randomized, parallel-group, placebo- and active-controlled, phase II, dose-finding 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 placebo, tolterodine 2 mg bid, or YM905 (2.5 mg, 5 mg, 10 mg, or 20 mg) once daily. Efficacy was evaluated on the basis of information obtained from patients' urinary diaries.

The primary efficacy variable was the change from baseline to endpoint in mean number of micturitions per 24 hours. The secondary efficacy parameters included mean number of incontinence episodes, urgency episodes per 24 hours, and mean volume voided per micturition. Safety assessment was done by reporting adverse events, clinical laboratory tests, vital signs, ECGs, and post-void residual volume (ultra-sonography).

For inclusion, urodynamic evidence of idiopathic detrusor overactivity (phasic contractions $\geq$ 10 cm H_2O) within 6 months before inclusion had to be demonstrated, patients had to experience frequency of micturition on average $\geq$ 8 times per 24 hours, and they had to have at least 3 urinary incontinence or 3 urgency episodes during a 3-day urinary diary period before randomization.

Results
Overall, 225 patients (22 to 83 years of age, mean age 57 years, 60% females) were randomized to treatment.

Efficacy: The results for micturition frequency show that the YM905 5-mg dose can be considered the minimal effective dose. The mean change in the tolterodine 2-mg bid group was within the mean changes of 2.5 and 5 mg YM905. A similar outcome was found for the mean change from baseline to endpoint in mean volume voided per micturition. The mean change of the tolterodine 2-mg bid group was between the mean changes of placebo and the YM905 2.5-mg group. No statistically significant differences to placebo were found for two other secondary efficacy variables—mean change in incontinence and urgency episodes/24 hours. However, the YM905 dose groups showed numerically better changes than placebo. The mean effect in the tolterodine 2-mg bid group was generally smaller compared with that of the YM905 dose groups for both parameters. The lack of statistical significance might be explained by the study not being powered for these secondary efficacy variables.

Safety: Because the 5-mg dose is considered to be the minimal effective dose of YM905, the 2.5-mg dose is not addressed here.

The total incidence of treatment emergent adverse events (TEAEs) with the 5-mg dose of YM905 (43%) was similar to that of the placebo group (47%). The total incidence compared with placebo was higher for YM905 10 mg (60%), 20 mg (65%), and also for tolterodine 2 mg bid (62%).
Dry mouth was the most common TEAE, reported in both the 5-mg and 10-mg YM905 dose groups by 14% of patients and by 38% in the 20-mg dose group, compared with 2.6% in the placebo group and 24% in the tolterodine group. None of the YM905 doses affected vital signs or any of the laboratory parameters in a clinically relevant manner.

Table 1. Efficacy of YM905 in patients with symptomatic idiopathic detrusor overactivity.

	Treatment Group					
	Placebo	YM905				Tolterodine
		2.5 mg	5 mg	10 mg	20 mg	
Micturitions/24 h	n=36	n=40	n=37	n=33	n=34	n=37
Baseline mean	11.1	11.9	11.5	11.4	11.7	12.1
Endpoint change from baseline	-1.03	-1.45	-2.21*	-2.47**	-2.75**	-1.79
Incontinence episodes/24 h	n=26	n=31	n=24	n=22	n=24	n=25
Baseline mean	2.3	2.1	2.3	2.5	1.5	2.3
Endpoint change from baseline	-0.46	-0.85	-1.32	-1.18	-0.90	-0.65
Urgency episodes/24 h	n=36	n=40	n=37	n=33	n=34	n=37
Baseline mean	5.2	5.9	5.6	5.3	5.2	5.7
Endpoint change from baseline	-1.03	-1.07	-2.35	-2.46	-2.24	-1.62
Volume voided	n=35	n=40	n=37	n=33	n=34	n=37
Baseline mean (mL)	135	148	162	153	152	160
Endpoint change from baseline	9.7	19.9	38.0**	43.2***	64.7***	14.7
*p<0.05; **p<0.01; ***p<0.001 in pairwise comparisons between treatment groups and placebo						

Conclusions

This phase II dose-finding study shows that YM905 has an apparent dose-response relationship on the primary efficacy variable (micturition frequency) and the most common TEAE (dry mouth). It can be concluded that YM905 5 mg, 10 mg, and 20 mg once daily are effective doses for the management of patients with symptomatic idiopathic detrusor overactivity. As the 5-mg and 10-mg doses appear to be better tolerated than the 20-mg dose, especially with regard to the occurrence of dry mouth, YM905 5 mg and 10 mg once daily have been selected for further evaluation in large-scale phase III studies.

The favorable efficacy–tolerability ratio for these doses of YM905 may be due to a higher selectivity of YM905 for the bladder than for the salivary gland when compared with tolterodine.