REVIEW ARTICLE

Evidence available on the use of the selective β3-adrenoceptor agonist mirabegron for the treatment of overactive bladder

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KEYWORDS
Mirabegron; Overactive bladder; Efficacy; Safety

Abstract
Context: Mirabegron, the selective β3-adrenoceptor agonist, heralds the latest development for the treatment of overactive bladder (OAB).

Objective: To present the evidence available on the efficacy and tolerability of mirabegron and to discuss this treatment’s potential in our setting.

Evidence acquisition: We reviewed 11 studies conducted with mirabegron in patients with OAB (2 phase II, 9 phase III), all studies were compared to placebo with 6 studies also including tolterodine as an additional arm. Greater emphasis shall be given to the main phase III trials performed in Europe, the USA and Australia evaluating efficacy and safety after 12 weeks (NCT00662909, NCT00689104, NCT00912964) and safety after 12 months (NCT00688688). The combined analyses of these 12-week studies are also available, with emphasis on global efficacy (FAS), efficacy with regard to incontinence (FAS i) and safety (SAF). More than 50% of patients had previously discontinued anticholinergics medication for OAB, thus allowing us to obtain data on the effectiveness of mirabegron in patients already treated with anticholinergics.

Evidence synthesis: Mirabegron is an efficacious drug which presents a statistically significant reduction in the number of incontinence episodes and in urinary frequency as of 4 weeks, with a higher percentage of dry patients and a higher percentage of patients with reduction ≥50% in the number of incontinence episodes than placebo. The efficacy of mirabegron 50 and 100 mg in the reduction of incontinence episodes occurs in de novo patients and who have received antimuscarinics, with adjusted mean difference and improvement in urinary frequency greater in treated patients. Its tolerability is very similar to placebo particularly for the adverse effects of the antimuscarinics (dry mouth, constipation and blurred vision). A minimal, non-clinically significant change is observed in systolic and diastolic blood pressure and pulse. Its efficacy is long-term. Mirabegron at the doses of 50 and 100 mg presents an improvement versus placebo in patient satisfaction, health-related quality of life (HRQoL),

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symptom bother and patient’s perception of bladder condition (PPBC). In the 12-week phase III European study tolterodine delivered a lesser degree of improvement than mirabegron versus placebo in patient satisfaction, HRQoL, symptom bother and PPBC.

**Conclusions:** Mirabegron is the first of a new class of compounds with a novel mechanism of action that is different to the antimuscarinics. It presents significant and clinically important efficacy in the treatment of the symptoms of OAB. It has advantages with regard to the results described by the patient in treatment satisfaction. Studies on its combined use with anticholinergics are ongoing.

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**A new agent for the treatment of overactive bladder**

The β3 adrenoreceptor is one of the three subtypes of adrenoreceptor (AR), named β1–β3. The β3-AR binds to the G protein and was identified at the end of the 1980s. Its functional response takes place in adipocytes, where it produces lipolysis while in the gallbladder, stomach, small intestine, prostate and colon, muscular it produces relaxation.

Despite the early identification of this receptor, the therapeutic potential of its agonists in human beings has had a slow development, as the compounds initially studied in rodents presented less potency in humans because they act as partial agonists. The recognition of the differences between ARs of humans and rodents has made it possible to
develop new potent and highly selective agonists for human β3-AR. Considerable differences have also been detected between different subtypes of human β-AR. With regard to bladder relaxation, barring subtypes 1 and 2, the expression of ARNm β3-AR predominates. β1-AR is mostly post-synaptic and located in the heart, salivary glands, platelets and the gastrointestinal tract. The β2-AR, also mostly post-synaptic, is located in the blood vessels, bronchus, skeletal muscle, liver, mastocytes and digestive tract. 97% of the AR expressed in the urinary bladder are β3-AR (Fig. 1). Whereas the antimuscarinics bind to the muscarinic receptors of the urinary bladder and inhibit involuntary bladder contractions, the stimulation of the β3-AR of the detrusor muscle involves bladder relaxation during the filling phase, thus improving bladder storage capacity. \(^{2,3}\) Herein lays the potential of the drugs that act as β3-AR agonists to treat OAB symptoms. \(^4\)

