

Mirabegron, a novel, non-antimuscarinic drug for the overactive bladder: An up-to-dated review

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Core tip: Mirabegron is a first-in-class, potent β_3 -adrenoceptors agonist that has been proven effective in the treatment of overactive bladder (OAB) based on multiple randomized multinational trials. The safety-tolerability profile of treatment with mirabegron has been extensively studied. The placebo-like incidence of classic adverse effects caused by antimuscarinics should improve long-term adherence to treatment with this new drug. Mirabegron can be an alternative in patients with contraindications to antimuscarinics or that discontinued previous antimuscarinic therapy. An updated review of the rationale of β_3 -agonism for OAB treatment and evidence of efficacy and safety of mirabegron is presented.

Abstract

Mirabegron opened a new era in the treatment of overactive bladder (OAB). For the first time physicians dealing with OAB have an effective alternative to the pharmacological mainstay of the therapy for this disorder, the antimuscarinic drugs. This first-in-class, potent β_3 -adrenoceptors agonist has recently received approval by regulatory authorities in Japan, United States and Europe, based on the favourable efficacy-tolerability profile demonstrated in multiple randomized, multinational, controlled trials, both short and long-term. There is substantial consistency through the studies in reporting the cardiovascular safety of treatment with mirabegron. The main advantage of mirabegron is the placebo-like incidence of classic adverse effects caused by antimuscarinics, dry mouth and constipation, that is expected to improve long-term adherence of patients to treatment. Mirabegron can be used in patients with contraindications to antimuscarinics and in those who discontinued previous antimuscarinic therapy. Herein, we reviewed the published literature on mirabegron, focusing on the rationale of β_3 -agonism for OAB treatment and on the preclinical and clinical evidence of efficacy and safety available on this new pharmacological principle.

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INTRODUCTION

Overactive bladder (OAB) is a syndrome characterized by the key symptom of urinary urgency, with or without urinary incontinence, usually associated with urinary frequency and nocturia^[1]. Detrusor muscle overactivity (DO) is often, but not always, the underlying condition^[2]. The differential diagnosis with stress or mixed urinary incontinence, based on clinical examination and urodynamic investigations, is of utmost importance in order to plan the more appropriate therapeutic strategy^[3].

The prevalence of OAB is high in western countries and increases with age^[4]. This bothersome and multifac-

torial bladder disorder that significantly impairs patient's health-related quality of life (HRQL), is also associated to significant comorbidities^[5] and high socioeconomic costs^[6].

The treatment of OAB is aimed to achieve symptom relief and improvement of HRQL. First-line treatment relies mainly on lifestyle advice and bladder training, functional electrical stimulation, clean intermittent catheterization and pharmacological treatment. Neuromodulation, intradetrusor botulinum toxin injection and surgery represent more invasive, second-line treatment options.

Antimuscarinics are the mainstay in the pharmacological treatment of OAB^[7]. However, these drugs are merely symptomatic and patients with unsatisfactory response due to lack of efficacy are frequent. Moreover, antimuscarinics are not completely bladder-selective causing bothersome adverse effects (AEs), including dry-mouth, nausea, constipation and central nervous system AEs. Because of these limitations, long-term adherence to treatment with antimuscarinics is low^[7-10].

The limitations of antimuscarinics prompted the research of novel pharmacological principles with a distinct mechanism of action and aimed to improve bladder storage phase symptoms, without affecting the voiding phase, and with a better tolerability profile^[11]. Among innovative peripherally acting compounds, several selective β_3 -adrenoceptors (β_3 -ARs) agonists have undergone clinical proof-of-concept studies including ritobegron (also known as KUC-7483 and as KUC-7322 for its active metabolite), solabegron (also known as GW427353) and mirabegron (also known as YM178).

Mirabegron reached the final stages of pharmacological development and has been recently granted marketing approval in Japan, United States (MyrbetriqTM) and Europe (BetmigaTM). The drug is formulated as Oral Controlled Absorption System (OCAS) tablets. OCAS is a hydrophilic gel-forming matrix tablet, a modified release system (also referred as extended-release or prolonged-release) that allows a release of drug from the tablets for an extended period, with more steady absorption, and avoids high peak-to-trough fluctuations in plasma concentration and the considerable food effect of immediate-release formulations. The drug product is available in two dosage strengths of 50 mg (recommended to-be-marketed, once daily dose, orally with or without food) and 25 mg (for patients with severe renal or moderate hepatic impairment).

