EXPERT OPINION

Mirabegron in the treatment of overactive bladder

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Introduction: Mirabegron is a selective β_3-adrenergic receptor agonist recently developed for the treatment of patients with overactive bladder (OAB), which offers an alternative pharmacological option to the well-established treatment with antimuscarinics (AMs).

Areas covered: This review offers an explanation of the mechanism of action, of the pharmacokinetics and pharmacodynamics of mirabegron and gives readers a complete overview of Phase II and III studies on the clinical efficacy, tolerability and safety of this agent in the setting of OAB treatment.

Expert opinion: Both Phase II and III trials have shown that mirabegron is efficacious and safe in treating patients with OAB. Future research should focus on the assessment of mirabegron concentrations in the CNS and on the evaluation of the potential of the combination of mirabegron with AMs. Another field for future research is represented by the investigation of the interaction of mirabegron with CYP2D6 inhibitors. Furthermore, current literature completely lacks studies on the efficacy and safety of mirabegron in the pediatric population and such trials are awaited.

Keywords: antimuscarinic, mirabegron, overactive bladder, urgency, urinary incontinence

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1. Introduction

The overactive bladder syndrome (OAB) is a symptom complex consisting of urinary urgency with or without urgency urinary incontinence (UUI), often associated with nocturia and frequency [1]. The overall prevalence of OAB is estimated to be about 12% of men and women [2], with a significant deterioration in the quality of life (QoL) of these patients and association with increased health risks [3].

Urgency is the hallmark of OAB and may be due to either dysfunction of the afferent neural pathways starting from the bladder epithelium up to the anterior cingulate region of the brain [4] or to efferent dysfunction leading to detrusor overactivity. OAB is not, therefore, synonymous with detrusor overactivity [5].

The management of OAB is multimodal and it includes both non-pharmacological and pharmacological therapeutic strategies. The first-line treatment includes bladder and pelvic floor retraining, lifestyle and dietary modifications. When these are ineffective, pharmacotherapy should be considered. Antimuscarinics (AMs) are the mainstay of pharmacological treatment of OAB and represent the most commonly prescribed drugs for this condition [6]. However, pharmacotherapy for OAB also includes other medications, such as vasopressin analogues, antidepressants, α-adrenoceptor antagonists and β-adrenergic receptor (AR) agonists.

Mirabegron (YM178, Myrbetriq™, Betanis®, Betmiga®) (**Box 1**) is the first β_3-AR agonist approved for use in OAB. The recommended starting dose is 25 mg once daily (QD) in the USA and Canada (Myrbetriq™, Astellas Pharma, Inc., Northbrook, IL), with the possibility of increasing to 50 mg, while the

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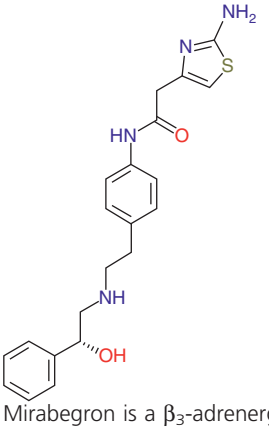
Box 1. Drug summary.

Drug name	Mirabegron
Phase	Launched
Indication	Overactive bladder syndrome
Chemical formula	2-(2-Amino-1,3-thiazol-4-yl)-*N*-[4-(2-{[(2*R*)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl] acetamide
Chemical structure [83]	
Pharmacology description	Mirabegron is a β_3-adrenergic receptor agonist
Route of administration	Oral
Dosage	25 or 50 mg once daily
Pivotal trial(s) with clinical efficacy, safety, and tolerability	See **Tables 1**,**2**,**3**

recommended dose in Japan (Betanis®, Astellas Pharma, Inc. Chuo-ku, Tokyo, Japan) and Europe (Betmiga™, Astellas Pharma BV, Leiden, the Netherlands) is 50 mg QD with the 25 mg dose reserved for special populations (i.e., patients with severe renal impairment or moderate hepatic impairment).

The objective of this manuscript is to review the literature regarding mirabegron in the treatment of OAB, offering the reader an overview of the mechanism of action, pharmacokinetics, pharmacological properties, clinical efficacy, safety and tolerability of the compound.

A literature search was performed to identify all the published studies evaluating the use of mirabegron in treating OAB from inception until December 2013. The following electronic databases were used: Medline, PubMed and Embase. The following search terms, alone or in combination, were used: mirabegron, adverse events, efficacy, overactive bladder, pharmacokinetics, safety and tolerability. All pertinent articles were carefully examined and their reference lists were assessed in order to find other manuscripts that could be included in this review. Current research registers (such as www.cliniclatrials.gov) were also considered. In addition, conference proceedings were consulted to identify further studies that could be reviewed even if published only in abstract form. Case reports and letters to the editor were excluded from the review. Only articles in English were included. Two independent researchers (SF and SS) screened the studies originally identified from the literature search; disagreement about inclusion/exclusion was resolved by consensus. The reviewers were not blinded to the names of investigators or sources of publication.

2. Overview of the market

OAB significantly affects the QoL of patients, is related to an increased health risk and represents a social burden [2,3,7]. The estimated average annual direct cost of OAB per patient ranges between €262 in Spain and €619 in Sweden. The estimated total direct cost burden for OAB per country is between €333 million in Sweden and €1.2 billion in Germany, and the total annual direct cost burden of OAB in six western countries (Canada, Germany, Italy, Spain, Sweden and the UK) is estimated at €3.9 billion. Furthermore, nursing home costs are around €4.7 billion per year and work absenteeism related to OAB costs may represent €1.1 billion per year [7]. In addition, the relevance of OAB may be also deduced from the market size of pharmacotherapy, which is around $4 billion per year [8]. Given this background, it is desirable to rely on treatments that guarantee long-lasting efficacy, which are safe and well tolerated by patients in order to maximize adherence to therapy, which is still low [9].

The first-line management of OAB consists of dietary modifications (decrease of fluid intake, potential bladder irritants such as caffeinated products [coffee, tea], alcohol and artificial sweetened carbonated drinks), weight loss, bladder retraining and pelvic floor retraining with or without biofeedback [10-12].

When first-line treatment is not successful, pharmacotherapy should be considered. AMs (such as darifenacin, solifenacin, fesoterodine, tolterodine, trospium, oxybutynin and propiverine) are the first choice of the pharmacological treatment of OAB [6,13,14]. AMs are efficacious in reducing incontinence episodes per day, number of micturitions per day and urgency episodes per day. AMs exert their action by increasing bladder relaxation through antagonism of muscarinic M_2 receptors and decreasing bladder contraction through antagonism of M_3 receptors [15]. Furthermore, different studies demonstrated the presence of a muscarinic receptor-mediated mechanism in urothelial sensory function, as well as in local contractions of the bladder wall, both of which contribute to generating afferent signals. A number of signaling molecules including ATP and prostaglandins, produced and released by the bladder urothelium, activate C-fiber afferent in the suburothelial layer of the bladder wall [16-21]. Furthermore, a suburothelial layer of myofibroblasts (interstitial cells) is in close apposition to afferent C-fiber nerves and plays a part in the amplification of the afferent system secondary to stimulatory mediators [22-24]. Therefore, recent evidence suggests that AMs act not only on the efferent pathway but also reduce the bladder afferent activity through the inhibition of the muscarinic receptors in the urothelium and suburothelial myofibroblasts.