The YM178 compound (Mirabegron) with effects on the bladder smooth muscle, both in vitro and in vivo, has been developed by Astellas Pharma Inc. (Ibaraki, Japan). \(^7\,^8\) Once the selectivity of this compound and its potency for the β3-AR in humans had been demonstrated, a new path was opened up for the development of the clinical phase of its application. Mirabegron has been studied in approximately 10,000 patients all over the world in the last 10 years. \(^5\,^6\)

The phase II studies provided fundamental data. The BLOSSOM study comparing mirabegron to placebo and tolterodine over a 4-week period in 262 patients was conducted in Europe and Japan. \(^9\) Mirabegron proved to be efficacious and well-tolerated in patients with OAB symptoms, producing an improvement over placebo in urinary frequency at doses of 100 and 150 mg, twice a day (−17% and −18%) versus placebo (−9%) and tolterodine (−11%). Mirabegron was also superior in the other variables analyzed, such as mean volume voided, mean number of incontinence episodes, nocturia or urge. \(^10\,^11\)

The DRAGON study (NCT00373090) establishing a dosage range for the daily intake of mirabegron comparing 25, 50, 100 and 200 mg with placebo was conducted in Europe in 928 patients. There was a dose-dependent reduction in mean urinary frequency for 25, 50, 100 and 200 mg (−1.9, −2.1, −2.1 and −2.2, respectively), which was statistically significant for the doses of 50, 100 and 200 mg. \(^12\,^13\)

Approximately half of the incontinent patients treated with mirabegron (41.7% with 50 mg and 55.9% with 100 mg) were dry after 12 weeks. This signifies an evident clinical benefit associated with improved quality of life (QoL). The proportion of responders, defined by an improvement ≥1 on the patient perception of treatment benefit (PPTB) scale, was 51% for placebo, 55% tolterodine 4 mg, 65% mirabegron 50 mg, 65.8% mirabegron 100 mg and 70.8% mirabegron 200 mg. \(^11\)

The large-scale phase III clinical trials have confirmed the drug's efficacy and safety. We have three large trials performed in the USA (NCT00662909, ARIES or 178-CL-047), Europe and Australia (NCT00689104, SCORPIO or 178-CL-046), Europe and the USA (NCT00912964, CAPRICORN or 178-CL-074) in the 12-week treatment regimen \(^4\,^15\) and an additional trial conducted in USA, Europe and Australia (NCT00688688, TAURUS) to evaluate the safety of Mirabegron over a 12 month period. \(^16\) Other completed studies are still unpublished. Several phase III studies have been conducted in Japan, including a 12-week randomized and placebo-controlled study (NCT00527033), a 52-week follow-up study (NCT00840645), and another 14-week randomized study with placebo and tolterodine (NCT00966004). Another controlled study with placebo and tolterodine has also been performed in an Asian population (China, India and Korea).

Available evidence from phase III studies

Study design

The three main studies were performed between April 2008 and May 2010 with mirabegron formulated in an oral controlled absorption system (OCAS). They included men and women ≥18 years with OAB symptoms for over more than 3 months. The inclusion criteria were urinary frequency ≥8 times/24h with at least 3 urgency episodes, with or without incontinence. The studies all began with a 2-week single-blind phase (placebo). This period was followed by the double-blind randomization of 1329 patients to placebo, mirabegron 50 mg, mirabegron 100 mg in the ARIES study; 1987 patients to placebo, mirabegron 50 mg, mirabegron 100 mg or extended-release (ER) tolterodine 4 mg in the
SCORPIO study and 1306 patients to placebo, mirabegron 25 mg or mirabegron 50 mg in the CAPRICORN study.

The patients completed a 3-day bladder diary at the beginning and at weeks 4, 8 and 12. Other variables were recorded, such as time of micturition, volume, severity of urgency, number of incontinence episodes and number of pads. The primary efficacy endpoints were change from the beginning to the end of the study in the number of incontinence episodes and the mean number of micturitions every 24 h. The change in mean volume voided per micturition and the reduction in the number of incontinence episodes and urinary frequency at week 4 of treatment were secondary endpoints. Other additional secondary efficacy variables were patient perception of quality of life (QoL) using the over-active bladder (OABq) and patient perception of bladder condition (PPBC) questionnaires and the treatment satisfaction visual analog scale (TS-VAS). The safety assessment included the description of adverse effects (AE), laboratory evaluations, vital signs, physical exploration, electrocardiogram (ECG) and post-void residual volume (PVRV). All the cardiovascular events were assigned following the Antiplatelet Trialists’ Collaboration (APTC) classification on the possible existence of major adverse cardiovascular events (MACE).