Thereafter we reviewed experimental and clinical data on mirabegron by searching English-language full papers and abstracts published by May 2013 in MEDLINE, clinicaltrials.gov, controlled-trials.com, clinicaltrialsfeeds.org, and proceedings of international scientific meetings.

RATIONALE OF β_3 -AGONISM FOR OAB TREATMENT

The fixation of noradrenalin to β -ARs activates the molecular pathway of cyclic adenosine monophosphate (cAMP) that is the most important mediator of detrusor

muscle compliance and relaxation in mammalian species, although there is evidence suggesting that a cAMP-independent, potassium channels-mediated mechanism may play an important role^[12-15].

β_1 -, β_2 - and β_3 -ARs have been demonstrated in both animal and human urinary bladder, although, β_3 -ARs represent the far most abundant subtype in the human bladder^[16,17]. β_3 -ARs have been found to be highly and preferentially expressed on bladder tissues including urothelium, interstitial cells, and detrusor smooth muscle^[12,18-21].

Detrusor muscle relaxes in response to β -AR agonists in a dose-dependent manner and human studies showed that this effect is mediated mainly through β_3 -AR^[17,22-25]. Targeting β_3 -ARs has a significant effect on reducing spontaneous uncoordinated detrusor contractile activity in human bladder^[23]. Interestingly, preliminary research showed that 49% of patients with idiopathic DO have a tryptophan 64 arginine mutation of the β_3 -AR gene that may be a useful genetic marker^[26].

Animal studies demonstrated that both non-selective and selective β_3 -AR agonists were able to increase bladder capacity and inhibit neurogenic or experimentally-induced DO and bladder outlet obstruction (BOO)-associated OAB, without changing voiding detrusor pressure or increasing residual volume^[17,21,27-30].

Although β_3 -ARs on detrusor muscle cells were believed to be the main site of action of β_3 -AR agonists in treating OAB, the main *in vivo* effect of these compounds could be on the afferent side of the micturition reflex, by a direct inhibition of afferent nerves or of the myogenic/urotheliogenic mechanisms involved in the promotion of afferent activity. In fact, there is evidence that selective β_3 -AR agonists can (1) inhibit the bladder filling-induced activity of mechanosensitive A δ -fibers (and C-fibers at higher doses inducing retention) in rats^[31], and (2) reduce autonomous bladder non-voiding contractions of myogenic origin^[27] that can generate localized microcontractions facilitating afferent nerves activity^[32]. It has been also reported that a direct influence on urothelial functions, such as the release of NO and urothelial-derived inhibitory factor, can contribute to the promotion of detrusor relaxation *via* the inhibition of C-fiber activity^[33-35]. Finally, experiments in spinal cord transected rats showed that β_3 -AR agonists can directly inhibit bladder afferent activity^[36].

As the main effect of β_3 -AR agonists *in vivo* remains unclear, so the detailed mechanism of action by which these drugs exert their beneficial effect in DO and OAB has not been completely established and further studies are needed. However, taken together, the available experimental evidence supports β_3 -AR agonism as a novel pharmacological principle intended for the treatment of OAB, including storage symptoms secondary to BOO^[37,38].

PRECLINICAL EVIDENCE ON MIRABEGRON

Mirabegron is a novel, once-daily, orally active, first-in-class, potent and selective β_3 -AR agonist. Cellular studies

showed that mirabegron stimulates the intracellular cAMP accumulation by acting with full agonistic activity and high efficacy on human β_3 -ARs; on the other hand, its efficacy on β_1 - and β_2 -ARs was very low (446 times less selective for these receptors in Chinese hamster ovary cells)^[30,39].

