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EFFICACY AND TOLERABILITY OF ONCE-DAILY MIRABEGRON, A POTENT AND SELECTIVE B3-ADRENOCEPTOR AGONIST, IN PATIENTS WITH OVERACTIVE BLADDER – RESULTS FROM A NORTH AMERICAN PHASE III TRIAL

Hypothesis / aims of study

Oral anti-muscarinic agents are currently the mainstay of the therapeutic armamentarium for the treatment of overactive bladder (OAB), However, some patients have a suboptimal response to anti-muscarinic agents or find that anti-muscarinic therapy is limited by associated adverse events (AEs; e.g. dry mouth) [1]. In the absence of another class of therapeutic agent for the treatment of OAB symptoms, these patients either persist with an unsatisfactory treatment or simply discontinue pharmacotherapy. Mirabegron, a potent and selective β3-adrenoceptor agonist, is currently in development for the treatment of OAB and may provide an alternative therapeutic option to anti-muscarinics in such patients. β3-adrenoceptor agonist-elicited relaxation of the detrusor is only manifested during the storage phase of the micturition cycle, improving the storage capacity of the bladder without impeding bladder contraction during voiding. The aim of this phase 3 study was to assess the efficacy and tolerability of once-daily mirabegron in North American patients with OAB.

Study design, materials and methods

This multicentre, randomised, double-blind, parallel-group, placebo-controlled trial enrolled patients (≥18 years of age) with OAB symptoms for ≥3 months. Patients who completed a 2-week, single-blind, placebo run-in and had ≥8 micturitions/24 h and ≥3 urgency episodes (with or without incontinence) during a 3-day micturition diary period, were randomised to receive once-daily placebo, mirabegron 50 mg, or mirabegron 100 mg for 12 weeks. Co-primary efficacy endpoints were the change from baseline to Final Visit (study end) in: 1) the mean number of incontinence episodes/24 h, and 2) micturitions/24 h. Efficacy was assessed according to patient micturition diaries; safety assessments included AE reporting, physical examinations, vital signs, ECG, and laboratory tests.

Results

A total of 1328 patients (mean age 60.1 years, 74.3% female) were randomised and received study drug (placebo: n=453; mirabegron 50 mg: n=442; mirabegron 100 mg: n=433). Randomised patients exhibited urgency incontinence (29.7%), mixed stress/urgency incontinence with urgency predominant (38.1%), or frequency without incontinence (32.2%) at baseline. At the Final Visit, compared with placebo, mirabegron 50 mg and 100 mg showed statistically significant improvements in both of the co-primary efficacy endpoints. In addition, statistically significant benefits versus placebo were also achieved for both doses of mirabegron in key secondary endpoints (change from baseline in mean volume voided/micturition at Final Visit and, change from baseline in number of incontinence episodes/24 h and number of micturitions/24 h at Week 4), and in several secondary endpoints assessing urgency at Final Visit (Table 1).

Table 1. Primary and Secondary Efficacy Endpoints: adjusted mean* (standard error) change from baseline

Endpoints	Placebo	Mirabegron	
		50 mg	100 mg
Co-primary endpoints at Final Visit			
Number of incontinence episodes/24 h	–1.13 (0.112)	–1.47† (0.114)	–1.63† (0.117)
Number of micturitions/24 h	–1.05 (0.132)	–1.66† (0.133)	–1.75† (0.135)
Key secondary endpoints			
Mean volume voided/micturition (mL) at Final Visit	7.0 (2.41)	18.2† (2.44)	18.0† (2.47)
Number of incontinence episodes/24 h at Week 4	–0.72 (0.116)	–1.20† (0.119)	–1.18† (0.122)
Number of micturitions/24 h at Week 4	–0.77 (0.127)	–1.19† (0.129)	–1.37† (0.131)
Other secondary endpoints at Final Visit			
Level of urgency	–0.08 (0.026)	–0.19‡ (0.026)	–0.21‡ (0.027)
Number of urgency incontinence episodes/24 h	–0.89 (0.100)	–1.32‡ (0.104)	–1.45‡ (0.105)
Number of Grade 3 and 4 urgency episodes/24 h	–0.82 (0.161)	–1.57‡ (0.162)	–1.76‡ (0.165)

*Least squares mean adjusted for baseline, gender and geographical region; † p<0.05 versus placebo with† or without‡ multiplicity adjustment

The incidence of treatment-emergent AEs (TEAEs) was similar across the placebo and mirabegron 50 mg and 100 mg groups (50.1, 51.6 and 46.9%, respectively). The most common TEAEs were hypertension (6.6, 6.1 and 4.9%, respectively), urinary tract infection (1.8, 2.7 and 3.7%), headache (2.0, 3.2 and 3.0%) and nasopharyngitis (2.9, 3.4 and 2.5%) (Table 2). There were no adjudicated APTC/MACE (Antiplatelet Trialists' Collaboration/Major Adverse Cardiovascular Events) events in mirabegron-

treated patients and APTC/MACE events occurred in two patients in the placebo group. There were no TEAEs of QTc prolongation or its sequelae in any group.

Table 2. Common (≥2%) and Selected* Treatment-Emergent Adverse Events			
	Placebo (n=453)	**Mirabegron**	
		50 mg (n=442)	**100 mg (n=433)**
Any adverse event	227 (50.1%)	228 (51.6%)	203 (46.9%)
Hypertension	30 (6.6%)	27 (6.1%)	21 (4.9%)
Urinary tract infection	8 (1.8%)	12 (2.7%)	16 (3.7%)
Headache	9 (2.0%)	14 (3.2%)	13 (3.0%)
Nasopharyngitis	13 (2.9%)	15 (3.4%)	11 (2.5%)
Upper respiratory tract infection	12 (2.6%)	12 (2.7%)	9 (2.1%)
Diarrhoea	6 (1.3%)	10 (2.3%)	10 (2.3%)
Sinusitis	10 (2.2%)	9 (2.0%)	9 (2.1%)
Dry mouth	7 (1.5%)	2 (0.5%)	9 (2.1%)
Constipation*	8 (1.8%)	6 (1.4%)	7 (1.6%)

Interpretation of results

In this study of North American patients, compared with placebo, mirabegron demonstrated significant improvements from baseline in key OAB symptoms and was well tolerated; exhibiting a low incidence of TEAEs.

The most commonly reported AEs in clinical trials assessing oral anti-muscarinic agents include dry mouth and constipation [1]. In this study, the incidence of each of these AEs was low and similar across placebo, mirabegron 50 mg and mirabegron 100 mg groups (dry mouth: 1.5, 0.5 and 2.1%; constipation 1.8, 1.4, 1.6%, respectively).

Concluding message

Mirabegron at doses of 50 and 100 mg once daily for 12 weeks demonstrated superior efficacy compared with placebo in the treatment of the symptoms of OAB.

Mirabegron was generally safe and well tolerated over 12 weeks of treatment in this study with a low incidence of TEAEs.

Mirabegron represents a “first in class” therapeutic agent and may provide a therapeutic alternative for the treatment of OAB symptoms in patients who are intolerant of, or have a suboptimal response to anti-muscarinic agents.

References

1. Chapple CR, et al. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. Eur Urol. 2008; 54:543-62.

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Is this study registered in a public clinical trials registry?	**Yes**
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Is this a Randomised Controlled Trial (RCT)?	**Yes**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Approval was provided by the Institutional Review Board of each individual study site**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**