UIJ UroToday International Journal®

www.urotodayinternationaljournal.com
Volume 4 - December 2011

A β3 Agonist, Mirabegron for the Treatment of Overactive Bladder

Motoaki Saito, Fotios Dimitriadis, Fumiya Ohmasa, Seiya Inoue, Keisuke Satoh
Division of Molecular Pharmacology, Tottori University School of Medicine, Yonago, Japan
Submitted Oct 10, 2011 - Accepted for Publication October 27, 2011

ABSTRACT

Overactive bladder syndrome (OAB) has a negative impact on quality of life and social functioning. Although antimuscarinic drugs are the first line of treatment for OAB, adverse effects and the limitations of efficacy hinder their use. β-adrenoceptors are found in the bladder body and mediate relaxation to noradrenalin. Stimulation of β3-adrenoceptor subtypes has been shown to relax bladder smooth muscle in humans. Mirabegron, a novel selective β3-adorenoceptor agonist, is in development for the treatment of OAB. Phase II placebo-controlled clinical trials showed that mirabegron significantly improved the majority of variables when administered to patients with OAB. Mirabegron is well tolerated with significant efficacy in reducing the number of incontinence episodes and the mean micturition frequency. Commonly reported adverse effects were gastrointestinal adverse events and headache. The lower propensity of dry mouth and constipation while taking mirabegron may make it an attractive drug candidate for the treatment of OAB symptoms.

OVERACTIVE BLADDER SYNDROME AND LOWER URINARY TRACT SYMPTOMS

Overactive bladder (OAB) syndrome, characterized by urgency with or without incontinence, frequency, and nocturia, is a common disorder [1]. OAB affects 16.6% of the European population over 40 years [2] old, and has a prevalence of 17% in the United States [3] and 12% in Japan [4]. Both men and women are equally affected by OAB, and the incidence rate increases with age [1-4]. It is assumed that OAB syndrome has been caused by detrusor overactivity (DO), which is a urodynamic diagnosis based on the occurrence of involuntary detrusor contraction during cystometry [5]. However, OAB is often but not always associated with DO. The multifactorial pathophysiology of OAB syndrome makes it difficult to conceive that one drug or drug principle would be effective in all patients with OAB syndrome.

KEYWORDS: Mirabegron; Adrenergic β3 receptor; Bladder; OAB (overactive bladder); LUTS (lower urinary tract symptoms)

CORRESPONDENCE: Fotios Dimitriadis, MD, PhD, Division of Molecular Pharmacology, Tottori University School of Medicine, 86 Nishimachi, Yonago 683-8503, Japan (helabio@yahoo.gr).

CITATION: *UroToday Int J*. 2011 Dec;4(6):art 70. http://dx.doi.org/10.3834/uij.1944-5784.2011.12.03

Acronyms and Abbreviations

ACh, acetylcholine
M1-4, muscarinic subtypes, 1-4 respectively
PLC, Phospholipase-C
IP3/DAG, Inositol 1,4,5 Trisphosphate/1,2-Diacylglycerol
NA, noradrenalin
AC, adenylyl cyclase
cATP, cyclic adenosine triphosphate

UroToday International Journal®

review

A β3 Agonist, Mirabegron for the Treatment of Overactive Bladder

REGULATION OF AUTONOMIC CONTROL OF URINARY BLADDER CONTRACTILITY

Branches of the autonomic nervous system innervate the lower urinary tract, and the response to the stimulation of these nerves is mediated through adrenergic and cholinergic receptors (Figure 1). The efferent parasympathetic pathway provides the major excitatory innervation of the bladder detrusor (Figures 1 and 2) [6, 7]. Preganglionic axons emerge, as does the pelvic nerve, from the sacral parasympathetic nucleus in the intermediolateral column of sacral spinal segments S2–S4 and synapse in the pelvic ganglia, as well as in small ganglia on the bladder wall, releasing acetylcholine (ACh). ACh excitation of postsynaptic neurons is mediated by nicotinic receptors. Postganglionic axons continue for a short distance in the pelvic nerve and terminate in the detrusor layer where they transmit ACh to the smooth muscle fibers with consequent contractions of the bladder. This stimulatory effect of ACh at the postganglionic axon terminal is mediated by muscarinic receptors in detrusor cells. Two muscarinic subtypes, M2 and M3, are present in the bladder. Although M2 is most abundant in detrusor cells (70 to 80%), the M3 subtype is the major receptor, mediating stimulation of detrusor contractions [6, 8].