Affinity for human β_3 -AR did not appear to be altered by several gene variants of the receptor^[40]. Studies on isolated strips of human detrusor muscle demonstrated an efficacy of mirabegron comparable to that of isoprenaline, a non-selective β_3 -AR agonist^[30]; this efficacy of mirabegron was maintained in isolated detrusor strips obtained from control patients and patients with BOO or BOO-associated DO^[41]. More interestingly, mirabegron induced a dose-dependent reduction of the frequency of rhythmic bladder contractions when given intravenously to urethane-anesthetized rats; however, unlike anticholinergics, it did not significantly decrease the contraction amplitude^[30]. In rat model of bladder dysfunctions, mirabegron was effective in improving storage-phase urodynamic parameters, without affecting voiding-phase parameters, such as micturition pressure, threshold pressure and residual volume; this pharmacological profile should decrease the risk of causing urinary retention^[39,42,43]. While mirabegron reduced the frequency of non-voiding bladder contractions, anticholinergics mainly reduced their amplitude^[44].

In vivo experiments also showed that, during bladder filling, mirabegron can directly inhibit in a dose-dependent manner the mechanosensitive bladder afferent nerves firing of both A δ - and C-fibers, that was more remarkable for A δ -fibers^[45]; in this study, mirabegron also inhibited both bladder microcontractions and A δ -fibers activity at doses that do not decrease bladder pressure, suggesting a possible additional action of β_3 -AR agonists as therapeutic agents for OAB or other bladder sensory disorders.

The aforementioned findings prompted several trials aimed to investigate efficacy, safety, tolerability and discontinuation rate of mirabegron in the clinical setting of OAB patients. In particular, the development of mirabegron by Astellas Pharma Inc. (Ibaraki, Japan) involved an extensive clinical development and clinical pharmacology programs including 41 studies^[46].

CLINICAL EVIDENCE OF EFFICACY

Proof-of-concept and dose-finding studies

Mirabegron has been extensively studied in more than 10000 individuals and about 40 clinical studies have been performed over the last 10 years. Safety and efficacy in OAB patients were evaluated in 5 global, 12-wk trials: two phase II (Clinicaltrials.gov number: NCT01604928 and NCT00337090) and three pivotal phase III (NCT00689104, NCT00662909, NCT00912964) studies that compared mirabegron with placebo and with tolterodine (a commonly prescribed oral anti-muscarinic agent). A further safety study (NCT00688688) evaluated long-term (12 mo) results.

A proof-of-concept, randomized, double-blind, paral-

lel group, phase II a dose-ranging trial (BLOSSOM trial, NCT01604928) was conducted in six European countries including 260 OAB patients that were assigned to four treatment arms: placebo ($n = 66$), mirabegron 100 mg *bid* ($n = 65$), mirabegron 150 mg *bid* ($n = 65$), and tolterodine 4 mg extended-release (ER) once-daily ($n = 64$), for a 4-wk period^[47]. With regard to mean micturition frequency, mirabegron was significantly superior to placebo and tolterodine: 2.2 micturitions/24 h *vs* 1.2 micturitions/24 h for both doses (adjusted $P \leq 0.01$ for both comparisons). Compared with placebo, mirabegron was also superior with respect to mean volume voided per micturition, mean number of incontinence episodes, nocturia episodes, urgency incontinence episodes, urgency episodes per 24 h and HRQL variables. No difference in efficacy was observed between the 100 and 150 mg twice-daily doses, leading to the conclusion that a total daily dose of 200 mg provides maximum therapeutic efficacy.

An European, dose-finding, phase II b randomized trial (DRAGON trial, NCT00337090) enrolled 919 OAB patients (mean age 57.2 years, 89.3% female) assigned to six study arms: placebo ($n = 166$), mirabegron 25 mg ($n = 167$), 50 mg ($n = 167$), 100 mg ($n = 168$), 200 mg ($n = 166$) and tolterodine 4 mg ER ($n = 85$), for a 12-wk period^[48]. In this study a once-daily OCAS formulation of mirabegron was used. Statistically significant, dose-dependent reductions in the mean number of micturitions per 24 h (primary endpoint) were seen with mirabegron 50 (-2.1), 100 (-2.1) and 200 (-2.2) mg, compared with placebo (-1.4). Mirabegron significantly increased mean volume voided per micturition and decreased mean number of urgency and urgency incontinence episodes per 24 h, level of urgency (at doses of 100 and 200 mg) and nocturia episodes (at doses of 50 mg): about half of the incontinent patients in each mirabegron group was dry at the end of treatment. Similarly to previous studies evaluating antimuscarinics^[49], the difference in response *vs* placebo was evident after 1 wk of treatment and the maximum effect was achieved and sustained from 8 to 12 wk. Although the study was not powered for head-to-head comparison with tolterodine, the authors observed that the magnitude of improvements in efficacy outcomes in the mirabegron groups was within the same range as that of the tolterodine group.