The global efficacy analysis (Full Analysis Set, FAS) was conducted for each trial on the population that took at least one dose in the double-blind regimen and had at least one pre- and post-treatment bladder diary evaluation. The incontinence efficacy analysis (FAS-Incontinence, FAS-I) focused on patients with at least one episode of urinary incontinence at the beginning of the study. The safety analysis (Safety Analysis Set, SAF) was conducted in all randomized patients that took at least one dose of medication in the double-blind phase.

The TAUROUS study evaluates the long-term safety of mirabegron, either as a continuation for ARIES (USA) and SCORPIO (Europe and Australia) patients after a 4-week washout period or in de novo patients. After placebo for 2 weeks they were randomized for 12 months to mirabegron 5050 mg, 100 mg or tolterodine ER 4 mg. The incidence and severity of emerging adverse effects was evaluated, and blood pressure and pulse were monitored. The efficacy endpoints (change in key OAB symptoms and OABq, PPBC and TS-VAS questionnaires) were regarded as secondary. In fact, the study was not designed to demonstrate statistically significant differences between groups in terms of efficacy but rather to be able to establish the drug’s long-term safety profile with the doses of 50 and 100 mg and to compare it to that of tolterodine ER 4 mg.

Results available

Clinical efficacy
Clinical efficacy was based fundamentally on 2 co-primary endpoints: change from baseline to end of treatment in the mean number of incontinence episodes in 24 h and mean change from baseline to endpoint in the mean number of micturitions in 24 h.17 SCORPIO randomized 1978 patients to placebo (n = 494), mirabegron 50 mg (n = 493), mirabegron 100 mg (n = 496), or tolterodine 4 mg ER (n = 495). Approximately half of the patients had already received antimuscarinic-based treatment for OAB and about 2 out of 3 had stopped their treatment due to lack of efficacy. The demographic and baseline data are specified in Table 1. The analysis of the primary variables presented a statistically significant reduction in the number of incontinence episodes (−1.17 for placebo, −1.57 mirabegron 50 [p = 0.003], −1.46 mirabegron 100 mg [p = 0.01] and −1.27 tolterodine ER [p = 0.1], respectively) and for the number of micturitions (−1.34 for placebo, −1.93 mirabegron 50 [p < 0.001], −1.77 mirabegron 100 mg [p = 0.005] and −1.59 tolterodine [p = 0.1], respectively) in 24 h. These data show a higher magnitude of action for mirabegron than for tolterodine ER. In fact, in the analysis of covariance model (ANCOVA) tolterodine did not reach statistical significance in the relative improvement of both primary endpoints15,16 (Fig. 2). With regard to the secondary variables, both doses of mirabegron reduced the number of incontinence episodes versus placebo after 4 weeks (p = 0.002), and this effect was maintained over time (weeks 8 and 12), whereas with tolterodine the difference was significant only at 4 weeks (p = 0.02). All the active treatments presented an improvement versus placebo in voided volume per micturition (p < 0.001).

These results were ratified in the ARIES trial, which did not include an active control with tolterodine. 1329 patients were randomized to placebo (n = 454), mirabegron 50 (n = 442) and mirabegron 100 mg (n = 433) during 12 weeks. In both groups of mirabegron there was a reduction in the number of incontinence episodes (−1.13, −1.47, and −1.63 for placebo, mirabegron 50 mg and 100 mg, respectively; p < 0.05) and in the number of micturitions (−1.05, −1.66 and −1.75; p < 0.05) in 24 h. An increase was also confirmed for both doses compared to placebo in voided volume/micturition (7.0 ± 2.4 ml placebo, 18.2 ± 2.4 ml mirabegron 50 and 18.0 ± 2.5 ml mirabegron 100 mg), level of urgency, number of urgency-incontinence episodes, number of urgency episodes grade 3/4 and number of nocturia episodes (p < 0.05).14,19,20

The CAPRICORN study, also pivotal, compared mirabegron 25 and 50 mg to placebo. The results of this trial were included in the FDA consultation committee document on the mirabegron safety and efficacy summary.17 1306 were randomized to placebo (n = 433), mirabegron 50 (n = 432) and mirabegron 100 mg (n = 440). Statistically significant reductions were observed vs placebo from the baseline for both doses of mirabegron in the number of incontinence episodes (−0.96 for placebo, −1.36 mirabegron 25 [p = 0.005] and −1.38 mirabegron 50 mg [p = 0.001], respectively) and in the number of micturitions (−1.18 for placebo, −1.65 mirabegron 25 mg [p = 0.007] and −1.60 mirabegron 50 mg [p = 0.015], respectively) in 24 h.