Although the definition of OAB relates to urinary urgency, the pivotal role in such a symptom complex syndrome, patient's preference for an OAB treatment is greatly influenced by the decrease of urinary incontinence and micturition episodes. Furthermore, the possibility of experiencing an AE may motivate a change in treatment preference [25]. Therefore, in view of the similar efficacy of most AMs [6], the choice of a specific compound should be tailored as much as possible, taking into consideration the compliance of the patient to different formulations and the mode of delivery of the drug, the tolerability profile in relation to different factors such as age, comorbidities, concomitant pharmacological therapies and specific needs. Patients with OAB may have a suboptimal response or find that AMs treatment is limited by associated AEs [26,27]. In this scenario, the development of a new class of drugs for the treatment of OAB, such as β_3-AR agonists (rafabegron [28], solabegron [29] and mirabegron), is crucial and represents a relevant innovation in the current armamentarium to treat this condition.

In patients with refractory OAB, more invasive treatment options, such as botulinum toxin A, neuromodulation and surgery may be considered [30]. The cystoscopic intradetrusor injection of botulinum toxin A represents a safe option; however, its efficacy is temporary with a significant risk of voiding difficulties at high dose [30]. Neuromodulation is another treatment option for women with refractory OAB. Few studies showed that percutaneous tibial nerve stimulation is efficacious and causes improvement in QoL similar to that achieved by AM drugs [16], whereas many investigations demonstrated that sacral neuromodulation is effective, but with limitations due to high costs and high reoperation rate [30,31].

For selected patients not responding to the previously mentioned treatments, reconstructive surgery, such as ileal conduit diversion, augmentation cystoplasty, detrusor myectomy and supravesical urinary diversion (ureteroileal conduit is the most frequent incontinent diversion), may be considered despite high morbidity rates and long-term complications [31].

3. Mirabegron

3.1 Chemistry

Mirabegron (**Box 1**) [2-(2-Amino-1,3-thiazol-4-yl)-*N*-[4-(2-{[(2*R*)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide has a molecular weight of 396.51 g/mol. It is a novel drug developed for symptomatic treatment of urgency, increased micturition frequency and/or UUI, as may occur in patients with OAB. Mirabegron has been approved at the 25 mg/day dose in Japan in 2010, at 25 or 50 mg/day dose in the USA in 2012 and has been recently approved by European authorities at a dose of 50 mg/day.

3.2 Mechanism of action

Mirabegron is a selective β_3-AR agonist that exerts its activity in a different way from the AMs, which act by blocking the muscarinic receptors [15]. Detrusor smooth muscle relaxation is of primary importance to achieve bladder compliance and guarantees low intravesical pressure during the bladder filling phase while the urethral sphincter is closed. Relaxation of the detrusor muscle depends on the activation of β-ARs by norepinephrine released from sympathetic nerves innervating the bladder [32]. The presence of all three β-ARs subtypes (β1, β2 and β3) has been demonstrated in the human detrusor muscle [33-35] and urothelium [36]. In particular, mirabegron plays a role in the neural control of the storage phase of the micturition acting on the β_3-ARs, which are the most common β-AR in the human bladder [37]. β_3-AR messenger RNA expression [34,36] and functional evidence suggest a prevalent involvement of this receptor in both normal and neurogenic bladders [34,38,39].

In vitro studies demonstrated the role of β_3-AR function in relaxation of the human detrusor muscle [33]. Bladder relaxation is obtained by the activation of β_3-AR and the subsequent activation of adenylyl cyclase, which brings to cAMP formation that is thought to be crucial for achieving the therapeutic effect in OAB. Furthermore, recent studies showed a possible role of potassium (K+) channels, and particularly, big potassium channels, in the β-AR-mediated bladder relaxation independently of cAMP [40-43].

In vivo studies conducted in several animal models showed that β_3-AR agonists cause an increase of bladder capacity without modifications in micturition pressure or residual volume [44-47]. Therefore, the clinical benefit achieved by using mirabegron in patients with OAB is related to an increase in bladder capacity and to the consequent decreased frequency of micturition [48]. Furthermore, mirabegron, in anesthetized rat model, causes a decrease of the mechanosensitive afferent activity of both Aδ-fiber and C-fiber in a dose-dependent way that is more evident for the Aδ-fiber. In addition, an inhibition of both bladder microcontractions and Aδ-fiber activity was observed at doses that do not decrease bladder pressure, while at higher doses, which also cause a decrease of bladder pressure, mirabegron inhibited C-fiber activity [49]. On the basis of these findings, it may be speculated as a possible additional action of β_3-AR agonists that involves the afferent nerves themselves.

3.3 Pharmacokinetics

The marketed formulation of mirabegron is oral controlled absorption system (OCAS), and its oral bioavailability is between 24 and 53% [50]. The bioavailability of mirabegron is influenced by dose and gender [51]. Mirabegron pharmacokinetics is linear after intravenous (i.v.) dosing (7.5 – 50 mg), but exposure increases more than proportionally after oral dosing due to increased absolute bioavailability (29% for 25 mg to 45% at 150 mg). AUC is 27 and 64% higher in females than males after i.v. and oral dosing, respectively; differences were principally due to body weight, and for oral dosing, also to absolute bioavailability [51]. C_{max} of the compound are comprised between 24.0 and 500 ng/ml and are achieved after long-term oral administration of mirabegron (dose from

50 to 200 mg) [52]. After oral administration, C_{max} occurs in 2.7 – 5.0 h (T_{max}) [53]. About 70% of the compound is bound to plasma proteins, mainly to albumin and then to α1-acid glycoprotein. At steady state, mirabegron shows a large volume of distribution of 1670 l [52]. The metabolism of mirabegron is mainly due to the liver; in particular, it is metabolized by different metabolic pathways such as *N*-dealkylation, oxidative metabolism catalysed by CYP 3A4/5 [54], with a minor role for CYP2D6, amide hydrolysis by esterases and uridine diphosphateglucuronosyltransferases-mediated glucuronidation [55]. At least 10 metabolites are derived from liver metabolism of mirabegron, but none of them has pharmacological activity [55]. About 20% [56] with OCAS mirabegron and about 55% with oral solution of mirabegron are excreted as the parent drug or metabolites in urine [55]. The terminal elimination half-life range is comprised between 26 and 65 h and allows for QD administration [53]. Food intake and age do not significantly influence the pharmacokinetics of mirabegron [53,56,57]. An increase of 6, 23 and 92% in C_{max} is observed in patients with mild, moderate and severe renal impairment, respectively [58]. Furthermore, C_{max} is increased by 9 – 19% and 17 – 65% in patients with mild and moderate hepatic impairments, respectively [58]. Mirabegron has no relevant drug–drug interactions for inhibition of CYP1A1/2,2B6, 2C8, 2C9, 2C19, 2E1, 3A4/5 while a time-dependent inhibition of CYP2D6 is observed [59], which may cause a metabolic drug–drug interaction when other drugs metabolized by CYP2D6 are co-administered [54].