Randomized large-scale pivotal trials

Based on the aforementioned results, three subsequent large-scale, phase III, randomized studies were conducted by Astellas (Table 1)^[50-52]. Efficacy analyses of these studies were based on two co-primary efficacy endpoints: (1) the change from baseline to endpoint in the mean number of incontinence episodes per 24 h; and (2) the mean change from baseline to endpoint in the mean number of micturitions per 24 h.

An European-Australian multicentre, randomised, double-blind, parallel-group, placebo and active controlled phase III trial (SCORPIO trial, NCT00689104) enrolled 1978 OAB patients (mean age 59.1 years, 72.2% female)

Table 1 Coprimary efficacy variables in 12-wk phase III pivotal randomized controlled trials

Trials	Patients (n)	Arms (n)	Change from baseline in incontinence episodes/d ¹ (FAS-I)	Change from baseline in micturitions/d ¹ (FAS)	Ref.
SCORPIO	1978	Placebo (494)	-1.17	-1.34	[50]
		Mirabegron 50 mg (493)	-1.57 ^a	-1.93 ^a	
		Mirabegron 100 mg (496)	-1.46 ^a	-1.77 ^a	
		Tolterodine 4 mg ER (495)	-1.27 (NS)	-1.59 (NS)	
ARIES	1328	Placebo (454)	-1.13	-1.05	[51]
		Mirabegron 50 mg (442)	-1.47 ^a	-1.66 ^a	
		Mirabegron 100 mg (433)	-1.63 ^a	-1.75 ^a	
CAPRICORN	1302	Placebo (433)	-	-	[52]
		Mirabegron 25 mg (433)	-0.40 ^a	-0.47 ^a	
		Mirabegron 50 mg (440)	-0.42 ^a	-0.42 ^a	
Pooled analysis	3542	Placebo (1328)	-1.10	-1.20	[53]
		Mirabegron 50 mg (1324)	-1.49 ^a	-1.75 ^a	
		Mirabegron 100 mg (890)	-1.50 ^a	-1.74 ^a	

^a $P < 0.05$ vs placebo. ¹Mean adjusted changes from baseline to final visit. FAS: Full analysis set; FAS-I: Full analysis set-incontinence (all FAS patients with \geq incontinence grade at baseline); NS: Not significant; ER: Extended release.

that were assigned to four arms: placebo, mirabegron 50 mg, mirabegron 100 mg or tolterodine slow-release (SR) 4 mg once-daily, for a 12-wk period (Table 1)^[50]. Compared to placebo, statistically significant reductions were observed with 50 and 100 mg of mirabegron in both co-primary efficacy measures. Although improvements in both co-primary endpoints were also observed with tolterodine SR, they did not reach statistical significance. Compared with placebo, all active treatment groups achieved statistically significant improvements from baseline in mean volume voided per micturition; the mirabegron 50 mg group achieved a statistically significant improvement also in the mean number of episodes with urgency (grade 3 or 4) per 24 h. No statistical comparison with tolterodine SR was performed in this study, however the magnitude of effect with mirabegron was at least as good as that observed with tolterodine SR.

Another multicentre, randomised, double-blind, parallel-group, placebo-controlled phase III trial (ARIES trial, NCT00662909) was conducted in the United States and Canada^[51]. This study enrolled 1328 OAB patients (mean age 60.1 years, 74.3% female) randomly assigned to three treatment arms: placebo, mirabegron 50 mg, mirabegron 100 mg once-daily, for a 12-wk period (Table 1). Compared to placebo, statistically significant decreases from baseline were observed with 50 and 100 mg mirabegron in the number of incontinence episodes and in the number of micturitions per 24 h. Significantly greater improvements *vs* placebo were observed for both mirabegron treatment groups also in mean level of urgency, mean number of urgency incontinence episodes per 24 h, mean number of urgency episodes (grade 3 or 4) per 24 h and mean number of nocturia episodes per 24 h.

