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FESOTERODINE A NEW EFFECTIVE AND WELL-TOLERATED ANTIMUSCARINIC FOR THE TREATMENT OF URGENCY-FREQUENCY SYNDROME: RESULTS OF A PHASE 2 CONTROLLED STUDY.

Hypothesis / aims of study

Fesoterodine is a novel derivative of 3,3-diphenylpropyl-amine developed by Schwarz Pharma for the treatment of urgency-frequency syndrome (UFS also known as overactive bladder). The drug is a potent antimuscarinic, rapidly absorbed and immediately hydrolyzed to the active metabolite, SPM 7605, without requiring hepatic metabolism.
The objective of this trial was to determine the optimal dose of fesoterodine measuring efficacy, tolerability and safety in subjects with UFS.

Study design, materials and methods

This trial was conducted at 81 sites in Europe, Israel, and South Africa. After a 1-week placebo run-in, eligible subjects were randomized to receive placebo or 4, 8, or 12 mg of fesoterodine once daily for 12 weeks.
Efficacy variables were measured as change from baseline to 12 weeks after treatment. Primary variables were change in the mean number of micturitions per 24 hours and change in the mean number of urge incontinence episodes per week. Treatment efficacy was assessed by comparing the change from baseline in a 7-day micturition diary.
Safety was assessed by monitoring adverse events and changes in clinical laboratory values, vital signs, ECGs, physical and urological examinations, and residual urinary volume. Treatment tolerance was evaluated subjectively.

Results

A total of 728 subjects were randomized and treated; 698 subjects were evaluable for the primary efficacy analysis. The mean age was 56 (age range 18–79 years) and 84% of subjects were female.

Mean changes from baseline to end of treatment

Variable	Placebo	4 mg fesoterodine	8 mg fesoterodine	12 mg fesoterodine
Micturitions/24 hours Mean change Difference from placebo (ANCOVA adjusted estimate)	-1.42	-2.20 -0.72; p=0.0030*	-2.37 - 0.82; p=0.0012*	-2.41 - 0.94; p=0.0002*
Urge incontinence episodes/week Mean change Difference from placebo (ANCOVA adjusted estimate)	-10.18	-12.79 -3.96; p=0.0045	-11.79 -2.54; p=0.0521	-13.43 -4.61; p=0.0013*

P-values are one-sided; "" means significant in the closed test procedure.*

There is a rapid improvement in both primary efficacy variables within the first two weeks of double-blind treatment as contrasted to placebo. Fesoterodine treatment results show significantly greater decreases in micturition frequency than placebo at all 3 doses. Early improvements were also seen in the reduction of the number of urge urinary incontinence episodes. The reduction was also seen in the 4 mg group.
The most frequently reported AE in this trial was dry mouth (placebo 9%, 4 mg 25%, 8 mg 26%) increasing to 34% in the 12 mg group. The use of a VAS (visual analogue scale) to assess dry mouth may have triggered the reporting. Dry mouth was rated as mild to moderate in most cases in the 4 and 8 mg groups. Drop out rates due to AE were 4% of subjects in placebo group, 6%, 2%, 12% in the 4 mg, 8 mg and 12 mg Fesoterodine groups, respectively.

Adverse events with a frequency greater than 1% in any treatment group

Adverse events > 1 %	Placeb	Fesoterodine	Fesoterodine	Fesoterodine

	o (N=183)	4mg (N=186)	8mg (N=173)	12mg (N=186)
Dry mouth*	9%	25%	26%	34%
Headache	16%	17%	16%	15%
Influenza-like symptoms	8%	9%	4%	4%
Abdominal pain	4%	3%	8%	8%
Nausea	7%	5%	2%	6%
Constipation	3%	2%	3%	6%
Back pain	3%	3%	4%	2%
Coughing	4%	3%	<1%	3%
Dizziness	3%	4%	1%	2%
Abnormal vision	1%	0%	0%	1%

**after randomisation*

All other adverse events were in the range of placebo for all the treatment groups. Low rates were seen for constipation and vision disorders, which were in the placebo range. Fesoterodine had no clinically relevant effects on vital signs or ECG parameters.

Based on patient assessments, the doses of 4 mg and 8 mg showed the best efficacy/tolerance ratios.

Interpretation of results

Fesoterodine once daily is an effective antimuscarinic agent in the treatment of urgency-frequency syndrome at all of the three doses tested. It significantly improved micturition frequency and urge incontinence episodes as compared to placebo.

Fesoterodine was generally well tolerated, and no safety concerns were raised. Except for dry mouth all side effects were low or in the range of placebo, including constipation and vision disorders.

Concluding message

In conclusion, fesoterodine is a potent and well-tolerated antimuscarinic in all doses tested (4 mg, 8 mg and 12 mg). The most favourable efficacy-safety ratio was observed in the 4 and 8 mg groups.