3.4 Pharmacodynamics

Various investigations have evaluated the efficacy of mirabegron in healthy subjects at different doses (25 – 200 mg) [52,53,56,57,60]. The half-maximal efficacy for decreasing micturition frequency over a 24 h time with a rise in the mean volume of voided urine is achieved at the dose of 25 mg [61], while the maximal efficacy is reported at 100 mg [56,57] and the 200 mg dose lies in the supramaximal range [61].

4. Clinical efficacy

4.1 Phase II studies

Two Phase II studies evaluated the use of mirabegron in patients with OAB [62,63]. A multinational, multicenter, randomized, double-blind, double-dummy, parallel group and placebo- and active-controlled Phase II proof-of-concept study assessed the potential of mirabegron for treatment of OAB symptoms in terms of efficacy and safety [62]. Out of the 314 patients eligible for the study, 262 were randomized to receive mirabegron 100 or 150 mg twice-daily (b.i.d.), placebo or tolterodine 4 mg extended release (QD) for 4 weeks. A significant improvement in mean change from baseline to end of treatment in the micturition frequency was observed with mirabegron 100 and 150 mg b.i.d. versus placebo (adjusted $p \leq 0.01$ for both comparisons). Furthermore, this study showed that mirabegron 100 or 150 mg b.i.d. causes a significant decrease from baseline to end of treatment in urgency episodes ($p \leq 0.05$ for both comparisons). Mirabegron 150 mg b.i.d. also results in a significant increase versus placebo from baseline to end of treatment in mean volume voided per micturition ($p \leq 0.05$). In addition, mirabegron 100 mg b.i.d. significantly improves incontinence episodes ($p \leq 0.01$), urgency incontinence episodes ($p \leq 0.05$) and nocturia episodes ($p \leq 0.01$) when compared with placebo. Mirabegron also shows a significant effect versus placebo for QoL variables. In detail, the percentage of patients classified as 'responders' at end of treatment for patients' perception of their bladder condition was superior for mirabegron than placebo (53, 55 and 68% for placebo, mirabegron 100 and 150 mg b.i.d., respectively; $p < 0.05$ for mirabegron 150 mg b.i.d. vs placebo), and the percentage of patients classified as 'responders' at end of treatment for patients' assessment of treatment benefit was higher for mirabegron than placebo at 50, 60 and 71% for placebo, mirabegron 100 and 150 mg b.i.d., respectively ($p < 0.05$ vs placebo for both comparisons) [62].

Another multinational, multicenter, randomized, double-blind, double-dummy, parallel-group placebo- and active-controlled Phase II study assessed the efficacy and safety of mirabegron in patients with OAB symptoms [63]. A total of 1108 patients were enrolled and 928 were included in a single-blind, 2-week placebo run-in period, followed by a 12-week double-blind treatment period in which patients were randomized to receive one of the following therapies: OCAS formulation of mirabegron QD at a dose of 25, 50, 100 or 200 mg, placebo or tolterodine extended release (ER) 4 mg QD. Mirabegron 25, 50, 100 and 200 mg caused dose-dependent reductions from baseline to end of treatment in micturition frequency versus placebo ($p \leq 0.05$ for the mirabegron 50, 100 and 200 mg comparisons). Furthermore, mean baseline to end-of-treatment improvements relative to placebo were statistically significant for mirabegron for mean volume voided per micturition (at doses of 50, 100 and 200 mg), incontinence episodes (at doses of 25 and 50 mg), urgency incontinence episodes (at doses of 25, 50, 100 and 200 mg), urgency episodes (at doses of 25, 100 and 200 mg), level of urgency (at doses of 100 and 200 mg), and nocturia episodes (at a dose of 50 mg; $p < 0.05$ for all comparisons). A dose-dependent improvement ($p \leq 0.05$) in all QoL scores from baseline to the end of treatment for all mirabegron groups versus placebo was observed (assessed by using the International Consultation on Incontinence Questionnaire Overactive Bladder) [63]. **Table 1** describes the main results of these studies in detail.

4.2 Phase III studies

Three large randomized Phase III trials investigated the efficacy, safety and tolerability in patients with OAB [56,57,64]. A randomized, parallel-group, placebo-controlled, double-blind, multicenter, multinational study, which was led at 151 sites in Europe (56 sites) and North America (95 sites),

Table 1. Mirabegron: clinical efficacy.