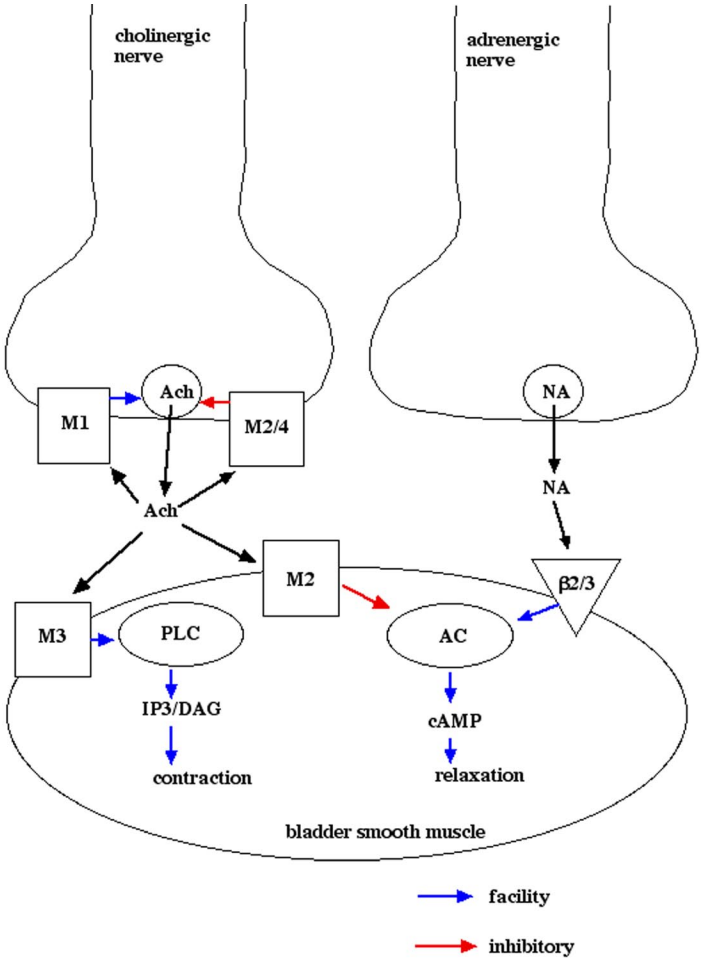
Sympathetic nerves stimulate smooth muscle contraction in the urethra and bladder neck and cause relaxation of the detrusor (Figure 1). Preganglionic sympathetic neurons are located in the intermediolateral column of thoracolumbar cord segments T11–L1 (Figure 2) [9-10]. Most of the preganglionic fibers synapse with postganglionic neurons in the inferior mesenteric ganglia. The preganglionic neurotransmitter is ACh, which acts via the nicotinic receptors in the postganglionic neurons. The postganglionic axons travel in the hypogastric nerve and transmit noradrenalin (NA) at their terminals. The major terminals are in the urethra and bladder neck, as well as in the bladder body and postganglionic parasympathetic neurons in the pelvic ganglia. The NA stimulates contraction of the urethral and bladder neck smooth muscle via α1-adrenoceptors, and causes relaxation of the detrusor via β3-adrenoceptors (Figure 2) [11].

EXPRESSIONS OF β3-ADRENOCEPTORS AND THEIR FUNCTIONS IN THE URINARY BLADDER

The β-adrenoceptors are members of the GTP-binding protein-(G-protein) coupled receptor (GPCR) family. They present 7 transmembrane regions and, currently, they are classified into β1-, β2-, and β3- subtypes [12-15]. All 3 types of β-adrenoceptor are expressed in smooth muscles, which exhibit relaxation in response to stimulation of the β-adrenoceptors. Each subtype

Figure 1. Typical regulation of muscarinic receptors and beta-adrenoceptors in the bladder smooth muscle.

