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COMBINATION TREATMENT WITH MIRABEGRON AND SOLIFENACIN IN PATIENTS WITH OVERACTIVE BLADDER (OAB) – EFFICACY AND SAFETY RESULTS FROM A RANDOMISED PHASE II STUDY (SYMPHONY)

Hypothesis / aims of study

Oral antimuscarinics are current first-line pharmacotherapy for treatment of overactive bladder (OAB). Adverse events (AEs) associated with antimuscarinics (eg dry mouth, constipation) are often dose-limiting and are known to affect tolerability and persistence with therapy [1]. The β 3-adrenoceptor agonist, mirabegron, has demonstrated improvements vs placebo in incontinence episode frequency (IEF) and micturition frequency (MF) per 24 h in patients with OAB in Phase III trials [2,3], and is now approved for treatment of OAB symptoms in Europe, the USA and Japan. Given their different mechanism of action, the combination of mirabegron and solifenacin may provide an attractive dual therapeutic approach to maximise efficacy in OAB treatment without the tolerability limitations seen with higher-dose antimuscarinics. The primary objective of the current study (NCT01340027) was to assess the efficacy and safety of mirabegron plus solifenacin combination therapy, compared with solifenacin monotherapy.

Study design, materials and methods

This Phase II, randomised, double-blind, factorial design, parallel-group, placebo- and monotherapy-controlled trial enrolled patients ≥ 18 years with symptoms of OAB for ≥ 3 months. Based on a sample size of 140 evaluable patients in the solifenacin 5 mg monotherapy arm and each of the 4 primary solifenacin + mirabegron combination arms, the study had 80% power to find a statistically significant difference between a combination and solifenacin 5 mg alone, if the real treatment difference in change from baseline to EOT in MVV was ≥ 17.3 mL – this calculation was performed based on a 2-sided t-test with $\alpha=0.05$ and a standard deviation of 50 mL. The groups associated with secondary comparisons planned to recruit 70 eligible patients. Following a 2-week, single-blind, placebo run-in, based on a 3-day micturition diary, patients with ≥ 8 micturitions per 24 h and ≥ 3 urgency episodes per 72 h (with/without incontinence) were randomised, using an interactive response system, to receive 1 of 6 combinations of mirabegron (25 or 50 mg) and solifenacin (2.5, 5 or 10 mg), monotherapy with mirabegron (25 or 50 mg) or solifenacin (2.5, 5 or 10 mg), or placebo once daily for 12 weeks. Efficacy data were collected using electronic patient micturition diaries. The primary efficacy variable was change from baseline to end of treatment (EOT) in mean volume voided per micturition (MVV). Key secondary variables included change from baseline to EOT in MF and IEF per 24 h. Additional secondary variables were change from baseline to EOT in number of urgency episodes (grade 3 and/or 4) per 24 h on the Patient Perception of Intensity of Urgency Scale (PPIUS); change from baseline to EOT in Symptom Bother and Health Related Quality of Life (HRQoL) scores, assessed by the Overactive Bladder Questionnaire (OAB-q); and change from baseline to EOT in patient Treatment Satisfaction on Visual Analog Scale (TS-VAS). Safety assessments included frequency of treatment-emergent adverse events (TEAEs), systolic/diastolic blood pressure, pulse rate, laboratory tests, ECG and post-void residual volume.