Clinical trial	Phase	Incontinence episodes per 24 h (change from baseline at 12 weeks)	Micturitions per 24 h (change from baseline at 12 weeks)	Urgency incontinence episodes per 24 h (change from baseline at 12 weeks)	Urgency episodes per 24 h (change from baseline at 12 weeks)	Urine volume voids per micturition (ml). (change from baseline at 12 weeks)	Severity of urgency (change from baseline at 12 weeks)
A proof-of-concept study: mirabegron, a new therapy for overactive bladder [62]	II	Placebo: -1.011 MIRA, 100 mg b.i.d. group: -2.167 MIRA, 150 mg b.i.d. group: -1.579 TOL, 4 mg ER QD group: -1.647	Placebo: -1.175 MIRA, 100 mg b.i.d. group: -2.191 MIRA, 150 mg b.i.d. group: -2.206 TOL, 4 mg ER QD group: -1.487	Placebo: -1.09 MIRA, 100 mg b.i.d. group: -2.058 MIRA, 150 mg b.i.d. group: -1.443 TOL, 4 mg ER QD group: -1.529	Placebo: -1.03 MIRA, 100 mg b.i.d. group: -2.298 MIRA, 150 mg b.i.d. group: -2.302 TOL, 4 mg ER QD group: -2.085	Placebo: 10.483 MIRA, 100 mg b.i.d. group: 26.041 MIRA, 150 mg b.i.d. group: 32.733 TOL, 4 mg ER QD group: 23.768	NA
A Phase II dose-ranging study of mirabegron in patients with overactive bladder [63]	II	Placebo: -0.53 MIRA, 25 mg QD group: -1.36 MIRA, 50 mg QD group: -1.15 MIRA, 100 mg QD group: -1.06 MIRA, 200 mg QD group: -1.10 TOL, 4 mg ER QD group: -0.81	Placebo: -1.44 MIRA, 25 mg QD group: -1.88 MIRA, 50 mg QD group: -2.08 MIRA, 100 mg QD group: -2.12 MIRA, 200 mg QD group: -2.24 TOL, 4 mg ER QD group: -1.99	Placebo: -0.44 MIRA, 25 mg QD group: -1.31 MIRA, 50 mg QD group: -1.13 MIRA, 100 mg QD group: -1.18 MIRA, 200 mg QD group: -1.24 TOL, 4 mg ER QD group: -0.76	Placebo: -1.07 MIRA, 25 mg QD group: -1.77 MIRA, 50 mg QD group: -1.67 MIRA, 100 mg QD group: -2.28 MIRA, 200 mg QD group: -2.48 TOL, 4 mg ER QD group: -1.46	Placebo: 7.29 MIRA, 25 mg QD group: 15.32 MIRA, 50 mg QD group: 27.34 MIRA, 100 mg QD group: 25.56 MIRA, 200 mg QD group: 33.34 TOL, 4 mg ER QD group: 23.86	Placebo: -0.10 MIRA, 25 mg QD group: -0.21 MIRA, 50 mg QD group: -0.18 MIRA, 100 mg QD group: -0.29 MIRA, 200 mg QD group: -0.38 TOL, 4 mg ER QD group: -0.14
A Phase III, randomized, double-blind, parallel-group, placebo-controlled, multicenter study to assess the efficacy and safety of the β_3-adrenoceptor agonist, mirabegron in patients with symptoms of overactive bladder [64]	III	Placebo: NA MIRA, 25 mg QD group: -1.36 MIRA, 50 mg QD group: -1.38	Placebo: NA MIRA, 25 mg QD group: -1.65 MIRA, 50 mg QD group: -1.60	Placebo: NA MIRA, 25 mg QD group: -1.31 MIRA, 50 mg QD group: -1.33	Placebo: NA MIRA, 25 mg QD group: NA MIRA, 50 mg QD group: NA	Placebo: NA MIRA, 25 mg QD group: 12.8 MIRA, 50 mg QD group: 20.7	Placebo: NA MIRA, 25 mg QD group: -0.22 MIRA, 50 mg QD group: -0.29
Efficacy and tolerability of mirabegron, a β_3-adrenoceptor agonist, in patients with overactive bladder: results from a randomized European-Australian Phase III trial [56]	III	Placebo: -1.13 MIRA, 50 mg QD group: -1.62 MIRA, 100 mg QD group: -1.51 TOL, 4 mg ER QD group: -1.21	Placebo: -1.37 MIRA, 50 mg QD group: -1.94 MIRA, 100 mg QD group: -1.75 TOL, 4 mg ER QD group: -1.57	Placebo: NA MIRA, 50 mg QD group: NA MIRA, 100 mg QD group: NA TOL, 4 mg ER QD group: NA	Placebo: -1.65 MIRA, 50 mg QD group: -2.25 MIRA, 100 mg QD group: -1.96 TOL, 4 mg ER QD group: -2.07	Placebo: 12.3 MIRA, 50 mg QD group: 24.2 MIRA, 100 mg QD group: 25.6 TOL, 4 mg ER QD group: 25.0	Placebo: NA MIRA, 50 mg QD group: NA MIRA, 100 mg QD group: NA TOL, 4 mg ER QD group: NA
Results of a randomized Phase III trial of mirabegron in patients with overactive bladder [57]	III	Placebo: -1.13 MIRA, 50 mg QD group: -1.47 MIRA, 100 mg QD group: -1.63	Placebo: -1.05 MIRA, 50 mg QD group: -1.66 MIRA, 100 mg QD group: -1.75	Placebo: -0.89 MIRA, 50 mg QD group: -1.32 MIRA, 100 mg QD group: -1.45	Placebo: -0.82 MIRA, 50 mg QD group: -1.57 MIRA, 100 mg QD group: -1.76	Placebo: 7.0 MIRA, 50 mg QD group: 18.2 MIRA, 100 mg QD group: 18.0	Placebo: -0.08 MIRA, 50 mg QD group: -0.19 MIRA, 100 mg QD group: -0.21

b.i.d.: Twice daily; ER: Extended release; MIRA: Mirabegron; QD: Once daily; TOL: Tolterodine.

assessed the efficacy and safety or tolerability of mirabegron 25 mg and 50 mg QD versus placebo in patients with OAB [64]. The study included 1306 patients ≥ 18 years with OAB symptoms for ≥ 3 months who were enrolled in a 2-week, single-blind, placebo run-in. Over a 3-day micturition diary period, patients with a ≥ 8 micturitions per 24 h and ≥ 3 urgency episodes, with or without incontinence, were randomly assigned to receive QD treatment with mirabegron 25 mg, mirabegron 50 mg, or placebo for 12 weeks. The co-primary end points of the study were changes from baseline to final visit in mean number of incontinence episodes and micturitions per 24 h. Both mirabegron 25 mg and mirabegron 50 mg caused significant improvements in co-primary end points compared with placebo. In particular, mean reductions in incontinence episodes were 1.36, 1.38 and 0.96 for mirabegron 25 mg, mirabegron 50 mg, and placebo groups, respectively; mean reductions in micturitions were 1.65, 1.60 and 1.18 for mirabegron 25 mg, mirabegron 50 mg and placebo groups, respectively. Mirabegron 50 mg was associated with significantly higher improvements versus placebo in the change to final visit in mean volume voided per micturition and change to week 4 in mean number of incontinence episodes per 24 h. Furthermore, there was a significant amelioration in all patient-reported outcome scales with no increase in the incidence of treatment-emergent AEs with mirabegron 50 mg versus placebo [64].

Another 12-week multinational and multicenter randomized double-blind, parallel-group placebo- and active-controlled trial conducted in 27 countries in Europe and Australia in 1978 patients ≥ 18 years of age with symptoms of OAB for ≥ 3 months aimed to assess the efficacy and tolerability of mirabegron versus placebo in treating OAB [56]. Co-primary efficacy end points were change from baseline to final visit in the mean number of incontinence episodes and micturitions per 24 h. After a 2-week single-blind placebo run-in period, patients were randomized to receive placebo, mirabegron 50 mg, mirabegron 100 mg, or tolterodine extended release 4 mg orally QD for 12 weeks. The mirabegron 50 and 100 mg groups had statistically significant improvements at the final visit in the number of incontinence episodes per 24 h ($p < 0.05$) and number of micturitions per 24 h ($p < 0.05$). In addition, statistically significant decreases in the number of incontinence episodes and micturitions per 24 h were reported at week 4 for both doses of mirabegron compared with placebo ($p < 0.05$ for both comparisons), which was maintained at either week 8 or 12. All active treatments caused significant amelioration from baseline in mean volume voided per micturition when compared with placebo ($p < 0.05$). The mirabegron 50 mg group achieved a statistically significant improvement from baseline to final visit in the mean number of episodes of urgency ($p < 0.05$). Furthermore, all patients actively treated had improvement in QoL outcomes assessed by using the OAB Questionnaire (OAB-q), the Patient Perception of Bladder Condition (PPBC), and the Treatment Satisfaction-Visual Analog Scale (TS-VAS) [56].