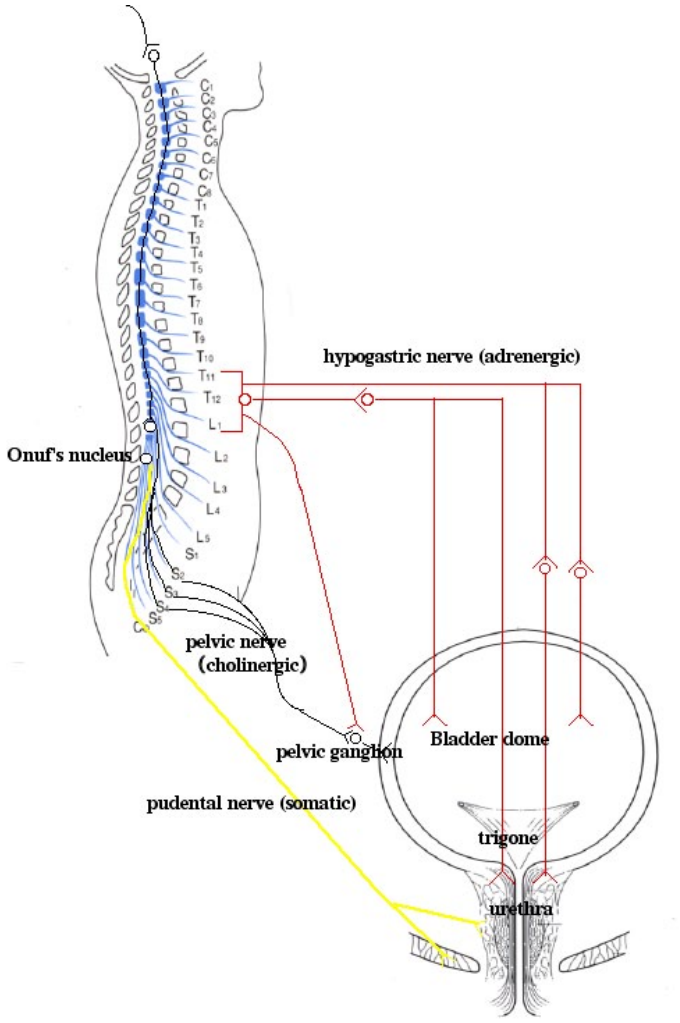
http://dx.doi.org/10.3834/uij.1944-5784.2011.12.03f1



shows tissue-specific expression patterns, which vary according to species. As mentioned above, the β1-, β2-, and β3-adrenoceptor subtypes are all coupled to the G_s-protein (G_s) and cAMP, elevated as a consequence of activation of adenylyl cyclase and is a key player triggering β-adrenoceptor-mediated smooth muscle relaxation (Figure 1) [15].

The presence of β-adrenoceptors in rat and human bladders at the mRNA level has been studied using Northern blots, PCR, and *in situ* hybridization. Studies in the human bladder have detected mRNA for all three β-adrenoceptor subtypes [11, 16-19]. Based on quantitative PCR experiments, it appears that the β3-adrenoceptor

Figure 2. The efferent sympathetic and parasympathetic innervations in the lower urinary tract.
http://dx.doi.org/10.3834/uij.1944-5784.2011.12.03f2



accounts for more than 95% of all β-adrenoceptor mRNA in the human bladder [11]. The presence of β3-adrenoceptors mRNA in the human detrusor has also been confirmed in *in situ* hybridization studies [19]. The identification of β-adrenoceptors at the protein level is typically based on binding studies with radioligands, such as [^{125}I]iodocyanopindolol, [^{125}I]iodopindolol, [^{3}H]CGP-12177, or [^{3}H]dihydroalprenolol. Radioligand-binding studies on bladder β-adrenoceptors have been reported for humans [18, 20-22]. Saturation-binding studies, with various radioligands, have reported 22 to 60 fmol mg^{-1} protein in humans [18, 20-22]. However, many β-adrenoceptor ligands are not so selective for β3 subtype and, at least in humans, have even slightly lower affinity for β3- than for β1- and β2-adrenoceptors [23]. In addition, the radioligands used in all of the above studies are unlikely to label a major fraction of possibly present β3-adrenoceptors due to their low affinity for this subtype, at least in humans. Thus, the currently available radioligand-binding techniques are probably inadequate to detect the presence of β3-adrenoceptors [24]. Early reports on human bladder relaxation already proposed that this does not occur via a β1- or β2-adrenoceptor [25]. This early hypothesis has been further supported by several recent studies confirming that human bladder relaxation indeed occurs via a β3-adrenoceptor and not via β1- or β2-adrenoceptors [11, 17, 19, 22, 26]. In agreement with the predominant expression of β3-adrenoceptor mRNA in the human bladder, these reports demonstrate that β3-adrenoceptor subtypes play a key role in bladder relaxation in vitro. In addition, it has been shown that β3-adrenoceptor agonists can improve bladder overactivity in experimental rat models [27-28].