The third pivotal phase III study is an European-North American, randomized, double-blind, placebo-controlled trial (CAPRICORN trial, NCT00912964), including 1306 eligible patients (mean age 59.0 years, 68.7% female) randomly assigned to receive placebo, mirabegron 25 mg or mirabegron 50 mg, for a 12-wk period (Table 1). The

results of this trial, submitted to regulatory authorities by Astellas and presented as meeting abstract, are still unpublished in peer-review journals^[52]. Both mirabegron 25 and 50 mg groups demonstrated statistically significant improvements for the co-primary efficacy endpoints, providing evidence that the lower dose also results in a clinically meaningful benefit, although greater efficacy was observed with mirabegron 50 mg.

Recently, a pooled analysis of data from the above-mentioned three pivotal randomised phase III studies has been reported as abstract; the efficacy of mirabegron (50 or 100 mg) was compared with placebo (Table 1)^[53]. This pooled analysis demonstrated similar statistically significant and clinically meaningful improvements for mirabegron 50 and 100 mg compared with placebo based on co-primary efficacy endpoints; the reduction with mirabegron of the micturition frequency per 24 h and the number of incontinence episodes per 24 h compared with placebo was of about 0.55 and 0.40, respectively.

Long-term efficacy data

A multinational randomised, double-blind, parallel group, active-controlled, phase III trial has been conducted in North America, Europe and other countries (TAURUS trial, NCT00688688) assessing long-term safety (primary outcome) and efficacy of mirabegron. In this study 2444 OAB patients were randomised to three study arms: mirabegron 50 mg ($n = 812$) and 100 mg ($n = 820$) and tolterodine SR 4 mg ($n = 812$), once daily for 12 mo^[54]. The study was not designed to demonstrate a statistically significant difference in efficacy between treatment groups and was not placebo-controlled. The authors reported that, for both doses of mirabegron, improvements in OAB symptoms were observed by month 1 and were maintained throughout the follow-up period, as measured by the change from baseline for mean number of micturitions per 24 h, mean number of incontinence episodes per 24 h and mean volume voided/micturition^[54]. Overall, data from this safety study provide evidence

demonstrating the durability of effect for mirabegron in the treatment of OAB and support the results of previous studies showing that the β_3 -AR, unlike other β -AR subtypes, is not prone to desensitization^[55].

QUALITY OF LIFE MEASURES AND TREATMENT SATISFACTION

In the DRAGON trial^[48], the International Consultation on Incontinence Questionnaire-Overactive Bladder (ICIQ-OAB) and the ICIQ-OABqol questionnaires were used for HRQL assessment. Dose-dependent improvements from baseline to the end of treatment were observed with the ICIQ-OAB questionnaire and were statistically significant *vs* placebo for all mirabegron groups. Improvements from baseline to the end of treatment were also observed with the ICIQ-OABqol questionnaire, although only the comparison between the mirabegron 200-mg group and placebo was statistically significant. Patient-reported benefit was also evaluated with the question “has the treatment been of any benefit to you?” (“no”, “yes, a little”, or “yes, very much”). The percentage of patients classified as “responders” (improvement of ≥ 1 category from baseline) at the end of treatment was 59.0%, 65.0%, 65.8% and 70.8% for the mirabegron 25-mg, 50-mg, 100-mg, and 200-mg groups, respectively, compared with 51% for placebo and 55% of the tolterodine groups.

All three active treatment groups (mirabegron 50 and 100 mg, tolterodine ER 4 mg) demonstrated a statistically significant improvement from baseline to final visit compared with placebo on the three HRQL measures used in the SCORPIO trial^[50]: OAB-Questionnaire (OAB-q), Patient Perception of Bladder Condition (PPBC), and Treatment Satisfaction-Visual Analog Scale (TS-VAS).

These results were replicated in the ARIES trial^[51]; both mirabegron treatment groups demonstrated significantly greater improvements from baseline to final visit *vs* placebo in OAB-q (symptom bother, HRQL total score and dimensions of coping, concern and sleep), TS-VAS and PPBC.