Nitti *et al*. conducted a Phase III, randomized, parallel group, double-blind, placebo-controlled, multicenter study in the USA and Canada, which enrolled a total of 1329 patients with an average of ≥ 8 micturitions per 24 h and ≥ 3 urgency episodes with or without incontinence during a 3-day period [57]. Patients included in the study were randomly assigned to 50 mg mirabegron group, 100 mg mirabegron group or placebo group. Treatment was administered QD during a 12-week, double-blind treatment period. The co-primary efficacy end points were change from baseline to final visit in mean number of incontinence episodes per 24 h and mean number of micturitions per 24 h. Compared with placebo, 50 and 100 mg mirabegron groups were associated with significantly higher decreases from baseline for incontinence episodes ($p < 0.05$) and micturitions per 24 h ($p < 0.05$) when compared with placebo. Furthermore, both mirabegron treatment groups had significantly greater improvement from baseline to final visit than placebo in OAB-q symptom bother and total health-related QoL scores [57]. A detailed description of the main results of these Phase III trials is presented in **Table 1**.

The long-term (12 months) efficacy and safety of mirabegron in OAB treatment was assessed by Chapple *et al.* [60]. After a 2-week single-blind placebo run-in, patients with ≥ 8 micturitions per 24 h and ≥ 3 urgency episodes in a 3-day micturition diary were randomized 1:1:1 to receive QD mirabegron 50 mg, mirabegron 100 mg, or tolterodine ER 4 mg for 12 months. The primary end point of the study was to evaluate the incidence and severity of treatment emergent AEs. Efficacy end points were secondary and consisted of modifications from baseline at months 1, 3, 6, 9 and 12 in key OAB symptoms recorded in the 3-day micturition diary and in patient-reported outcomes assessed using the OAB-q, PPBC and the TS-VAS. Improvements in efficacy end points were observed from the first month and were maintained until 12-month follow-up. In particular, there was a reduction in the adjusted mean change from baseline for the mean number of micturitions per 24 h (-1.27 for mirabegron 50 mg, -1.41 for mirabegron 100 mg and -1.39 for tolterodine ER 4 mg), for the mean number of incontinence episodes per 24 h (-1.01 for mirabegron 50 mg, -1.24 for mirabegron 100 mg and -1.26 for tolterodine ER 4 mg), and there was an improvement in the mean volume voided/micturition (17.5 ml for mirabegron 50 mg, 21.5 ml for mirabegron 100 mg, and 18.1 ml for tolterodine ER 4 mg). Furthermore, ameliorations in OAB-q symptom bother, health-related QoL, treatment satisfaction, number of nocturia episodes and PPBC were recorded [60]. A *post hoc*, subgroup analysis of the European-Australian study [56] evaluated the efficacy of mirabegron in the subgroups of patients who had not previously received AMs (treatment-naive) and in those who discontinued prior AM therapy because of insufficient efficacy or poor tolerability [65]. Mirabegron (50 and 100 mg QD) caused similar improvement in the number of incontinence episodes and micturitions in patients with OAB who were

AMs-naive and who had discontinued prior AMs therapy. In AM treatment-naive patients, all active treatment groups caused improvement compared with placebo in the mean number of micturitions/24 h from baseline to final visit: -1.61 for placebo, -2.13 for mirabegron 50 mg, -1.98 for mirabegron 100 mg and -1.90 for tolterodine. In patients previously treated with AMs, mirabegron caused improvement in the number of micturition episodes compared with placebo. Adjusted mean changes from baseline to final visit were -1.06 for placebo, -1.74 for mirabegron 50 mg, -1.57 for mirabegron 100 mg and -1.26 for tolterodine. Furthermore, mirabegron was efficacious in reducing incontinence and micturition frequency in patients who had discontinued prior AMs therapy due to insufficient efficacy, while the efficacy of tolterodine was similar to that of placebo [65].

In another recent investigation, Otsuki *et al.* examined the safety and efficacy of mirabegron for patients with OAB that is unresponsive to AMs or is related to benign prostatic hyperplasia [66]. This prospective study included 52 newly diagnosed patients with OAB and 45 patients with OAB previously treated without success with AMs who were both treated with mirabegron 50 mg QD. Twenty-seven newly diagnosed patients with OAB treated with AMs (tolterodine, solifenacin, propiverine, or imidafenacin) were used as controls. The period of this study was 8 weeks. Mirabegron was effective in 85.2% of patients with newly diagnosed OAB. All domains of OAB symptom score had improvement, and there was no significant difference with AMs. In patients with OAB unresponsive to AMs, the efficacy of mirabegron was 61.6% and there were significant decreases in OAB symptom score and international prostate symptom score QoL. Furthermore, there was an improvement in voiding symptoms both in men with new diagnosis of OAB and in those with OAB unresponsive to AMs. In particular, post-void residual urine volumes before and after treatment were 32.1 and 34.8 ml, and 26.2 and 31.3 ml in the two groups, respectively, and there was no significant difference between the study groups [66].

5. Safety and tolerability

5.1 General safety and tolerability

Chapple *et al*. investigated the efficacy and safety of mirabegron in treating OAB in a Phase II proof-of-concept study [60]. In this trial, the incidence of treatment-related AEs was similar between the different treatment groups. The rate of discontinuation due to AEs was 1.5% in the placebo group, 4.6% in the mirabegron 100 mg b.i.d. group, 7.7% in the mirabegron 150 mg b.i.d. group, and 3.1% in the tolterodine ER 4 mg QD group. The causes of discontinuation were angina pectoris in one patient in the placebo group, exanthema, fatigue, nausea, and dizziness, each occurring in one patient in the mirabegron 100 mg group. In addition, in the mirabegron 150 mg group, one patient discontinued treatment due to palpitations, vertigo, blurred vision and dry mouth, one due to nausea, dizziness and hot flush, one due to rash and increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and one patient each due to vomiting, allergic dermatitis, urticaria and rash [62].

Another Phase II study by Chapple *et al*. assessed the efficacy and safety of mirabegron in the treatment of OAB symptoms [63]. No significant difference was observed in the incidence of treatment-related AEs between the different treatment groups. The rate of discontinuation due to AEs was 3.0% in the placebo group, 2.4 – 5.3% in mirabegron group and 1.2% in tolterodine group. Serious AEs were observed in < 2% of patients across treatment groups; one case of pneumonia and one case of hypothyroidism were considered to be possibly related to mirabegron [63].

Table 2 describes the main AEs reported in Phase II trials.

