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# THE EFFICACY AND TOLERABILITY OF MIRABEGRON, A POTENT AND SELECTIVE B3-ADRENOCEPTOR AGONIST, COMPARED WITH PLACEBO AND TOLTERODINE SLOW RELEASE IN PATIENTS WITH OVERACTIVE BLADDER – RESULTS FROM A EUROPEAN–AUSTRALIAN PHASE III TRIAL

Hypothesis / aims of study

Oral anti-muscarinic agents are currently the mainstay of pharmacotherapy for the treatment of overactive bladder (OAB). In the absence of an alternative therapeutic class, patients who 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 and constipation) [1], either persist with an unsatisfactory treatment or discontinue therapy. Mirabegron, a potent and selective β3-adrenoceptor agonist, is currently in clinical development for the treatment of OAB and may provide an alternative therapeutic option in such patients. β3-adrenoceptor agonists elicit relaxation of the detrusor during the storage phase of the micturition cycle, improving the storage capacity of the bladder without impeding bladder voiding. In animal studies mirabegron reduced the frequency of rhythmic bladder contractions, but unlike anti-muscarinic agents, did not decrease the amplitude of contraction [2]. The aim of this phase 3 study was to assess efficacy and tolerability of mirabegron in European and Australian patients with OAB.

Study design, materials and methods

This multicentre, randomised, double-blind, parallel-group, placebo- and tolterodine slow release (SR)-controlled trial enrolled patients (≥18 years of age) with symptoms of OAB for ≥3 months into a 2-week, single-blind, placebo run-in period. Patients with ≥8 micturitions/24h and ≥3 urgency episodes during a 3-day micturition diary, were randomised to receive once-daily placebo, mirabegron 50 mg or 100 mg, or tolterodine SR 4 mg for 12 weeks. The co-primary endpoints were change from baseline to final visit in the mean number of incontinence episodes/24h and micturitions/24h. Efficacy was assessed according to patient micturition diaries and safety assessments included AE reporting, physical examinations, vital signs, ECG, and laboratory tests.

Results

Patients were randomised to receive: placebo (n=494); mirabegron 50 mg (n=493); mirabegron 100 mg (n=496); or tolterodine SR 4 mg (n=495). Of the 1978 patients that received study drug (mean age 59.1 years, 72.2% female) 39.5% had urgency incontinence, 37.8% had frequency without incontinence and 22.7% had mixed stress/urgency incontinence with predominant urgency at baseline. At the Final Visit, compared with placebo, both 50 and 100mg mirabegron groups demonstrated statistically significant improvements from baseline in both co-primary endpoints; although improvements in both co-primary endpoints were also observed with tolterodine SR, these did not reach statistical significance versus placebo (Table 1). Statistically significant improvements in these co-primary efficacy measures were observed for both mirabegron and tolterodine versus placebo at the first measured time point (Week 4), and in volume voided per micturition at Final Visit (Table 1).

**Table 1. Primary and Key Secondary Efficacy Endpoints**

| | **Placebo** | **Mirabegron** | | **Tolterodine SR** |
|---|---|---|---|---|
| | **-** | **50mg** | **100mg** | **4mg** |
| **Co-primary endpoints at final visit: adjusted mean* (standard error) change from baseline** | | | | |
| Incontinence episodes/24 h | –1.17 (0.113) | –1.57† (0.113) | –1.46† (0.115) | –1.27NS (0.115) |
| Number of micturitions/24 h | –1.34 (0.110) | –1.93† (0.111) | –1.77† (0.110) | –1.58NS (0.110) |
| **Key secondary endpoints: adjusted mean* (standard error) change from baseline** | | | | |
| Volume voided/micturition (mL) at Final Visit | 12.4 (1.88) | 24.1† (2.16) | 25.5† (2.02) | 25.0† (1.94) |
| Incontinence episodes/24 h at Week 4 | –0.65 (0.118) | –1.04 (0.118) † | –1.03† (0.120) | –1.00† (0.117) |
| Number of micturitions/24 h at Week 4 | –0.77 (0.096) | –1.16 (0.097) † | –1.29† (0.096) | –1.10† (0.096) |

*Least squares mean adjusted for baseline, gender and geographical region; † p<0.05 versus placebo, NS = nonsignificant