The change in mean voided volume from baseline to end of treatment was 8.3 ± 2.2 ml for placebo, 12.8 ± 2.2 ml mirabegron 25 mg (p = 0.15) and 20.7 ± 2.2 ml mirabegron 50 mg (p < 0.001), respectively.

The TAUROUS double-blind trial evaluates the safety of mirabegron OCAS 50 and 100 mg, and an arm with tolterodine ER 4 mg was also included in the study, for 12 months. This study was designed as a safety study and the intention was not to demonstrate statistically significant differences in efficacy between groups. 2444 patients were randomized to mirabegron 50 mg (n = 812), 100 mg (n = 820) and
Table 1  Demographic characteristics and baseline situation for each group of the SCORPIO trial.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Mirabegron 50 mg</th>
<th>Mirabegron 100 mg</th>
<th>Tolerodine ER 4 mg</th>
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<tr>
<td><strong>SAF population</strong></td>
<td>n = 494</td>
<td>n = 493</td>
<td>n = 496</td>
<td>n = 495</td>
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<tr>
<td>Gender (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>138 (27.9)</td>
<td>136 (27.6)</td>
<td>141 (28.4)</td>
<td>134 (27.1)</td>
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<tr>
<td>Female</td>
<td>356 (72.1)</td>
<td>357 (72.4)</td>
<td>355 (71.6)</td>
<td>361 (72.9)</td>
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<td>Age (years)</td>
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<td>59.1 (12.4)</td>
<td>59.0 (12.7)</td>
<td>59.1 (12.9)</td>
</tr>
<tr>
<td>Age group (n, %)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>313 (63.4)</td>
<td>315 (63.9)</td>
<td>313 (63.1)</td>
<td>303 (61.2)</td>
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<tr>
<td>≥65</td>
<td>181 (36.6)</td>
<td>178 (36.1)</td>
<td>183 (36.9)</td>
<td>192 (38.8)</td>
</tr>
<tr>
<td>&lt;75</td>
<td>450 (91.1)</td>
<td>447 (90.7)</td>
<td>450 (90.7)</td>
<td>458 (92.5)</td>
</tr>
<tr>
<td>≥75</td>
<td>44 (8.9)</td>
<td>46 (9.3)</td>
<td>46 (9.3)</td>
<td>37 (7.5)</td>
</tr>
<tr>
<td><strong>Race (n, %)</strong></td>
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<td></td>
<td></td>
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<tr>
<td>White</td>
<td>490 (99.2)</td>
<td>488 (99.0)</td>
<td>492 (99.2)</td>
<td>490 (99.0)</td>
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<tr>
<td>Black/African American</td>
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<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>2 (0.4)</td>
<td>2 (0.4)</td>
<td>2 (0.4)</td>
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<tr>
<td>Other</td>
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<td>1 (0.2)</td>
<td>0</td>
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<tr>
<td><strong>BMI (kg/m^2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean (SD)</td>
<td>27.8 (5.0)</td>
<td>27.5 (4.9)</td>
<td>28.0 (5.0)</td>
<td>27.8 (5.0)</td>
</tr>
<tr>
<td><strong>FAS population</strong></td>
<td>n = 480</td>
<td>n = 473</td>
<td>n = 478</td>
<td>n = 475</td>
</tr>
<tr>
<td>Type of OAB (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Urge incontinence</td>
<td>201 (41.9)</td>
<td>192 (40.6)</td>
<td>179 (37.4)</td>
<td>184 (38.7)</td>
</tr>
<tr>
<td>n Frequency</td>
<td>177 (36.9)</td>
<td>173 (36.6)</td>
<td>183 (38.3)</td>
<td>186 (39.2)</td>
</tr>
<tr>
<td>Both</td>
<td>102 (21.3)</td>
<td>108 (22.8)</td>
<td>116 (24.3)</td>
<td>105 (22.1)</td>
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<td>Previous on AB medication (n, %)</td>
<td>238 (49.6)</td>
<td>240 (50.7)</td>
<td>237 (49.6)</td>
<td>231 (48.6)</td>
</tr>
<tr>
<td>Reason for drop-out (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insufficient effect</td>
<td>159 (66.8)</td>
<td>160 (66.7)</td>
<td>159 (67.1)</td>
<td>155 (67.1)</td>
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<tr>
<td>Poor tolerability</td>
<td>68 (28.6)</td>
<td>65 (27.1)</td>
<td>64 (27.0)</td>
<td>56 (24.2)</td>
</tr>
<tr>
<td>Duration of OAB symptoms (months)</td>
<td>76.9 (92.2)</td>
<td>78.7 (85.7)</td>
<td>85.3 (95.2)</td>
<td>76.3 (93.4)</td>
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<tr>
<td>Mean (SD)</td>
<td>50.5</td>
<td>49.9</td>
<td>53.4</td>
<td>47.2</td>
</tr>
<tr>
<td>Median</td>
<td>3–688</td>
<td>3–637</td>
<td>3–567</td>
<td>3–711</td>
</tr>
</tbody>
</table>