In their Phase III study, Herschorn *et al*. assessed the efficacy and safety of mirabegron at different dosages (25 and 50 mg) versus placebo [64]. In this study, mirabegron was well tolerated at both dosages and the overall incidence of treatment-emergent AEs between the three groups was similar (48.6% in the mirabegron 25 mg group, 47.3% in the mirabegron 50 mg group, and 50.1% in the placebo group). Furthermore, most of the treatment-emergent AEs were mild or moderate and the incidence of severe treatment-emergent AEs was higher in the placebo group (3.7%) than in the mirabegron 25 mg (1.9%) and 50 mg groups (1.8%) [64]. The tolerability of mirabegron for treating OAB was investigated in a multicenter randomized double-blind, parallel-group placebo- and active-controlled trial, which was conducted in Europe and Australia [56]. The rate of treatment-emergent AEs was similar between the placebo, mirabegron 50 mg and 100 mg and tolterodine ER 4 mg groups. Most treatment-emergent AEs were mild or moderate in all study groups. The number of patients discontinuing study drug due to a treatment-emergent AE was 2.6, 4.9, 3.2 and 4.4% for placebo, mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg groups, respectively. Hypertension was the most common AE; it was reported in 7.7, 5.9, 5.4 and 8.1% for placebo, mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg groups, respectively. Interestingly the incidence of dry mouth in the mirabegron 50 and 100 mg groups was similar to placebo (2.8, 2.8 and 2.6%, respectively) while it was much higher in the tolterodine ER 4 mg group (10.1%) [56].

A safety evaluation of mirabegron was also performed in another Phase III, randomized, parallel group, double-blind, placebo-controlled, multicenter trial by Nitti *et al*. [57]. The overall proportion of patients with treatment-emergent AEs and the proportion with more commonly reported treatment-emergent AEs were similar between the study groups with the exception of urinary tract infections, which were observed with a higher incidence in both mirabegron groups. Two deaths were reported; however, neither death was considered related to the study drug [57].

Table 2. Mirabegron (Phase II studies): main adverse events (%).

Clinical trial	Overall	Cardiac	Palpitations	Nausea	Dry mouth	Nervous system disorders	Dizziness	Headache
A proof-of-concept study: Mirabegron, a new therapy for overactive bladder [62]	Placebo: 24.2 MIRA, 100 mg b.i.d. group: 18.5 MIRA, 150 mg b.i.d. group: 24.6 TOL, 4 mg ER QD group: 26.6	Placebo: 4.5 MIRA, 100 mg b.i.d. group: 0 MIRA, 150 mg b.i.d. group: 4.6 TOL, 4 mg ER QD group: 1.6	Placebo: 1.5 MIRA, 100 mg b.i.d. group: 0 MIRA, 150 mg b.i.d. group: 4.6 TOL, 4 mg ER QD group: 0	Placebo: 0 MIRA, 100 mg b.i.d. group: 1.5 MIRA, 150 mg b.i.d. group: 1.5 TOL, 4 mg ER QD group: 3.1	Placebo: 1.5 MIRA, 100 mg b.i.d. group: 0 MIRA, 150 mg b.i.d. group: 6.2 TOL, 4 mg ER QD group: 4.7	Placebo: 6.1 MIRA, 100 mg b.i.d. group: 6.2 MIRA, 150 mg b.i.d. group: 7.7 TOL, 4 mg ER QD group: 10.9	Placebo: 0 MIRA, 100 mg b.i.d. group: 1.5 MIRA, 150 mg b.i.d. group: 4.6 TOL, 4 mg ER QD group: 1.6	Placebo: 3.0 MIRA, 100 mg b.i.d. group: 4.6 MIRA, 150 mg b.i.d. group: 4.6 TOL, 4 mg ER QD group: 6.3
A Phase II dose-ranging study of mirabegron in patients with overactive bladder [63]	Placebo: 15.4 MIRA, 25 mg QD group: 20.1 MIRA, 50 mg QD group: 22.5 MIRA, 100 mg QD group: 21.4 MIRA, 200 mg QD group: 22.2 TOL, 4 mg ER QD group: 15.3	Placebo: 0.6 MIRA, 25 mg QD group: 2.4 MIRA, 50 mg QD group: 4.1 MIRA, 100 mg QD group: 1.2 MIRA, 200 mg QD group: 3.0 TOL, 4 mg ER QD group: 1.2	Placebo: NA MIRA, 25 mg QD group: NA MIRA, 50 mg QD group: NA MIRA, 100 mg QD group: NA MIRA, 200 mg QD group: NA TOL, 4 mg ER QD group: NA	Placebo: 1.2 MIRA, 25 mg QD group: 1.2 MIRA, 50 mg QD group: 1.2 MIRA, 100 mg QD group: 4.2 MIRA, 200 mg QD group: 0.6 TOL, 4 mg ER QD group: 1.2	Placebo: 1.8 MIRA, 25 mg QD group: 3.0 MIRA, 50 mg QD group: 1.8 MIRA, 100 mg QD group: 3.0 MIRA, 200 mg QD group: 1.8 TOL, 4 mg ER QD group: 3.5	Placebo: 3.6 MIRA, 25 mg QD group: 4.1 MIRA, 50 mg QD group: 5.9 MIRA, 100 mg QD group: 4.2 MIRA, 200 mg QD group: 3.6 TOL, 4 mg ER QD group: 1.2	Placebo: 0.6 MIRA, 25 mg QD group: 0 MIRA, 50 mg QD group: 3.6 MIRA, 100 mg QD group: 1.2 MIRA, 200 mg QD group: 0 TOL, 4 mg ER QD group: 0	Placebo: 2.4 MIRA, 25 mg QD group: 3.6 MIRA, 50 mg QD group: 3.0 MIRA, 100 mg QD group: 2.4 MIRA, 200 mg QD group: 1.8 TOL, 4 mg ER QD group: 1.2

b.i.d.: Twice daily; ER: Extended release; MIRA: Mirabegron; QD: Once daily; TOL: Tolterodine.

A randomized double-blind, active-controlled Phase III study investigating the 12-month efficacy and safety of mirabegron was conducted at 306 sites in Europe, the USA, Canada, South Africa, Australia and New Zealand [60]. Treatment-emergent AEs were recorded in 59.7, 61.3 and 62.6% of patients, respectively, and the majority were mild or moderate. Serious treatment-emergent AEs were reported in 5.2, 6.2 and 5.4% of patients, respectively. Discontinuations related to AEs were similar across study groups, occurring in 6.4, 5.9 and 6.0% of patients on mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg, respectively. During the study, five deaths occurred (three in the mirabegron 50 mg group and two in the tolterodine ER 4 mg group), and all five were considered unrelated to the study drug [60]. **Table 3** summarizes the incidence of AEs reported in the different Phase III trials.