Oral administration of the β3-adrenoceptor agonist, FK-175 (ethyl [(S)–8–[(R)–2–(3–chlorophenyl)–2–hydroxyethylamino]–6, 7, 8, 9–tetrahydro–5H–benzocyclohepton–2–yloxy] acetate monohydrochloride monohydrate) at a dose of 10 mg/kg, significantly increased bladder capacity by 158 µl during conscious cystometry in rats with increased urinary frequency induced by ibotenic acid injection [29]. The increase in bladder capacity produced by FK-175 was not associated with any change in micturition pressure or threshold pressure during cystometry in the rat model [29]. The efficacy of β3-adrenoceptor agonists against bladder instability was evaluated in a BOO rat model by cystometry under urethane anesthesia [28]. Oral and IV administration of β3-adrenoceptor agonist CL-316243, at a dose of 10 mg/kg, significantly increased the voiding interval, bladder compliance, and capacity without any change in the residual bladder volume [28]. Recently, roles of β3-adrenoceptors in urothelium have been investigated. Murakami and his associates [30] (2007) reported that the relaxation responses of the bladder to isoprenaline do not appear to involve the urothelium or NO release in vitro [30]. However, contractile responses to carbachol were inhibited in the presence of an intact urothelium, and this might reflect the release of an inhibitory factor other than NO [30]. Otsuka and his colleague [31] (2008) reported the presence of β1-, β2-, and β3-adrenoceptors in human urinary bladder urothelium [31]. Furthermore, they suggest that urothelial β-adrenoceptors induce the release of a urothelium-derived factor, which inhibits the β-adrenoceptor agonist-induced relaxation of the human detrusor smooth muscle. This inhibitory mechanism might not involve NO [31]. These data indicate that urothelial β-adrenoceptors may have direct and/or indirect effects on relaxation responses in the detrusor smooth muscle.

UroToday International Journal®

review

A β3 Agonist, Mirabegron for the Treatment of Overactive Bladder

CURRENT PHARMACOTHERAPY AGAINST OAB

OAB can be managed with bladder and behavioral training, biofeedback, electric stimulation, pharmacological treatments, or with a combination of these therapies. However, antimuscarinic agents (muscarinic antagonists), such as oxybutynin, propiverine, tolterodine, trospium, darifenacin, solifenacin, imidafenacin, and fesoterodine are currently the first-line pharmacotherapy for OAB [32, 33]. Antimuscarinic agents were developed to target the main pathway controlling detrusor contraction in which acetylcholine released from parasympathetic nerves activated muscarinic receptors. As aforementioned, of the 5 subtypes of muscarinic receptors, M2 and M3 subtypes are the main subtypes found in the bladder. An M3 receptor directly mediates detrusor contraction [34, 35], whereas an M2 receptor is thought to have a minor role in normal contraction. Recently, there is increasing evidence that stimulation of muscarinic receptors on urothelium causes the release of a urothelium-derived inhibitory factor that can regulate detrusor contraction [36, 37]. In addition, there is evidence indicating that antimuscarinic agents might inhibit detrusor contraction through the modulation of sensory pathways [33]. In fact, the muscarinic receptors in the urothelium/suburothelium have been confirmed, but their role in the sensory afferent pathways remains unclear. Recently, however, muscarinic receptors on the urothelium and suburothelium have been an important component of sensory function [8], and there is evidence that stimulation of these receptors can alter the release of other transmitters and regulate bladder-voiding reflexes [36, 38-39]. Thus, muscarinic receptor pathways could be directly involved in afferent function of the bladder.

