490

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SAFETY AND EFFICACY OF MIRABEGRON ADD-ON TREATMENT TO SOLIFENACIN IN INCONTINENT OAB SUBJECTS WITH AN INADEQUATE RESPONSE TO INITIAL 4-WEEK SOLIFENACIN MONOTHERAPY

Hypothesis / aims of study
The combination of an antimuscarinic agent (e.g. solifenacin [SOLI]) and a β3-adrenoceptor agonist (e.g. mirabegron [MIRA]) may provide benefits as a pharmacotherapy in patients with overactive bladder (OAB). The primary objective of this Phase IIIb study was to evaluate the efficacy of MIRA in combination with SOLI 5 mg (Combination therapy) vs SOLI 5 mg monotherapy, in incontinent patients with OAB and an inadequate response to initial 4 week SOLI 5 mg monotherapy. Secondary objectives were to evaluate the safety and tolerability of combination therapy vs SOLI 5 mg and 10 mg monotherapy, and to evaluate the efficacy of combination vs SOLI 10 mg monotherapy.

Study design, materials and methods
Adult patients with symptoms of OAB for ≥3 months, entered a 2-week washout period (Visit 1), followed by single-blind SOLI 5 mg daily for 4 weeks (Visit 2). Eligible subjects still reporting ≥1 incontinence episode during a 3-day micturition diary were then randomized (1:1:1) at baseline (Visit 3) to receive daily, double-blind treatment with combination (SOLI 5 mg + MIRA 25 mg; titrating up to MIRA 50 mg after 4 weeks [Visit 4]), SOLI 5 mg, or SOLI 10 mg for 12 weeks; further assessments were conducted at Week 8 (Visit 5), Week 12 (end of treatment [EoT]; Visit 6), and Week 14 (safety follow up; Visit 7). The primary efficacy endpoint was change from baseline to EoT in mean number of incontinence episodes/24 h. Key secondary efficacy variables were change from baseline to EoT in mean number of micturitions/24 h and number of incontinence episodes during a 3-day diary at EoT. Safety assessments included treatment-emergent adverse events (TEAEs), including AEs of special interest and antimuscarinic AEs, and change from baseline in vital signs. Superiority of combination vs SOLI 5 mg (primary and key secondary efficacy endpoints) and non-inferiority of combination vs SOLI 10 mg (key secondary efficacy endpoints only) were analyzed using an ANCOVA model (stratified rank ANCOVA for the primary endpoint), and a mixed effects Poisson regression model (incontinence episodes during 3-day diary at EoT). Non-inferiority was concluded if the resulting upper limit of the two-sided 95% CI of the Rate Ratio was <1.11 (incontinence episodes) or if the resulting upper limit of the two-sided 95% CI was <0.20 (micturition frequency). Vital signs were analyzed by an ANCOVA model. All statistical models included treatment group, randomization stratification factors and baseline value.

Results
Overall, 2174 patients were randomized to combination (n=727), SOLI 5 mg (n=728) or SOLI 10 mg (n=719). Patient demographics and baseline characteristics were similar across the study arms. At EoT, reductions in the mean number of incontinence episodes/24 h (adjusted mean difference [95% CI]: −0.26 [−0.47, −0.05]), mean number of micturitions/24 h (adjusted mean difference [95% CI]: −0.45 [−0.67, −0.22]) and incontinence episodes during a 3-day diary (rate ratio [95% CI]: 0.82 [0.71, 0.96]) were statistically significantly greater in the combination group vs SOLI 5 mg. The combination was non-inferior to SOLI 10 mg for the change from baseline to EoT in mean number of micturitions/24 h (adjusted mean difference [95% CI]: −0.54 [−0.77, −0.32]) and incontinence episodes during a 3-day diary at EoT (rate ratio [95% CI]: 0.90 [0.76, 1.05]). Combination was also superior to SOLI 10 mg for reduction in micturitions/24 h. The overall incidence of any TEAE with combination was between the incidences observed in the SOLI 5 mg and 10 mg groups (Table). The incidence of dry mouth in the combination group was similar to SOLI 5 mg and lower than SOLI 10 mg. The adjusted mean change from baseline to EoT in vital signs was comparable across all treatment arms, except for systolic blood pressure (SBP) where a treatment difference of 1 mm Hg was evident between the combination and SOLI monotherapy groups (Table).