5.2 Cardiac safety

The impact of mirabegron on cardiac function is a relevant concern due to the presence of β_3-adrenoceptors on cardiac and vascular tissue. A four-arm, parallel, two-way, double-blind and placebo- and active (moxifloxacin)-controlled crossover study was conducted to evaluate the cardiac safety in 352 healthy volunteers [67]. Patients treated with mirabegron 50 or 100 mg did not have a prolongation of the QT interval, while at supratherapeutic dosage (200 mg) the QT interval was prolonged in women but not in men. The heart rate (HR) increased in a dose-dependent manner: in females, the maximum mean HR increases were 8.53, 13.63, and 20.24 beats per min (bpm) for 50, 100 and 200 mg mirabegron treatments, occurring at 5, 4 and 5 h, respectively. In males, the corresponding HR increases were 5.46, 10.90, and 14.37 bpm, occurring at 4.5, 8 and 5 h, respectively [67]. Clinical investigations reported a mean increase in the HR during treatment, but this was not associated with an increased incidence of cardiovascular AEs such as tachycardia and palpitations [62,63]. A prespecified pooled analysis of three Phase III randomized, double-blind, placebo-controlled, 12-week studies [56,57,64] evaluated efficacy and safety of QD mirabegron [68]. This analysis observed that there was a dose-dependent raise (0.6 – 2.3 bpm) from baseline to final visit in pulse rate (AM and PM measurements) in the mirabegron groups, but this was not related to a higher incidence of cardiovascular AEs [68].

6. Regulatory affairs

Mirabegron (25 or 50 mg) is the first β_3-AR agonist approved for treating OAB. It is approved in the US [69] and Japan [70], and more recently in the European Union [71] and Canada [72], for the symptomatic treatment of urgency, increased micturition frequency, and/or urgency incontinence occurring in adults with OAB [71].

7. Expert opinion

Mirabegron is the progenitor of β_3-AR agonists, and it is currently approved in all Western countries [69,71,72] and Japan [70] for the symptomatic treatment of urgency, increased micturition frequency, and/or urgency incontinence occurring in adults with OAB [71].

Phase II studies demonstrated that mirabegron was effective and safe in treating patients with OAB. It should be noticed that PPBC after treatment and the number of 'responders' were significantly higher among patients treated with mirabegron than with placebo, although with a minimal difference in terms of absolute numbers. Based on these findings, the real clinical efficacy of mirabegron may be questioned. However, these were the results from Phase II studies designed to identify the dose for subsequent Phase III trials where a significant reduction in clinical and objective parameters such as volume voided or episodes of incontinence was observed in the mirabegron group compared with placebo. Moreover, in many RCTs on OAB, the effects of the placebo are quite high; this may be explained by an actual active treatment that patients in the placebo group usually receive: a bladder retraining. All patients have, in fact, to fill in a bladder diary during the trial recording the voided volume, the urgency, as well as the incontinence episodes. This is, by all means, a form of bladder retraining that has a level of evidence 1 with a grade of recommendation A according to the 2012 International Consultaion on Incontinence.

All Phase III trials demonstrated that this compound is efficacious, safe, and tolerable in treating patients with OAB; in particular, it decreases the number of urinary incontinence and micturition episodes, as well as the number of urgency and urgency incontinence episodes, and the mean volume voided [56,57,60,62]. Furthermore, mirabegron causes clinical benefit without significant AEs in those patients who have been previously treated with AMs [65] or who were unresponsive to these drugs [66]. Current literature shows that mirabegron causes less dry mouth, constipation, urinary retention, or blurred vision than tolterodine, and interestingly the incidence of dry mouth, which is the most frequent AE with AM treatment, was similar to placebo, 50 and 100 mg mirabegron [73]. However, no study has still compared the clinical efficacy of mirabegron with other AMs in the treatment of OAB, but only in the Phase III study by Khullar *et al.* tolterodine was included as active control [56]. Therefore, head-to-head comparisons against new-generation AMs are necessary to establish the exact role of mirabegron.

Despite the current lack of evidence, mirabegron has two potential safety benefits over AM treatment. First, this agent shows a good safety profile in terms of neurological AEs, while AMs are frequently associated with headache, somnolence, and cognitive impairment; this is due to the activity of AMs on muscarinic receptors (M_1-M_5), all of which are expressed in brain tissue, and the possibility of blood–brain

Table 3. Mirabegron (Phase III studies): main adverse events (%).

Clinical trial	Any adverse event	Hypertension	Dry mouth	Nasopharyngitis	Headache	Urinary tract infection	Dizziness	Cardiac arrhythmia
A Phase III, randomized, double-blind, parallel-group, placebo-controlled, multicenter study to assess the efficacy and safety of the β_3- adrenoceptor agonist, mirabegron in patients with symptoms of overactive bladder [64]	Placebo: 50.1 MIRA, 25 mg QD group: 48.6 MIRA, 50 mg QD group: 47.3	Placebo: 8.5 MIRA, 25 mg QD group: 11.3 MIRA, 50 mg QD group: 10.5	Placebo: 2.1 MIRA, 25 mg QD group: 1.9 MIRA, 50 mg QD group: 1.6	Placebo: 3.2 MIRA, 25 mg QD group: 3.5 MIRA, 50 mg QD group: 5.7	Placebo: 4.4 MIRA, 25 mg QD group: 2.1 MIRA, 50 mg QD group: 2.7	Placebo: 2.3 MIRA, 25 mg QD group: 4.2 MIRA, 50 mg QD group: 4.8	Placebo: 0.5 MIRA, 25 mg QD group: 2.3 MIRA, 50 mg QD group: 0.9	Placebo: NA MIRA, 25 mg QD group: NA MIRA, 50 mg QD group: NA
Efficacy and tolerability of mirabegron, a β_3-adrenoceptor agonist, in patients with overactive bladder: results from a randomized European-Australian Phase III trial [56]	Placebo: 43.3 MIRA, 50 mg QD group: 42.8 MIRA, 100 mg QD group: 40.1 TOL, 4 mg ER QD group: 46.7	Placebo: 7.7 MIRA, 50 mg QD group: 5.9 MIRA, 100 mg QD group: 5.4 TOL, 4 mg ER QD group: 8.1	Placebo: 2.6 MIRA, 50 mg QD group: 2.8 MIRA, 100 mg QD group: 2.8 TOL, 4 mg ER QD group: 10.1	Placebo: 1.6 MIRA, 50 mg QD group: 2.8 MIRA, 100 mg QD group: 2.8 TOL, 4 mg ER QD group: 2.8	Placebo: 2.8 MIRA, 50 mg QD group: 3.7 MIRA, 100 mg QD group: 1.8 TOL, 4 mg ER QD group: 3.6	Placebo: 1.4 MIRA, 50 mg QD group: 1.4 MIRA, 100 mg QD group: 1.8 TOL, 4 mg ER QD group: 3.6	Placebo: NA MIRA, 50 mg QD group: NA MIRA, 100 mg QD group: NA TOL, 4 mg ER QD group: NA	Placebo: 1.0 MIRA, 50 mg QD group: 2.2 MIRA, 100 mg QD group: 1.8 TOL, 4 mg ER QD group: 3.2
Results of a randomized Phase III trial of mirabegron in patients with overactive bladder [57] Randomized double-blind, active-controlled Phase III study to assess 12-month safety and efficacy of mirabegron, a β_3-adrenoceptor agonist, in overactive bladder [60]*	Placebo: NA MIRA, 50 mg QD group: NA MIRA, 100 mg QD group: NA MIRA, 50 mg QD group: 59.7 MIRA, 100 mg QD group: 61.3 TOL, 4 mg ER QD group: 62.6	Placebo: 6.6 MIRA, 50 mg QD group: 6.1 MIRA, 100 mg QD group: 4.9 MIRA, 50 mg QD group: 9.2 MIRA, 100 mg QD group: 9.8 TOL, 4 mg ER QD group: 9.6	Placebo: 1.5 MIRA, 50 mg QD group: 0.5 MIRA, 100 mg QD group: 2.1 MIRA, 50 mg QD group: 2.8 MIRA, 100 mg QD group: 2.3 TOL, 4 mg ER QD group: 8.6	Placebo: 2.9 MIRA, 50 mg QD group: 3.4 MIRA, 100 mg QD group: 2.5 MIRA, 50 mg QD group: 3.9 MIRA, 100 mg QD group: 4.3 TOL, 4 mg ER QD group: 3.1	Placebo: 2.0 MIRA, 50 mg QD group: 3.2 MIRA, 100 mg QD group: 3.0 MIRA, 50 mg QD group: 4.1 MIRA, 100 mg QD group: 3.2 TOL, 4 mg ER QD group: 2.5	Placebo: 1.8 MIRA, 50 mg QD group: 2.7 MIRA, 100 mg QD group: 3.7 MIRA, 50 mg QD group: 5.9 MIRA, 100 mg QD group: 5.5 TOL, 4 mg ER QD group: 6.4	Placebo: NA MIRA, 50 mg QD group: NA MIRA, 100 mg QD group: NA MIRA, 50 mg QD group: 2.7 MIRA, 100 mg QD group: 1.6 TOL, 4 mg ER QD group: 2.6	Placebo: NA MIRA, 50 mg QD group: NA MIRA, 100 mg QD group: NA MIRA, 50 mg QD group: 3.9 MIRA, 100 mg QD group: 4.1 TOL, 4 mg ER QD group: 6.0