In a recent meta-analysis of 83 studies, Chapple and his associates [32] (2008) investigated the efficacy, tolerability, and safety of antimuscarinic agents, and demonstrated that antimuscarinics are more effective than a placebo [32]. Although tolerability was good, the patients treated with antimuscarinics were found to have significantly higher withdrawal rates compared to the patients treated with a placebo. In addition, no serious adverse events for any product were statistically significant in comparison to a placebo. The most commonly reported adverse event was dry mouth (mild, moderate, severe) (29.6% on treatment vs. 7.9% on a placebo), followed by pruritus (15.4% on treatment vs. 5.2% on a placebo). Moreover, the following adverse events were reported at statistically and significantly higher levels in active treatments than in a placebo: blurred vision, constipation, erythema, fatigue, pruritus, increased sweating, and urinary retention. Health-related quality of life has been improved after treatment with antimuscarinic drugs. However, they noticed that the study presented some limitations, including restrictions on the types of patients typically included in overactive bladder trials and topics that have not been adequately addressed in the current antimuscarinic literature [32].

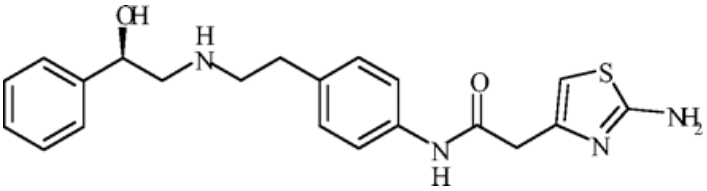
EFFECT OF MIRABEGRON (YM178) ON BLADDER FUNCTION IN HUMANS AND IN ANIMAL EXPERIMENTAL MODELS

The chemical structure of mirabegron (YM178) is shown in Figure 3. Takasu and co-workers [40] (2007) first reported the pharmacological properties of mirabegron in human β-adrenoceptor expressed in Chinese hamster ovary (CHO) cells and in rat and human bladder strips [40]. Mirabegron increased cyclic AMP accumulation in CHO cells expressing human β3-adrenoceptor, and its EC50 value was 22.4 nM, out of which mirabegron for human β1- and β2-adrenoceptors were 500 times or more. The ratio of intrinsic activities of mirabegron versus maximal response induced by isoproterenol was 0.1, 0.1, and 0.8 for human β1-, β2-, and β3-adrenoceptors, respectively. The relaxant effects of mirabegron were evaluated in rats and human bladder strips precontracted with carbachol and were compared with those of isoproterenol. EC50 values of mirabegron and isoproterenol in rat bladder strips were 5.1 and 1.4 μM, respectively, whereas those in human bladder strips were 0.78 and 0.28 μM, respectively. In in vivo study, mirabegron, at a dose of 3 mg/kg IV, decreased the frequency of rhythmic bladder contraction induced by intravesical filling of saline without suppressing its amplitude in anesthetized rats. This data suggests that mirabegron has good selectivity and agonist potency for human β3-adrenoceptors. There are some reports indicating that mirabegron dose-dependently decrease the frequency of non-micturition bladder contraction without the increase in residual urine in a rat bladder outlet obstruction model [41, 42]. These data indicated that mirabegron has different effects on bladder activity during filling due to antimuscarinics [44, 45]. Someya and his colleagues [43] (2010) reported that while using a conscious, water-loaded cynomolgus monkey model, mirabegron significantly increased the mean voided volume per micturition and decreased micturition frequency [43]. Furthermore, in a recent report, mirabegron enhanced urine storage function at low-pressure bladder filling via activation of β3-adrenoceptors in the bladder without affecting the voiding contraction in the anesthetized rat bladder [41]. This data suggests that mirabegron significantly increases bladder capacity and does not directly inhibit voiding bladder contractions.