BMI, body mass index; SD, standard deviation; FAS, full analysis set; SAF, safety analysis set.

tolerodine ER 4 mg (n = 812). 81.3% had participated in previous phase III trials with mirabegron. The reduction from baseline in the mean number of incontinence episodes in 24 h was similar between groups (−1.01, −1.24 and −1.26) and also in the mean number of micturitions (−1.27, −1.41 and −1.39; for mirabegron 50 mg, 100 mg and tolterodine). The changes in mean voided volume were also similar (17.5, 21.5 and 18.1 ml; respectively). The main improvement in OAB symptoms was observed after 1 month and continued to month 3, and the effect was maintained over 12 months.16,21 The percentage of responders with zero episodes of incontinence after one year was 43.4% for mirabegron 50 mg and 45.8% for 100 mg; similarly, both doses improved other secondary variables such as symptom bother and health-related QoL in the QoL-q, treatment satisfaction and PPBC.16 These data confirm the durability of the effect of mirabegron on the one hand and the absence of potential tachyphylaxis on the other.

Patient-reported outcomes

Patient-reported outcomes (PRO) are very important in evaluating OAB treatments.22 There is no doubt that patient dissatisfaction with treatment is high in this disease, but the data indicate that mirabegron, with its distinct mode of action, improves the patient’s described perception of their condition and quality of life.23 The patient’s perception of symptom bother (QoL-q, 8 of 33 elements), improvement in QoL with treatment (25 remaining elements), and improvement in PPBC (6-point scale) and TS-VAS (0–10) scales were studied as secondary efficacy variables.23,24 After 12 weeks, mirabegron, at the doses of 50 and 100 mg, demonstrated a statistically significant improvement versus placebo in treatment satisfaction, health-related quality of life, symptom bother and PPBC. Tolerodine also demonstrated a significant improvement over placebo in treatment satisfaction, symptom bother and PPBC; but it did not demonstrate a significant improvement in health-relate QoL15,23 (Fig. 2).

Safety

Possibly the most novel data for mirabegron are those pertaining to safety. The BLOSSOM and DRAGON trials demonstrated an excellent tolerability profile, being the most common adverse effects (AE) the gastrointestinal ones (13.8 and 8.3%, respectively).10,25 There was no urinary retention. The BLOSSOM study showed headache in 6.9% and the DRAGON returned a much lower incidence of dry mouth than with antimuscarinics, and there were no
Figure 2 Co-primary efficacy variables in the SCORPIO trial: mean change from the baseline to the final visit in (A) number of incontinence episodes in 24 h and (B) micturitions in 24 h. Secondary variables in the SCORPIO trial related to patient-reported outcomes (PRO): mean change from the baseline to the final visit in (C) treatment satisfaction (TS-VAS); (D) total HRQoL (OAB-q); (E) symptom bother (OABq) and (F) patient perception of bladder condition (PPBC). Data regarding placebo, mirabegron 50 mg and tolterodine ER 4 mg.

Treatment benefit on placebo statistically significant (0.05 level).