In the CAPRICORN trial both mirabegron groups (25 and 50 mg) demonstrated statistically significant improvements *vs* placebo for the TS-VAS; for the OAB-q, the mirabegron 50 mg group demonstrated statistically significant improvements *vs* placebo in the Symptom Bother scale^[52].

Long-term data on both doses of mirabegron, 50 and 100 mg, also showed numerical improvements on the OAB-q (symptom bother and HRQL total score), PPBC scale, and TS-VAS, similar to those seen using a well-established antimuscarinic treatment for OAB^[54].

SUBPOPULATION ANALYSES

Clinical data in specific subpopulations of OAB patients are still scant in published literature.

With regard to the influence of gender, it must be

noted that most of patients enrolled in phase III trials were females and limited data are available on the efficacy of mirabegron in males, especially in those with benign prostatic hyperplasia (BPH). A non-randomized study, focusing on males, reported that mirabegron was effective in male patients with OAB and improved not only OAB symptoms, but also voiding symptoms in BPH men, without increasing post-voiding residual urine^[56]. In this study, with a small number of participants, a greater improvement of urgency urinary incontinence based on OAB Symptom Questionnaire was observed in BPH patients treated with α_1 -blocker compared to those not treated with α_1 -blocker, suggesting that combining mirabegron with α_1 -blocker might benefit males with wet OAB. Accordingly, pooled pivotal trial efficacy data reported by the FDA showed that mirabegron 50 mg and 100 mg were effective for both male and female subjects, although a larger reduction *vs* placebo in mean number of incontinence episodes was observed in female subjects compared to male subjects; however, it was suggested that this observation could be due to a lower baseline level of incontinence in males, overlapping symptomatology with male co-morbid conditions (*e.g.*, BPH), increased mirabegron exposure in females, or some combination of all 3 factors^[57]. The same document reports that mirabegron 50 and 100 mg did not appear effective in decreasing the mean number of incontinence episodes in men with BPH^[57]. In a phase II, double-blind, parallel-group, placebo-controlled urodynamic study (NCT00410514) including 200 men with LUTS and BOO, Nitti *et al.*^[58] reported that 50 and 100 mg mirabegron do not adversely affect Q_{max} , detrusor pressure at Q_{max} and bladder contractility index, and are well tolerated in these patients. However, because of the limited number of men with BPH included in available studies, it is not possible to draw meaningful conclusions.

A non-randomized, active-controlled study reported that mirabegron is effective for those whose OAB is unresponsive to antimuscarinic drugs, although its effectiveness was less in these patients compared to newly diagnosed OAB patients^[56]. In this study, 38.4% of OAB patients did not respond to mirabegron as well as to antimuscarinics; as noted by the authors, this subject deserves further elucidation. Accordingly, a post-hoc analysis of the SCORPIO trial^[59] showed that both mirabegron 50 and 100 mg once-daily were effective in improving both mean number of incontinence episodes and micturitions per 24 h *vs* placebo, not only in antimuscarinic-treatment-naïve patients but also in those patients who failed prior OAB antimuscarinic therapy, regardless of the reason for discontinuation.

With regard to the effect of the age, the pooled data from the three pivotal randomised studies were analysed in the OAB population aged ≥ 65 years in order to investigate the benefit of mirabegron in elderly OAB patients^[60]. Approximately 38% of patients were ≥ 65 years of age (placebo $n = 504$; mirabegron 50 mg $n = 499$; mirabegron 100 mg $n = 340$). Mirabegron 50 and 100 mg re-

sulted in reduction in incontinence episodes per 24 h and micturitions per 24 h in patients ≥ 65 years of age, with an adjusted mean difference *vs* placebo of -0.66 and -0.68, respectively, and of -0.62 and -0.75, respectively. These results are of great value, given the increasing prevalence of OAB with age and the common adverse events associated with antimuscarinics in the aging population^[7].

SAFETY, TOLERABILITY AND DISCONTINUATION

There is substantial consistency through the studies in reporting safety and tolerability of treatment with mirabegron.