UIJ / Vol 4 / Iss 6 / December / http://dx.doi.org/10.3834/uij.1944-5784.2011.12.03

ISSN 1944-5792 (print), ISSN 1944-5784 (online)

Figure 3. Chemical structure of mirabegron (YM178).
http://dx.doi.org/10.3834/uij.1944-5784.2011.12.03f3



PHARMACOKINETIC AND PHARMACODYNAMIC DATA OF MIRABEGRON

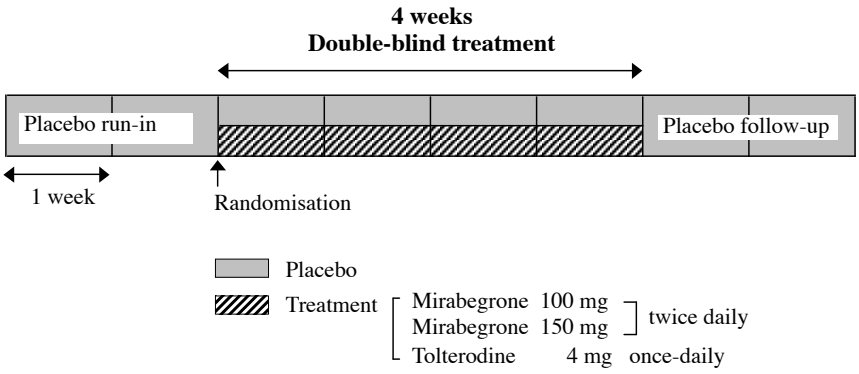
Mirabegron is an orally active β3-adrenoceptor (AR) agonist, developed by Astellas Pharmaceuticals, Inc. The new drug application of mirabegron is currently being reviewed by the FDA for the indication of symptomatic treatment of OAB and is currently undergoing Phase III clinical trials in several countries. The highly lipophilic nature of mirabegron makes the hepatic route the most preferred route of metabolism for mirabegron. In the Phase I pharmacokinetic study on mirabegron, 16 healthy volunteers enrolled, phenotyped prior to going into the study as either poor (n = 8) or extensive (n = 8) metabolizers of cytochrome P450 2D6 (CYP2D6), a member of the cytochrome P450 mixed-function oxidase system, based on the rate of dexamethasone metabolism [44]. The volunteers in the study received a 160 mg single oral dose of mirabegron after overnight fasting. Volunteers previously phenotyped as poor metabolizers excreted a slightly higher urinary fraction of mirabegron (15.4 ± 4.2%) than extensive metabolizers (11.7 ± 3.0%). This variability in the urinary excretion of mirabegron has prompted its disposition study in patients with mild, moderate, or severe renal impairment. Mirabegron took nearly the same time to reach Tmax in both extensive and poor metabolizers, and its respective half-life of 23 and 25 hours was demonstrably longer. There was a greater variation in the values of Cmax and AUC_{∞} between groups. The pharmacokinetic parameters of mirabegron do not show the conventional dose-independent behavior seen with most drugs [44]. Like other orally absorbed drugs, its oral bioavailability is prone to influence from the timing of food intake. The effect of food on the pharmacokinetics of mirabegron is currently being investigated. Mirabegron is also liable to undue influence on its pharmacokinetics due to the different oral formulations with different release rates. This potential drawback is the subject of a current study comparing the pharmacokinetics of different oral mirabegron formulations against mirabegron administered intravenously. The results of these studies are currently awaited [45-47].