Another phase II trial evaluated urodynamic safety in men with lower urinary tract symptoms and bladder outlet obstruction and showed that mirabegron 50 and 100 mg are well tolerated by these patients and that it does not adversely affect detrusor pressure or maximum flow or bladder contractile index.16

In SCORPIO, the incidence of AEs was very similar in the different groups: 43.3% placebo, 42.8% mirabegron 50 mg, 40.1% mirabegron 100 mg and 46.7% tolterodine ER 4 mg. The most frequent AEs were high blood pressure (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%) (Table 2).15,18,19,27 These data demonstrate that the clinical superiority of mirabegron versus placebo in fighting the main symptoms of OAB is accompanied by excellent tolerability. The incidence of dry mouth, the most frequent adverse effect of the oral antimuscarinics, was similar for mirabegron and placebo.15 The ARIES trial also showed a similar incidence of AEs for placebo, mirabegron 50 and 100 mg (50.1, 51.6 and 46.9%) and a similar rate of discontinuation (3.8, 4.1 and 4.4%). The findings on ECG and RPM were also comparable between groups.14,19,20 Moreover, a specifically designed ocular safety study in 321 subjects showed that mirabegron is non-inferior to placebo with regard to increased intraocular pressure,
without the glaucoma AE associated with mirabegron in this study.\textsuperscript{28}

The safety and long-term tolerability of mirabegron were the main objective of the TAURUS trial. The incidence and severity of treatment-related AEs were similar for mirabegron 50 mg, 100 mg and tolterodine ER 4 mg (59.7, 61.3 and 62.6\%, respectively).\textsuperscript{16,21} The safety profile was the same as in the short-term studies. Treatment was discontinued in 6.4\%, 5.9\% and 6.0\% for the same groups, and the rate of serious AEs was 5.2, 6.2 and 5.4\%. One patient in each of the mirabegron 50 and 100 mg groups and 3 patients in the tolterodine ER 4 mg group reported urinary retention. There were no consistent trends in ECG changes and the patients with QTc interval prolongation were consistent across treatment groups: 3.2 and 3 patients in mirabegron 50 mg, mirabegron 100 mg and tolterodine 4 mg, respectively.\textsuperscript{16} This study made no formal comparison of the efficacy of mirabegron and tolterodine, but 3.6\% of patients treated with mirabegron and 5.5\% of those treated with tolterodine dropped out due to lack of efficacy. The incidence of dry mouth with tolterodine was three times greater than mirabegron, whereas the corresponding figure for mirabegron was low (2.8\%) and consistent with the one for placebo in the 12-week studies.\textsuperscript{14-16} This fact is likely to translate into greater treatment compliance, since dry mouth is regarded as a treatment dropout sentinel AE.\textsuperscript{25}

### Available evidence from the combined analysis

**Combined analysis 046/047/074**

The three large trials that analyze the efficacy and safety of mirabegron after 12 weeks have demonstrated mirabegron’s superiority in terms of efficacy and safety and tolerability in the treatment of OAB symptoms at the doses of 25, 50 and 100 mg. The 25 mg dose, which had only been studied in a single study, was excluded from the combined efficacy analysis (FAS and FAS-I). The demographic characteristics for FAS and FAS-I were very similar, with 72\% and 82\% women, respectively. The safety analysis (SAF) included all the doses and was performed on a total of 4611 patients (Fig. 3). The analysis of all the accumulated data allows us to carry out a global analysis on a broader and more representative population of the general population of patients with OAB, particularly with regard to demographic aspects, history of prior treatments and prevalence of comorbidities.\textsuperscript{29,30}

### Results available

#### Clinical efficacy

This analysis provides a better knowledge of the assessment of the risks and benefits involved in treatment. Both the doses of 50 and 100 mg were associated with statistically significant improvement in the mean number of micturitions in 24 h and in the number of incontinence episodes in 24 h (\(p < 0.05\)) after 4, 8 and 12 weeks. Similarly, both doses significantly increased micturition volume versus placebo in the same terms (Fig. 4). An improvement was also observed in other efficacy variables such as adjusted mean change from the baseline to the final visit versus placebo for the number of urgency incontinence episodes in 24 h (FAS-I), the number of urgency episodes (grade 3 or 4) in 24 h (FAS) or mean level of urgency (FAS) (\(p < 0.05\), for all comparisons) (Fig. 5).

