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EFFICACY AND SAFETY OF THE β_3 -ADRENOCEPTOR AGONIST MIRABEGRON IN THE TREATMENT OF OAB PATIENTS FOR WHOM COMORBID NEUROLOGIC DISORDERS CANNOT BE RULED OUT AS ETIOLOGY FOR BLADDER SYMPTOMS: A POST-HOC ANALYSIS OF POOLED DATA FROM 3 RANDOMISED PHASE III TRIALS

Hypothesis / aims of study

The β_3 -adrenoceptor agonist mirabegron has been approved in Europe, the US, Canada and Japan for the treatment of overactive bladder (OAB). In a prospective pooled analysis of 3 randomised, double-blind, placebo-controlled, 12-week Phase III trials (NCT00689104, NCT00662909, NCT00912964) mirabegron (50 & 100 mg once-daily [OD]), resulted in statistically significant improvements in the co-primary endpoints—change from baseline (BL) to Final Visit (FV/End-of-Treatment) in mean number of incontinence episodes and micturitions/24 h vs placebo as well as in a number of secondary endpoints. As therapy for Neurogenic Lower Urinary Tract Dysfunction (NLUTD) has not been extensively studied, we conducted a post-hoc analysis of the pooled data from these 3 trials to evaluate the efficacy and safety of mirabegron in the subset of OAB patients with comorbid neurological disorders whose role in the etiology of bladder symptoms cannot be ruled out. At the same time, it is recognized that a limitation of this analysis is that, in some patients, the underlying neurological condition may not be the driver of OAB symptoms.

Study design, materials and methods

The Safety Analysis Set (SAF) was all randomised patients who received ≥ 1 dose of study drug. The Full Analysis Set (FAS) was SAF patients with micturition measurements in the 3-day micturition diary at BL and at least one post-BL diary. The FAS-incontinence (FAS-I) was FAS patients who also had ≥ 1 incontinence episode in the BL diary. Exclusion criteria included diabetic neuropathy and self-intermittent catheterization, but not neurogenic bladder. Co-primary endpoints are as noted above. Secondary endpoints included change from BL to FV in mean number of urgency episodes (Patient's Perception of Intensity and Urgency Scale [PPIUS] grade 3 or 4)/24 h and mean level of urgency (based on PPIUS). Assuming that $\geq 85\%$ of randomised patients were evaluable, ~430 patients were to be randomised to each treatment group within each study. Safety variables included incidence and severity of treatment-emergent adverse events (TEAEs) and post-void residual (PVR) volume.

Results

There were 3684 SAF patients in the combined, placebo, mirabegron 50 mg and 100 mg pooled groups and 3542 and 2317 in the pooled FAS and pooled FAS-I, respectively (Table). Patient demographics and baseline characteristics were comparable across pooled treatment groups (~72% of FAS was female; mean age of ~59 years). Of the 3684 SAF patients in the pooled placebo, mirabegron 50 mg and 100 mg groups, 79 reported OAB symptoms with specific comorbid neurological conditions. These were (high level terms): Spinal stenosis/ spine deformities (n=41 of total pooled SAF); Parkinson's disease and parkinsonism (n=13); cervical spinal cord and nerve root disorders (n=10); central nervous system haemorrhages and cerebrovascular accidents (n=4); neurogenic bladder disorders (n=6); spinal cord and nerve root disorders NEC (n=4); and spinal cord injuries NEC (n=2). In these patients, mirabegron 50 mg and 100 mg improved all primary and secondary outcomes from BL to FV, and in all cases improvements were numerically greater than seen with placebo with the exception of the effect of mirabegron 50 mg on the mean number of urgency episodes/24 h. Mirabegron was well tolerated in this patient subgroup and its tolerability profile was similar across treatment groups. The most common TEAEs (occurring in $\geq 5\%$ of the combined mirabegron SAF group [n=50]) were diarrhoea, urinary tract infection, depression and hypertension (all occurring in 3 [6.0%] patients). Mean change (SD) from BL to FV in PVR volume in patients with OAB of neurogenic origin was -12 (72.8), -14 (34.2), and 1.5 (40.2) mL in the pooled placebo, mirabegron 50 mg and 100 mg groups.

Interpretation of results

In patients with OAB and comorbid neurological disorders whose role in the etiology of bladder symptoms cannot be ruled out, mirabegron 50 mg and 100 mg OD resulted in improvements in the symptoms of OAB that were numerically larger than seen with placebo. There was no difference between mirabegron and placebo in effect on PVR. While conclusions may be limited by the small number of patients and the possibility that OAB symptoms are not driven by the comorbid neurological disorder, the data provides some useful insights into the potential use of mirabegron in the treatment of OAB patients with comorbid neurological disorders.

