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YM905 IS EFFECTIVE AND SAFE AS TREATMENT OF OVERACTIVE BLADDER IN WOMEN AND MEN: RESULTS FROM PHASE II STUDY

Aims of Study

YM905 is a bladder-selective antimuscarinic being developed for the treatment of overactive bladder (OAB) with symptoms of frequency, urgency, and urge incontinence. Its selectivity has the potential to decrease anticholinergic side effects, such as dry mouth, constipation, somnolence, blurred vision, and impaired cognitive function while providing effective relief of OAB symptoms. The objective of this 4-week, placebo-controlled, dose-ranging Phase II study was to determine which dose levels (YM905 2.5, 5, 10, or 20 mg once daily) provide optimum efficacy, while maintaining optimal safety and tolerability, in reducing symptoms associated with OAB.

Methods

The study employed a randomized, double-blind, placebo-controlled, parallel-group, fixed-dose, dose-ranging design. During a 3-day screening period, prospective subjects were required to document an elevated number of micturitions per 24 hours (on average, 8 or more), at least one urinary incontinence episode per 24 hours, or at least one urinary urgency episode per 24 hours. The study enrolled 265 subjects (aged 30 to 86 years; mean, 60 years) of whom 264 took at least one dose of study medication, and 261 had at least one post-treatment assessment. The trial consisted of a 2-week placebo run-in screening period, a 4-week treatment period, and a 2-week post-treatment follow-up period. Subjects were randomized to double-blind treatment with single daily doses of placebo or 2.5, 5, 10, or 20 mg YM905. Efficacy was evaluated on the basis of information contained in subject diaries. The primary efficacy parameter was mean change from baseline to endpoint in number of micturitions per 24 hours. Other efficacy endpoints included mean number of incontinence and urgency episodes per 24 hours and mean volume voided per micturition. Safety was evaluated by reporting of adverse events, physical examinations, clinical laboratory analysis, recording of vital signs, and ECGs.

Results

Overall, 265 patients were randomized to treatment, and 261 were included in the efficacy analysis. A total of 26 patients failed to complete the study. The most common reason for discontinuation was adverse events (16 subjects).

Efficacy results appear in the Table below. Both the 10- and 20-mg YM905 doses were significantly superior to placebo in reducing the number of micturitions over 24 hours ($p<0.01$ and $p<0.001$, respectively). The 10-mg YM905 dose also significantly reduced the number of incontinence episodes per 24 hours ($p<0.01$), and the 5-, 10-, and 20-mg YM905 doses all significantly increased average voided volume ($p<0.05$, $p<0.001$, and $p<0.01$ versus placebo, respectively).

Table 1. Efficacy of YM905 in patients with OAB.

	Treatment Group				
		YM905			
	Placebo	2.5 mg	5 mg	10 mg	20 mg
No. of micturitions/24 h	n=53	n=53	n=52	n=51	n=52
Baseline mean	10.9	11.4	11.1	12.5	11.6
Endpoint change from baseline	-1.0	-2.0	-1.8	-3.0***	-2.8**
Incontinence episodes/24 h	n=43	n=45	n=45	n=39	n=43
Baseline mean	2.3	2.9	2.3	3.7	2.7
Endpoint change from Baseline	-1.3	-1.5	-1.3	-2.5**	-1.4
Urgency episodes/24 h	n=53	n=53	n=52	n=51	n=52
Baseline mean	6.7	8.0	7.2	7.7	7.3
Endpoint change from Baseline	-2.1	-2.4	-2.0	-3.0	-2.9
Volume voided	n=53	n=53	n=50	n=51	n=51
Baseline mean (mL)	196	182	170	189	184
Endpoint change from Baseline	6	30	36*	56***	48**
*p<0.05; **p<0.01; ***p<0.001 in pairwise comparisons between treatment groups and placebo					

Treatment-emergent adverse events (TEAEs) were reported by 29 of 53 patients (55%) who received placebo, and 29 of 54 (54%), 33 of 52 (63%), 32 of 51 (63%), and 44 of 54 (81%) patients treated with 2.5, 5, 10, and 20 mg YM905, respectively. Dry mouth was the most common TEAE. It occurred in 8% of patients who received placebo and in 9%, 12%, 33%, and 48% of those treated with 2.5, 5, 10, or 20 mg YM905, respectively. There were no statistically significant differences among groups in the incidences of abnormal hematology, chemistry, urinalysis values, or ECG findings.

Conclusions

The results of this Phase II, fixed-dose study indicate that 5, 10, and 20 mg/o.d. YM905 are effective and safe. The 5-, 10-, and 20-mg doses were all statistically significantly superior to placebo in increasing volume voided; the 10- and 20-mg doses were significantly superior to placebo in decreasing number of micturitions; and the 10-mg dose was significantly superior in decreasing incontinence episodes. The 5- and 10-mg doses were associated with fewer anticholinergic side effects than was the 20-mg dose. Phase III studies should further evaluate efficacy and safety of YM905.