An improvement was also observed in the number of nocturia episodes in 24 h, as well as normalization of the bladder diary versus placebo, including an improvement in the percentage of dry patients and in that of patients with reduction \(\geq 50\%\) in the number of incontinence episodes every 24 h, or even in the percentage of patients with \(\leq 8\) micturitions in 24 h (\(p < 0.05\) for all comparisons).\textsuperscript{31} Another datum to be taken into account is the speed of action in response. In fact, mirabegron’s efficacy was demonstrated early, in week 4, and remained significant versus placebo until the end of the treatment in all efficacy variables.\textsuperscript{32} Moreover, mirabegron was efficacious in the group of patients \(\geq 65\) years old.\textsuperscript{33,34}

#### Safety

The treatment of OAB has been based mainly on the use of antimuscarinics that act through the parasympathetic nervous system, reducing contraction of the detrusor muscle. The non-selective character of this type of drug entails actions on the salivary glands, eyes, intestine and central

### Table 2 Main adverse effects (\(\geq 2\%\)) for each group of the SCORPIO (SAF)\textsuperscript{a} group.

<table>
<thead>
<tr>
<th>Adverse effect according to MedDRA (v9.1)</th>
<th>Placebo (n = 494)</th>
<th>Mirabegron 50 mg (n = 493)</th>
<th>Mirabegron 100 mg (n = 496)</th>
<th>Tolterodine ER 4 mg (n = 495)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE (n (%)</td>
<td>214 (43.3)</td>
<td>211 (42.8)</td>
<td>199 (40.1)</td>
<td>410 (41.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38 (7.7)</td>
<td>29 (5.9)</td>
<td>27 (5.4)</td>
<td>56 (5.7)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>8 (1.6)</td>
<td>14 (2.8)</td>
<td>14 (2.8)</td>
<td>28 (2.8)</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>13 (2.6)</td>
<td>14 (2.8)</td>
<td>14 (2.8)</td>
<td>28 (2.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (2.8)</td>
<td>18 (3.7)</td>
<td>9 (1.8)</td>
<td>27 (2.7)</td>
</tr>
<tr>
<td>Influenza</td>
<td>8 (1.6)</td>
<td>11 (2.2)</td>
<td>10 (2.0)</td>
<td>21 (2.1)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7 (1.4)</td>
<td>7 (1.4)</td>
<td>9 (1.8)</td>
<td>16 (1.6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>7 (1.4)</td>
<td>8 (1.6)</td>
<td>8 (1.6)</td>
<td>16 (1.6)</td>
</tr>
</tbody>
</table>

\(\text{EA, adverse effect; SAF, safety analysis set.}\)

\textsuperscript{a} After the first dose and \(\leq 30\) days after the last dose.
Mirabegron and overactive bladder

The combined analysis showed that mirabegron’s safety profile is similar to placebo for the most commonly reported adverse events. In this same study, tolterodine demonstrated a 5-times greater risk of dry mouth (10.1%) and of pruritus (1.4%) than placebo (or than mirabegron). However, in the acknowledged safety reference standard of antimuscarinic treatment, the incidence of these same adverse effects is regarded as much greater (29.6% and

Table 3

<table>
<thead>
<tr>
<th>Adverse effect according to MedDRA (v9.1)</th>
<th>Data from the combined analysis 046 (SCORPIO)/047 (ARIES)/074 (CAPRICORN)</th>
<th>Data from systematic reviews and meta-analyses</th>
<th>Antimuscarinic therapy</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=1,380)</td>
<td>Mirabegron overall (n=2,736)</td>
<td>Tolterodine ER 4 mg (n=495)</td>
<td></td>
</tr>
<tr>
<td>Any AE</td>
<td>658 (47.7)</td>
<td>1259 (46.0)</td>
<td>231 (46.7)</td>
<td>53.4</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>29 (2.1)</td>
<td>54 (2.0)</td>
<td>50 (10.1)</td>
<td>29.6</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5 (0.4)</td>
<td>7 (0.3)</td>
<td>7 (1.4)</td>
<td>15.4</td>
</tr>
<tr>
<td>Constipation</td>
<td>20 (1.4)</td>
<td>44 (1.6)</td>
<td>10 (2.0)</td>
<td>7.7</td>
</tr>
<tr>
<td>Erythema</td>
<td>2 (0.1)</td>
<td>2 (0.1)</td>
<td>1 (0.2)</td>
<td>6.9</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>3 (0.2)</td>
<td>6 (0.2)</td>
<td>0 (0.0)</td>
<td>3.8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (1.0)</td>
<td>30 (1.1)</td>
<td>9 (1.8)</td>
<td>1.6</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>6 (0.4)</td>
<td>1 (&lt; 0.1)</td>
<td>3 (0.6)</td>
<td>1.1</td>
</tr>
</tbody>
</table>