Concluding message

Few studies have investigated the treatment of NLUTD. This post-hoc analysis of pooled data from 3 large, randomised, Phase III trials demonstrates the safety and efficacy of the β_3 -adrenoceptor agonist mirabegron 50 and 100 mg OD in patients with OAB and comorbid neurological disorders. Prospective studies investigating the efficacy and safety of mirabegron in patients with NLUTD are required in order to more clearly define the role of mirabegron therapy in these patients.

Table: Effect of mirabegron (50 mg and 100 mg) and placebo (Pbo) on primary and secondary outcome measures (mean values (SE) with [95% CI])						
	Total pooled population			Patients with neurogenic bladder		
<i>Mean number of incontinence episodes/24 h (FAS-I)</i>						
	Placebo	mirabegron		Placebo	mirabegron	
		50 mg	100 mg		50 mg	100 mg
Patients, n	878	862	577	17	18	17
BL value	2.73 (0.09)	2.71 (0.09)	2.79 (0.10)	2.06 (0.51)	3.19 (0.69)	3.27 (0.48)
Adjusted change from BL to FV	-1.10 (0.07) [-1.23, -0.97]	-1.49 (0.07) [-1.63, -1.36]	-1.50 (0.09) [-1.67, -1.34]	-1.08 (0.48) [-2.02, -0.14]	-2.08 (0.47) [-2.99, -1.17]	-1.91 (0.48) [-2.86, -0.97]
Adjusted difference vs Pbo	na	-0.40 (0.09)† [-0.58, -0.21]	-0.41 (0.11)† [-0.62, -0.19]	na	-1.00 (0.67) [-2.31, 0.31]	-0.83 (0.68) [-2.16, 0.50]
<i>Mean number of micturitions/24 h (FAS)</i>						
Patients, n	1328	1324	890	29	28	20
BL value	11.58 (0.09)	11.70 (0.09)	11.58 (0.10)	10.71 (0.55)	12.23 (0.78)	12.77 (0.84)
Adjusted change from BL to FV	-1.20 (0.07) [-1.34, -1.06]	-1.75 (0.07) [-1.89, -1.61]	-1.74 (0.09) [-1.91, -1.56]	-0.92 (0.48) [-1.85, 0.01]	-1.02 (0.48) [-1.96, -0.07]	-2.53 (0.57) [-3.65, -1.40]
Adjusted difference vs Pbo	na	-0.55 (0.10)† [-0.75, -0.36]	-0.54 (0.12)† [-0.77, -0.31]	na	-0.10 (0.68) [-1.42, 1.23]	-1.61 (0.75) [-3.07, -0.15]
<i>Mean number of urgency episodes (Grade 3 or 4)/24 h (FAS)</i>						
Patients, n	1324	1320	885	29	28	20
BL value	5.61 (0.10)	5.80 (0.10)	5.96 (0.12)	5.57 (0.62)	6.27 (0.70)	7.08 (0.97)
Adjusted change from BL to FV	-1.29 (0.09) [-1.47, -1.11]	-1.93 (0.09) [-2.11, -1.75]	-1.89 (0.12) [-2.11, -1.66]	-1.81 (0.61) [-3.01, -0.61]	-1.51 (0.62) [-2.73, -0.28]	-3.69 (0.74) [-5.14, -2.24]
Adjusted difference vs Pbo	na	-0.64 (0.13)† [-0.89, -0.39]	-0.60 (0.15)† [-0.89, -0.31]	na	0.30 (0.87) [-1.41, 2.01]	-1.88 (0.96) [-3.77, 0.00]
<i>Mean level of urgency (FAS)</i>						
Patients, n	1325	1323	886	29	28	20
BL value	2.39 (0.02)	2.42 (0.02)	2.46 (0.02)	2.36 (0.10)	2.57 (0.08)	2.53 (0.12)
Adjusted change from BL to FV	-0.15 (0.02) [0.18, -0.12]	-0.26 (0.02) [-0.30, -0.23]	-0.26 (0.02) [-0.30, -0.22]	-0.17 (0.11) [-0.38, 0.05]	-0.33 (0.11) [-0.55, -0.11]	-0.55 (0.13) [-0.80, -0.29]
Adjusted difference vs Pbo	na	-0.11 (0.02)† [-0.16, -0.07]	-0.11 (0.03)† [-0.16, -0.06]	na	-0.16 (0.16) [-0.47, 0.14]	-0.38 (0.17) [-0.72, -0.05]
Adjusted mean change from BL and adjusted difference vs placebo and corresponding 95% CIs were derived from an ANCOVA model with treatment group, sex, and study as fixed factors and BL as a covariate for the total pooled population and from an ANCOVA model with treatment group, sex, study, subgroup (neurogenic or not), and treatment by subgroup interaction as fixed factors and BL as a covariate for the patients with neurogenic bladder. †p<0.05 versus placebo with multiplicity adjustment; ANCOVA, analysis of covariance; BL, Baseline; CI, confidence interval; FAS, Full Analysis Set; FAS-I, FAS-Incontinence; FV, Final Visit; na, not applicable; SE, standard error.						

Disclosures

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