Results

This study was conducted at 134 sites in 20 European countries between March 2011 and July 2012. In total, 1307 patients (mean age 54.8 years, 66.1% female, 22% with urgency incontinence at baseline) were randomised and received ≥ 1 dose of study drug. For all combinations including 5 or 10 mg solifenacin, the mean change from baseline in MVV was statistically significantly greater than with solifenacin 5 mg alone (Table 1). The combinations 5 + 50, 10 + 25 and 10 + 50 showed statistically significant differences vs solifenacin 5 mg in MF per 24 h: -0.80 ($p=0.007$), -0.88 ($p=0.016$), and -0.98 ($p=0.007$), respectively. IEF results were inconclusive due to low numbers of incontinent patients. On the additional secondary variables, all combinations except for 2.5 + 25 showed statistically significant differences vs solifenacin 5 mg in mean number of urgency episodes. All combinations except 2.5 + 25 and 10 + 50 showed statistically significant differences vs solifenacin 5 mg in OAB-q Symptom Bother. All combinations except 2.5 + 25 showed statistically significant differences vs solifenacin 5 mg in OAB-q total score. The combinations 5 + 25, 10 + 25 and 10 + 50 showed statistically significant differences vs solifenacin 5 mg in TS-VAS. In total, 1239 patients (94.8%) completed the study, with 18 patients (1.4%) discontinuing due to an AE. In general, the incidence of TEAEs was not higher in combination treatment vs monotherapy. There were two treatment-related serious TEAEs: confusion (solifenacin 10 group) and acute urinary retention (2.5 + 25 combination). Among the most commonly reported TEAEs ($\geq 5\%$ in any treatment group) no clear pattern or dose-related trend was seen between combination and monotherapy groups, with the possible exception of constipation where there was a slightly increased frequency with combination therapy (Table 2). However, due to low patient numbers, this finding should be interpreted with caution. No clear or dose-related differences between combination and monotherapy groups were observed in mean change from baseline in pulse rate, QTcF, or other ECG or laboratory parameters.

Interpretation of results

In this study, combination therapy of mirabegron (25 mg and 50 mg) with solifenacin (≥ 5 mg) demonstrated greater efficacy than solifenacin 5 mg alone on change from baseline in MVV and MF. As expected, results on incontinence were inconclusive. Results on secondary efficacy parameters (QoL, TS-VAS) also suggested clinically relevant improvements for combination therapy vs monotherapy. Combination therapy appeared safe and well-tolerated.

Concluding message

Combination therapy with mirabegron and solifenacin appears both safe and efficacious and has the potential to provide a therapeutic benefit for patients who require increased efficacy and/or tolerability over currently available treatments for OAB. Larger studies are needed to confirm the clinical efficacy of combination treatment on incontinence.

	Mirabegron		S 0	S 2.5	S 5	S 10
Adjusted difference ^a vs solifenacin 5 mg	0 mg	Mean (SE)	---	---	---	0.3 (7.44)
		95% CI	---	---	---	(-14.3,14.9)
		p-value	---	---	---	0.97
	25 mg	Mean (SE)	---	3.4 (6.15)	17.6 (6.20)	21.7 (7.37)
		95% CI	---	(-8.6,15.5)	(5.4,29.8)	(7.2,36.1)
		p-value	---	0.58	0.005*	0.003*
	50 mg	Mean (SE)	---	5.9 (6.13)	18.2 (6.10)	26.3 (7.32)
		95% CI	---	(-6.1,18.0)	(6.2,30.2)	(11.9,40.7)
		p-value	---	0.33	0.003*	<0.001*

^aStatistically significantly superior vs solifenacin 5 mg. ^aMeans (LS means), 95% CIs and p-values for pairwise comparisons from the ANCOVA model. Differences of the adjusted means: adjusted mean of combination treatment group – adjusted mean of solifenacin succinate 5 mg.

	P	M 25	M 50	S 2.5	S 5	S 10	S 2.5 + M 25	S 2.5 + M 50	S 5 + M 25	S 5 + M 50	S 10 + M 25	S 10 + M 50
Number of patients randomised, n	81	77	78	79	156	78	149	149	144	153	81	81
TEAE, %												
Dry mouth	3.7	2.6	5.1	7.6	11.5	29.5	12.8	8.7	14.6	13.1	19.8	17.3
Hypertension	8.6	11.7	14.1	10.1	11.5	6.4	7.4	7.4	7.6	5.9	8.6	13.6
Naso-pharyngitis	2.5	6.5	6.4	6.3	3.8	2.6	2.7	4.0	4.9	3.9	7.4	7.4
Constipation	0	0	3.8	1.3	1.9	5.1	4.7	4.0	2.8	1.3	7.4	9.9
Escherichia UTI	2.5	1.3	2.6	1.3	3.8	6.4	2.0	1.3	2.1	2.6	3.7	1.2
UTI	3.7	1.3	2.6	1.3	2.6	6.4	0.7	1.3	1.4	2.0	0	3.7
Tachycardia	1.2	3.9	2.6	2.5	3.8	2.6	2.0	4.7	3.5	2.0	4.9	3.7

TEAE=treatment-emergent adverse event; P=placebo; M=mirabegron; S=solifenacin; UTI=urinary tract infection

References

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Disclosures

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