EA, adverse effect.

a After the first dose and ≤30 days after the last dose
b 5 times more than the respective placebo/mirabegron.
c Significantly more with tolterodine vs placebo
d Significantly more with other antimuscarinics vs placebo.
In fact, while in the combined analysis the incidence of adverse effects was globally similar among the different therapeutic groups, in the systematic review and meta-analyses, some adverse events (constipation, dry mouth, blurred vision and tiredness) were significantly more frequent with tolterodine than with placebo, whereas others (erythema, pruritus and urinary retention) were more frequent with other antimuscarinics. All the safety data derived from the combined study confirm an excellent tolerability profile for mirabegron (Table 3).

Moreover, and with regard to the risk of presenting urinary retention, in the combined study this risk with tolterodine (0.6%) and with placebo (0.4%) was greater than with mirabegron (<0.1%). This may have favorable implications for its use in males. New studies have also confirmed the safety of this drug in men with micturition filling symptoms associated with benign prostatic hypertrophy.

**Data in patients with antimuscarinic treatment**

Many patients treated with antimuscarinics have a suboptimal response. Furthermore, the effectiveness of anticholinergic treatment is enormously limited by the associated adverse effects. This often leads to the discontinuation of treatment due to an insufficient response to treatment or due to dissatisfaction associated with the presence of adverse effects, tolerable but undesired. In fact, persistence with treatment for OAB with antimuscarinics, either due to inefficacy or tolerability, is around 50% after 6 months and 25% after a year.

In the combined analysis, more than 50% of the patients had already taken medication for OAB, allowing us to obtain data on the effectiveness of mirabegron in patients already treated with anticholinergics. The population of patients already treated was similar in the patients who received placebo (53%), mirabegron 50 mg (52%) or mirabegron 100 mg (51.7%). Two thirds had stopped anticholinergics due to lack of effectiveness and a 25% for poor tolerability. Additional data from large-scale prospective studies are needed, but the findings of a post hoc analysis carried out on a subgroup of the SCORPIO trial show that mirabegron, at the doses of 50 and 100 mg, demonstrated a similar improvement in reduction of incontinence episodes and in the number of micturitions both in patients who had not taken antimuscarinics previously and in patients that had suspended antimuscarinic treatment, either due to an insufficient effect or poor tolerability (Fig. 6).

In summary, the clinical evidence accumulated to date with regard to mirabegron make this new drug the ideal treatment for OAB patients. The incidence of dry mouth, the most common and bothersome adverse event associated with antimuscarinic treatment, is at placebo level with mirabegron. New data related to combined or sequential use with α-blockers in men, as well as to its use in combination with other anticholinergics, have yet to be confirmed. Specific studies focusing on patients with neurogenic bladder are required. For the moment, mirabegron clearly heralds a veritable revolution in the treatment of patients with OAB, and its favorable adverse effect profile may possibly lead it to become a standard treatment in this kind of patients.
Mirabegron and overactive bladder

Figure 5 Mean adjusted change from the baseline to the final visit in the combined study for the placebo and mirabegron 50 mg groups with regard to the main secondary variables: level of urgency (FAS), number of urgency episodes (grade 3 or 4) in 24 h (FAS) and number of UUI episodes in 24 h (FAS-I). Treatment benefit on placebo statistically significant (0.05 level).

Figure 6 Post hoc analysis in a subgroup of SCORPIO patients. Relative improvement with mirabegron 50 mg and tolterodine ER 4 mg in number of incontinence episodes (FAS-I) and number of micturitions (FAS), both in patients that had not previously taken antimuscarinics and in those who had taken them and discontinued due to insufficient effect or poor tolerability.

Conflict of interests

Dr. Angulo, Dr. Khullamar and Dr. Nitti have been researchers in some clinical trials analyzed in this review (numbers NCT00689104, NCT00688688 and NCT00912964, ClinicalTrials.gov).

Dr. Siddiqui works for Astellas Pharma Europe Ltd.

References