Interpretation of results
The combination was superior to SOLI 5 mg for the primary and key secondary endpoints and was non-inferior to SOLI 10 mg for the key secondary endpoints, and superior vs SOLI 10 mg for reduction in micturitions/24 h. All treatment arms were well tolerated; the AE profile for the combination was consistent with the known profiles of SOLI and MIRA with no signal for new AEs. Vital signs in the combination group showed no additive/synergistic effect beyond those known for either monotherapy.

Concluding message
Add-on treatment with mirabegron provides additional benefit compared with SOLI 5 mg or an increase to SOLI 10 mg in incontinent OAB patients with an insufficient response to SOLI 5 mg. All treatment arms were well tolerated with no signal for new AEs.

Table. Incidence of TEAEs and change from baseline to EoT in vital signs (SAF)			
	SOLI + MIRA COMBINATION (n=725)	**SOLI 5 mg (n=728)**	**SOLI 10 mg (n=719)**
Any TEAE, n (%)	260 (35.9)	241 (33.1)	283 (39.4)
Any serious TEAE, n (%)	13 (1.8)	9 (1.2)	15 (2.1)
Any TEAE leading to discontinuation, n (%)	11 (1.5)	11 (1.5)	11 (1.5)
Common TEAEs occurring in ≥2% of patients in any treatment group, n (%)*			
Dry mouth	43 (5.9)	41 (5.6)	68 (9.5)
Constipation	33 (4.6)	22 (3.0)	34 (4.7)
Oedema peripheral	6 (0.8)	16 (2.2)	2 (0.3)
*TEAE of special interest and antimuscarinic AEs**, n (%)*			
Increased blood pressure	12 (1.7)	6 (0.8)	13 (1.8)
QT prolongation	1 (0.1)	1 (0.1)	2 (0.3)
Increased heart rate, Palpitations, Tachycardia, Atrial fibrillation	7 (1.0)	5 (0.7)	4 (0.6)
Tachycardia	2 (0.3)	3 (0.4)	1 (0.1)
Urinary tract infection	17 (2.3)	16 (2.2)	20 (2.8)
Urinary retention	4 (0.6)	3 (0.4)	7 (1.0)
Hypersensitivity reactions	11 (1.5)	6 (0.8)	6 (0.8)
Glaucoma	0	0	0
Dry mouth	43 (5.9)	41 (5.6)	70 (9.7)
Blurred vision	10 (1.4)	10 (1.4)	5 (0.7)
Constipation	33 (4.6)	22 (3.0)	34 (4.7)
Dyspepsia	6 (0.8)	4 (0.5)	8 (1.1)
Change from baseline to EoT in vital signs			
Mean adjusted change in SBP, mm Hg (SE) [95% CI]	0.07 (0.38) [–0.68, 0.83]	–0.93 (0.38) [–1.68, –0.18]	–1.28 (0.38) [–2.03, –0.52]
Mean treatment difference (combination vs monotherapy) (SE) [95% CI]		1.01 (0.54) [–0.06, 2.07]	1.35 (0.54) [0.29, 2.42]
Mean adjusted change in DBP, mm Hg (SE) [95% CI]	–0.35 (0.26) [–0.86, 0.16)	–0.45 (0.26) [–0.96, 0.05]	–0.48 (0.26) [–0.99, 0.03]
Mean treatment difference (combination vs monotherapy) (SE) [95% CI]		0.10 (0.36) [–0.61, 0.82]	0.13 (0.37) [–0.59, 0.85]
Mean adjusted change in pulse rate, bpm (SE) [95% CI]	0.47 (0.28) [–0.09, 1.02]	0.43 (0.28) [–0.12, 0.98]	0.27 (0.28) [–0.28, 0.83]
Mean treatment difference (combination vs monotherapy) (SE) [95% CI]		0.04 (0.40) [–0.75, 0.82]	0.19 (0.40) [–0.59, 0.98]
* Based on single MedDRA Preferred Terms **Based on standard MedDRA queries (SMQs) or sponsor-defined lists of Preferred Terms if no SMQ was available Safety Analysis Set (SAF), included all randomized subjects who received ≥1 dose of double-blind treatment bpm=beat per minute; CI=confidence interval; DBP=diastolic blood pressure; SBP=systolic blood pressure; SE=standard error			

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