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10- AND 20-MG ORAL DOSES OF YM905, A NOVEL, BLADDER-SELECTIVE ANTIMUSCARINIC: PHARMACOKINETICS, PHARMACODYNAMICS, AND SAFETY IN HEALTHY, ELDERLY MEN AND WOMEN

Aims of Study

Overactive bladder (OAB) is common in the elderly, and it has a dramatic negative impact on quality of life. Anticholinergic therapy is often used to treat OAB, but its use is often limited by unacceptable side effects (eg, dry mouth, blurred vision, constipation, somnolence, impaired cognitive function). YM905 is a novel, bladder-selective antimuscarinic with the potential to ameliorate OAB while being associated with minimal anticholinergic side effects. The objective of this study was to evaluate multiple-dose pharmacokinetics, pharmacodynamics, and safety of two oral doses (10 and 20 mg) of YM905 in elderly, healthy men and women.

Methods

The study was carried out using a double-blind, placebo-controlled, escalating-dose design. It included 33 healthy men and women (aged 65 to 80 years, mean 70.6). The first cohort of 17 subjects received either 10 mg YM905 (n=13) or placebo (n=4), and the second group was treated with either 20 mg YM905 (n=12) or placebo (n=4). Subjects in each cohort received a single dose of YM905 or placebo on day 1 and single daily doses on days 5 through 19. Pharmacodynamic assessments, including visual nearpoint (a measure of convergence), R-R interval variability, and salivary flow, were carried out pre-dose and for up to 96 hours after the first and last YM905 doses. Blood samples for determination of plasma YM905 concentrations were also collected before dosing and for up to 96 hours after the first and last doses. Urine was collected for determination of YM905 concentrations. Plasma pharmacokinetic parameters calculated included maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the time versus plasma concentration curve from time zero to infinity ($AUC_{0\text{-}INF}$, first dose) and until 24 hours after administration ($AUC_{0\text{-}24h}$, last dose), and elimination half life ($t_{½}$). Safety was evaluated by reporting of adverse events, physical examinations, clinical laboratory tests, recording of vital signs, and ECGs.

Results

Thirty-three subjects were enrolled, and results from all are included in the safety analysis. Results from 32 subjects are included in the pharmacokinetic and pharmacodynamic analyses.

Pharmacokinetic results (Table 1) indicate that increasing doses of YM905 resulted in proportional rises in C_{max} and AUC for the elderly male subjects. A less than proportional increase was seen in the women. Multiple doses of YM905 resulted in modest increases in both C_{max} and AUC, suggesting some accumulation of drug with repeated administration. Approximately 5% to 10% of the administered dose of YM905 was excreted in the urine as unchanged drug.

Table 1. Pharmacokinetic parameters for 10 and 20 mg YM905 in healthy elderly subjects.

	Males (10 mg)		Females (10 mg)		Males (20 mg)		Females (20 mg)	
	First dose	Last dose	First dose	Last dose	First dose	Last dose	First dose	Last dose
C_{max} (ng/mL)	9.7	41.4	15.6	56.0	24.8	88.2	20.1	72.1
AUC* (ng·h/mL)	672.9	879.0	986.2	1156.8	1187.6	1800.5	1168.9	1428.1
t_{max} (hours)	5.8	8.0	6.2	9.0	5.2	6.2	5.8	7.3
$t_{½}$ (hours)	51.2	65.3	52.9	69.5	65.3	82.3	48.1	56.9

*$AUC_{0\text{-}INF}$ for the first dose and $AUC_{0\text{-}24h}$ for the last dose

Assessment of visual nearpoints indicated no significant effect of single or multiple doses of either 10 or 20 mg YM905. Salivary flow decreased slightly relative to placebo during multiple-dose treatment with 10 or 20 mg YM905.

YM905 was well tolerated. Overall, 68% (17 of 25) of subjects who received active treatment reported adverse events versus 62.5% (5 of 8) of subjects who received placebo. The most common side effects possibly or probably related to YM905 included dry mouth and constipation. Nearly all side effects were mild in severity. There were no clinically significant effects of treatment on physical examinations, clinical laboratory values, vital signs, or ECGs. YM905 treatment had no significant effect on R-R intervals.

Conclusions

YM905 is well tolerated in healthy, elderly subjects, with no differences in tolerability between men and women. Multiple YM905 doses produce small reductions in salivation relative to placebo but no changes in visual nearpoint. It exhibits dose-proportional increases in C_{max} and $AUC_{0\text{-}24h}$ in men, but in women, the relationship was less proportional, perhaps owing to the small study population. The pharmacokinetic, pharmacodynamic, and safety profiles for YM905 suggest it may be useful for the treatment of OAB in the elderly.