The incidence of treatment-emergent AEs (TEAEs) was similar across the placebo, mirabegron 50 mg, mirabegron 100 mg, and tolterodine SR groups (43.3, 42.8, 40.1 and 46.7%, respectively). The most common TEAEs were hypertension (7.7, 5.9, 5.4 and 8.1%), dry mouth (2.6, 2.8, 2.8 and 10.1%), headache (2.8, 3.7, 1.8 and 3.6%), and nasopharyngitis (1.6, 2.8, 2.8 and 2.8%). Dry mouth is the most common AE associated with the use of oral anti-muscarinic agents [1], the incidence of this AE was similar in placebo and mirabegron groups, and lower than observed in patients receiving tolterodine SR. However, the

incidence of constipation, another AE commonly associated with the use of oral anti-muscarinic agents [1], was similar across all treatment groups (Table 2). There were no APTC/MACE (Antiplatelet Trialists' Collaboration/Major Adverse Cardiovascular Events) events in mirabegron-treated patients; there was one adjudicated APTC/MACE event in a tolterodine treated patient. There were no TEAEs of QTc prolongation or its sequelae in the mirabegron treatment groups

**Table 2. Common Treatment-Emergent Adverse Events (≥2% of patients in any group)**

| | **Placebo** | **Mirabegron** | | **Tolterodine SR** |
|---|---|---|---|---|
| | **(n=494)** | **50mg (n=493)** | **100mg (n=496)** | **4mg (n=495)** |
| Any AE | 214 (43.3%) | 211 (42.8%) | 199 (40.1%) | 231 (46.7%) |
| Hypertension | 38 (7.7%) | 29 (5.9%) | 27 (5.4%) | 40 (8.1%) |
| Dry mouth | 13 (2.6%) | 14 (2.8%) | 14 (2.8%) | 50 (10.1%) |
| Headache | 14 (2.8%) | 18 (3.7%) | 9 (1.8%) | 18 (3.6%) |
| Nasopharyngitis | 8 (1.6%) | 14 (2.8%) | 14 (2.8%) | 14 (2.8%) |
| Influenza | 8 (1.6%) | 11 (2.2%) | 10 (2.0%) | 7 (1.4%) |
| Urinary tract infection | 7 (1.4%) | 7 (1.4%) | 9 (1.8%) | 10 (2.0%) |
| Constipation | 7 (1.4%) | 8 (1.6%) | 8 (1.6%) | 10 (2.0%) |

Interpretation of results

In this study, compared with placebo, mirabegron demonstrated significant improvements from baseline in key OAB symptoms and was well tolerated, exhibiting a low incidence of AEs. Although no statistical comparison with tolterodine SR was performed in this study, the magnitude of effect with mirabegron was numerically greater than that observed with tolterodine SR (a commonly prescribed oral anti-muscarinic agent). Furthermore, the incidence of dry mouth, the most common AE associated with the use of oral anti-muscarinic agents [1], was similar between placebo and mirabegron groups, and markedly lower than observed in those receiving tolterodine SR. However, the incidence of constipation, another AE commonly associated with the use of oral anti-muscarinic agents, was similar across all treatment groups in this study.

Concluding message

Mirabegron at doses of 50 and 100 mg once-daily over 12 weeks demonstrated superior efficacy compared with placebo against key symptoms of OAB. Mirabegron was well tolerated in patients with OAB and exhibited a low incidence of TEAEs. The incidence of dry mouth, the most common AE associated with oral anti-muscarinic agents [1], in this study was similar across the placebo and mirabegron groups, and was markedly lower than the incidence observed in those receiving tolterodine SR. Mirabegron, a potent and selective β3-adrenoceptor agonist, represents a 'first in class' therapeutic agent whose distinct mechanism of action and safety profile, may provide a therapeutic alternative for the treatment of OAB in patients who are intolerant of , or have a suboptimal response to anti-muscarinic agents.

References


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2. Toshiyuki T, et al. Effect of (R)-2-(2-Aminothiazol-4-yl)-4-{2-(2-hydroxy-phenylethyl)aminoethyl} Acetanilide (YM178), a Novel Selective-Adrenoceptor Agonist, on Bladder Function. JPET 321:642–647, 2007



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|---|---|
| ***Specify source of funding or grant*** | **Astellas Pharma** |
| ***Is this a clinical trial?*** | **Yes** |
| ***Is this study registered in a public clinical trials registry?*** | **Yes** |
| ***Specify Name of Public Registry, Registration Number*** | **clinicaltrials.gov, NCT00689104** |
| ***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*** | **This study was approved by the relevant institutional review board at each of the participating study sites** |
| ***Was the Declaration of Helsinki followed?*** | **Yes** |
| ***Was informed consent obtained from the patients?*** | **Yes** |