Despite a small increase in pulse rate, mirabegron demonstrated good safety and tolerability in the BLOSSOM trial^[47]. An incidence of treatment-emergent adverse effects (TEAEs) of 39.2% with mirabegron *vs* 36.4% with placebo and 48.4% with tolterodine has been reported. AEs in the mirabegron group were mild or moderate in intensity, the most commonly reported class of TEAEs being gastrointestinal disorders (13.8%), followed by headache (6.9%), with a lower incidence compared to tolterodine group (23.4%, 9.4%, respectively). Treatment-related dizziness and palpitations were more common with mirabegron compared to placebo and tolterodine. Of note, no episodes of acute urinary retention were reported. Discontinuation rates due to AEs were 4.6% and 7.7% with mirabegron 100 and 150 mg, respectively, 1.5% with placebo and 3.1% with tolterodine.

In the DRAGON trial, one or more TEAEs were reported by 43.8%-47.9% of patients in the mirabegron groups (25, 50, 100 and 200 mg) *vs* 43.2% in the placebo group^[48]. Again, the most common reported TEAEs were gastrointestinal disorders (7.2%-8.3% with mirabegron *vs* 5.3% with placebo), including constipation, dry mouth, dyspepsia and nausea. Of note, the incidence of dry mouth, reported to be an important factor for determining persistence with antimuscarinic agents^[10], was higher with tolterodine ER 4 mg (3.5%) than with mirabegron (1.8% to 3.0%, depending on dose). Again, no episodes of acute urinary retention were reported with mirabegron. A statistically significant, dose-dependent increase from baseline in mean pulse rate *vs* placebo was detected with 100 and 200 mg mirabegron (1.6 and 4.1 bpm, respectively, AM; 2.7 and 4.7 bpm PM); however, this change in pulse rate was not associated with an increase in cardiovascular AEs and no differences between treatment groups were observed in ECG parameters and blood pressure. Discontinuation owing to AEs was low at 3.0% with placebo, 2.4%-5.3% with mirabegron, and 1.2% with tolterodine.

An incidence of TEAEs similar across the placebo, mirabegron 50 mg, mirabegron 100 mg, and tolterodine SR groups (43.3%, 42.8%, 40.1% and 46.7%, respectively) was reported in the SCORPIO trial^[50]. The most common TEAEs in this study 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%). At the final visit, mirabegron was associated with small dose-dependent, not clinically meaningful increases in pulse rates compared with placebo, that were similar to those seen with tolterodine; the overall incidence of adjudicated cardiovascular events was similar in placebo- and mirabegron-treated patients, and slightly higher in tolterodine-treated patients. The discontinuation rate owing to TEAE was low, at 2.6%, 4.9%, 3.2%, and 4.4%, respectively.

The ARIES trial^[51] confirmed a similar incidence of TEAEs across placebo, mirabegron 50 mg and 100 mg groups (50.1%, 51.6% and 46.9%, respectively). In this study, the incidence of hypertension was 6.6%, 6.1% and 4.9%, and headache 2.0%, 3.2% and 3.0% in the placebo, mirabegron 50 mg and 100 mg groups, respectively. An increase incidence of urinary tract infections was noted with mirabegron 50 mg (12%) and 100 mg (16%), compared with placebo (8%). Changes in laboratory assessments, vital signs, physical examination, ECG and post-void residual volume were small and consistent across treatment groups. No AEs of QTc prolongation and no proarrhythmic events were observed. Discontinuation rates due to AEs were 3.8%, 4.1% and 4.4% in the placebo, mirabegron 50 mg and 100 mg groups.

In the CAPRICORN trial, common TEAEs included hypertension in 5.3%, 6.9%, and 7.0%, and headache in 2.1%, 0.9% and 0.9%, in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively^[52].

In compliance with abovementioned studies, long-term safety and tolerability have been confirmed by the results of the TAURUS trial (Table 2)^[54]. The most frequent TEAEs were hypertension, dry mouth, constipation and headache, which occurred at a similar incidence across all treatment groups, while the incidence of dry mouth was more than three fold higher in the tolterodine group. A higher incidence of neoplasms (benign, malignant, and unspecified including cysts and polyps) was seen in the mirabegron 100 mg group (1.3%) compared with mirabegron 50 mg (0.1%) or tolterodine ER 4 mg (0.5%), but was not considered to be treatment-related. Discontinuations due to AEs were comparable across treatment groups, occurring in only 6.4%, 5.9%, and 6.0% of patients on mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg, respectively.