*Results are shown at 12-month follow-up.

b.i.d.: Twice daily; ER: Extended release; MIRA: Mirabegron; QD: Once daily; TOL: Tolterodine.

barrier penetration (with the exception of trospium chloride). Thus, future research should focus on the assessment of mirabegron concentrations in the central nervous system, clinical evaluation of neurocognition and memory, since β_3-AR mRNA has been observed in discrete regions of the human brain (such as hippocampus, hypothalamus, amygdala, and cerebral cortex) [73,74]. If the neurological advantages are confirmed, mirabegron may become a first-line option for the treatment of patients with cognitive impairment. However, this potential advantage of mirabegron in the elderly population should be balanced against the risk of cardiovascular AEs, in particular in women; on the other hand, also AMs may also cause QT prolongation and increase HR and the CV risk due to drug–drug interactions in patients with OAB [75].

The second advantage is that in animal studies mirabegron decreases the frequency of rhythmic bladder contractions during the filling phase without suppressing amplitude during micturition [73,76-78]. This may be of help for treating OAB associated with bladder outlet obstruction diminishing the risk of voiding difficulties in comparison with AMs [73]. In line with these considerations, a recent study evaluating urodynamic parameters in men with lower urinary tract symptoms and bladder outlet obstruction treated with mirabegron demonstrated that the compound does not negatively affect voiding urodynamics (maximum urinary flow and detrusor pressure at maximum urinary flow) compared with placebo after 12 weeks of treatment [79].

Research should also evaluate the potential of the combination of mirabegron with AMs [80,81]. In the Symphony trial, Abrams *et al.* investigated combinations of mirabegron (25 or 50 mg) with solifenacin (2.5, 5 or 10 mg) or placebo QD for 12 weeks compared with monotherapy with mirabegron or solifenacin [80]. Preliminary results from the Symphony trial concluded that the combination of the two compounds provided higher efficacy than solifenacin 5 mg alone for change from baseline to end of treatment in mean volume voided/micturition (all dose combinations) and in the number of episodes of micturitions/24 h (10 + 25 mg, 5 + 50 mg, 10 + 50 mg) [80]. A randomized, double-blind, parallel-group, placebo- and active-controlled, multicenter sponsored trial (Synergy) is ongoing, and it is currently recruiting patients to evaluate the efficacy, safety, and tolerability of combinations of solifenacin succinate and mirabegron compared with solifenacin succinate and mirabegron monotherapy in the treatment of OAB [81]. If the positive findings from the Symphony trial are confirmed, pharmaceutical companies should be encouraged to develop combinations of two agents (one β_3-AR agonist and one AM) at lower doses to raise efficacy while lowering the incidence of AEs.

Further studies should be designed to assess the impact of mirabegron on heart function. In normal heart, β_3-ARs may mediate a moderate negative inotropic effect, but in heart failure it may protect against adverse effects of excessive catecholamine stimulation by action on excitation–contraction coupling, electrophysiology, or remodeling. No evidence suggests direct action of β_3-ARs agonists on the sinus node and, therefore, modifications in HR [82]. However, a study conducted in healthy volunteers demonstrated that mirabegron increased the HR in a dose-dependent manner [67]. On the other hand, in clinical studies mirabegron did not cause relevant changes in HR [68]. It is unclear whether this discrepancy is caused by different administration schedules and, therefore, this topic should be further deepened.

Another field for future research is represented by the investigation of the interaction of mirabegron with CYP2D6 inhibitors. For example, a commonly prescribed anti-hypertensive such as metoprolol is metabolized by CYP2D6 and caution is required since hypertension is a frequent comorbidity of OAB and hypertension is a common AE of the treatment with mirabegron. Finally, current literature completely lacks studies on the efficacy and safety of mirabegron in the pediatric population and such trials are awaited.

In conclusion, both Phase II and III trials have shown that mirabegron is efficacious and safe in treating patients with OAB [56,57,62-64]. In particular, all Phase III trials showed that treatment with mirabegron significantly decreases the number of incontinence episodes and micturitions per 24 h. Furthermore, mirabegron improves secondary end points such as number of urgency and urgency incontinence episodes per 24 h, urine volume voids per micturition and QoL [56,57,64]. Phase II and III trials also showed that mirabegron is safe and well tolerated by patients, with an incidence of reported AEs quite similar to placebo [56,57,62-64].

Declaration of interest

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