ONGOING STUDIES AND AWAITED RESULTS

Several studies are ongoing in order to evaluate efficacy and safety of mirabegron in selected groups of patients or in comparison with other drugs. Some of these studies are still recruiting patients, while others have been completed and their results should be published on peer-review journals. Many studies are also ongoing focusing on several pharmacokinetic features of mirabegron and pharmacological interactions.

A randomized, phase II, double-blind, factorial, paral-

Table 2 Most frequent (> 2% in any treatment group) treatment emergent adverse events and adverse events of interest¹ n (%)

MedDRA (v.9.1), preferred term	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Tolterodine ER 4 mg (n = 812)
Any AE	485 (59.7)	503 (61.3)	508 (62.6)
Hypertension	75 (9.2)	80 (9.8)	78 (9.6)
Urinary tract infection	48 (5.9)	45 (5.5)	52 (6.4)
Dry mouth	23 (2.8)	19 (2.3)	70 (8.6)
Nasopharyngitis	32 (3.9)	35 (4.3)	25 (3.1)
Headache	33 (4.1)	26 (3.2)	20 (2.5)
Influenza	21 (2.6)	25 (3.0)	28 (3.4)
Constipation	23 (2.8)	25 (3.0)	22 (2.7)
Back pain	23 (2.8)	29 (3.5)	13 (1.6)
Dizziness	22 (2.7)	13 (1.6)	21 (2.6)
Diarrhea	15 (1.8)	24 (2.9)	16 (2.0)
Sinusitis	22 (2.7)	18 (2.2)	12 (1.5)
Arthralgia	17 (2.1)	19 (2.3)	16 (2.0)
Tachycardia	8 (1.0)	19 (2.3)	25 (3.1)
Cystitis	17 (2.1)	11 (1.3)	19 (2.3)
Adverse events of interest			
Corrected QT interval prolongation ²	3 (0.4)	2 (0.2)	3 (0.4)
Hypertension ²	89 (11.0)	83 (10.1)	86 (10.6)
Cardiac arrhythmia ²	32 (3.9)	34 (4.1)	49 (6.0)
Urinary retention	1 (0.1)	1 (0.1)	3 (0.4)
Acute urinary retention	0	1 (0.1)	1 (0.1)
Hypersensitivity	45 (5.5)	44 (5.4)	42 (5.2)
Syncope/seizure	1 (0.1)	0	1 (0.1)
Hepatotoxicity ²	17 (2.1)	19 (2.3)	15 (1.8)

¹In the safety analysis set; ²Definition based on standardized medical dictionary for regulatory activities (MedDRA) query. Adverse event not based on standardized MedDRA queries were predefined. Reprinted from reference^[54], with permission. AE: Adverse Event; ER: Extended release.

lel-group, active and placebo-controlled, multicenter, dose-ranging study (SYMPHONY trial, NCT01340027) has been conducted to evaluate efficacy, safety and tolerability of six dose combinations of solifenacin and mirabegron compared to mirabegron and solifenacin monotherapies in the treatment of OAB.

The BEYOND trial (NCT01638000) is an ongoing double-blind, randomized, multi-center, phase III study of mirabegron *vs* solifenacin in 1692 subjects with OAB treated with antimuscarinics and dissatisfied due to lack of efficacy.

A post-marketing study (NCT01745094) is recruiting patients in order to evaluate safety and efficacy of concomitant use (add-on-therapy) of mirabegron in patients with OAB under treatment with solifenacin.

CONCLUSION

After 30 years of predomination of antimuscarinics, a new compound, with a novel mechanism of action, is for the first time available in the pharmacological armamentarium aimed to treat OAB. Mirabegron has proven effective across multiple randomized controlled trials, both short and long-term, and showed a favourable safety profile with a placebo-like dry mouth incidence. Mirabe-

gron can be used for patients with contraindications to antimuscarinics and its effectiveness has been confirmed in patients who discontinued previous antimuscarinic therapy. Although the tolerability profile of mirabegron offers the potential to improve adherence to OAB treatment, this optimal efficacy-tolerability balance is to be demonstrated in clinical real-world every day practice.

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