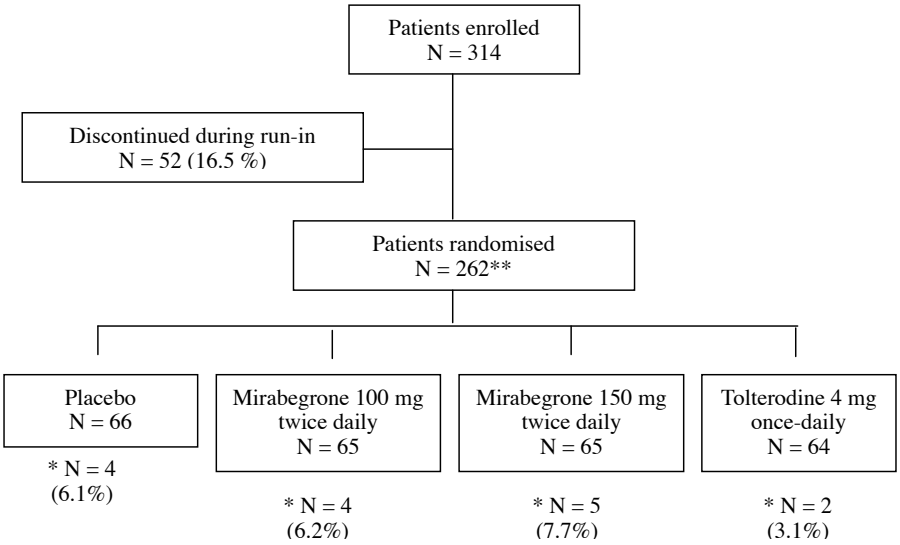
CLINICAL APPLICATION AND EFFICACY OF MIRABEGRON

The efficacy, safety, and tolerability of oral mirabegron in treating OAB was first evaluated in a multi-center, randomized, double-blind, Phase II dose-finding study on 262 patients in 2006 at 31 clinical sites in 6 European countries [51]. The study named "BLOSSOM" (β3-adrenoceptor agonist in Lowering OAB Symptoms Study compared to Oral anti-Muscarinic) was conducted as a randomized, double blind, parallel-group, proof-of-concept study, which tested the efficacy of mirabegron (100 or 150 mg/twice daily [b.i.d.]) against placebo or tolterodine extended release (4 mg once daily). The main inclusion criteria were, at study entry, both genders aged over 16 years; symptoms of OAB for more than 3 months; the capability to complete micturition diary, and a randomized average micturition frequency of more than 8 times per 24-hour period during the 3-day micturition diary period; and more than 3 episodes of urgency with or without incontinence during the 3-day micturition diary period. The protocol of this study is shown in Figure 4. The enrolled patients were first recruited into a single-blind, 2-week placebo run-in period after which they were blindly randomized to any of 4 treatment arms for 4 weeks, including mirabegron 100 mg b.i.d. (n = 65 patients), mirabegron 150 mg b.i.d. (n = 65), placebo (n = 66), or tolterodine extended release, 4 mg once daily (n = 64). Treatment with mirabegron was statistically and significantly superior to a placebo with respect to the secondary efficacy variables of the mean volume per micturition and the mean number of incontinence episodes, nocturia episodes, and urge incontinence episodes per 24 hours in 1 or both doses (Figure 5). The results of a second Phase II multi-center, dose-ranging study named "DRAGON" (a dose-ranging study [Phase IIb] using mirabegron [a novel, selective β3-adrenoceptor agonist]) was recently presented in conference in which a single daily dose regimen of mirabegron (25, 50, 100, 200 mg oral [p.o.]) was evaluated over 12 weeks in OAB patients (n = 1110) [48]. This study was designed as a 12-week, multicenter, double blind, randomized parallel-group, placebo- and active-controlled (tolterodine [4 mg/day]). Enrolled patients were aged over 18 years, symptoms of OAB were more than 3 months, patients experienced more than 8 micturitions per 24 hours, and more than 3 urgency episodes occurred with or without incontinence during a 3-day micturition diary period. Data from 919 patients was analyzed at the end of the study with a nearly equal number of patients at each dose level of mirabegron and in the

Figure 4. The protocol of BLOSSOM (β3-adrenoceptor agonist in Lowering OAB Symptoms Study compared to Oral anti-Muscarinic) study. YM178, mirabegron.

http://dx.doi.org/10.3834/uij.1944-5784.2011.12.03f4





* Discontinued

** 1 patient randomised to tolterodine did not take study medication;
1 patient randomised to tolterodine had not post baseline data

placebo group. Regarding the primary end-point of the study, the analysis of the results, 12 weeks post-treatment, showed statistically significant dose-dependent reductions in the mean number of micturitions in range of 1.9 to 2.2 in a 24-hour period with mirabegron compared to a reduction of 1.4 for the placebo group. The study also noted that mirabegron caused a dose-dependent increase in the mean urine volume voided in each micturition in range of 15.3 to 33.3 ml compared to 7.3 ml for a placebo. It decreased the number of incontinence episodes by 1.1 to 1.4 compared to only 0.5 for a placebo, decreased

Figure 5. Efficacy of mirabegron in the BLOSSOM study. * Significantly different from the placebo group.
http://dx.doi.org/10.3834/uij.1944-5784.2011.12.03f5

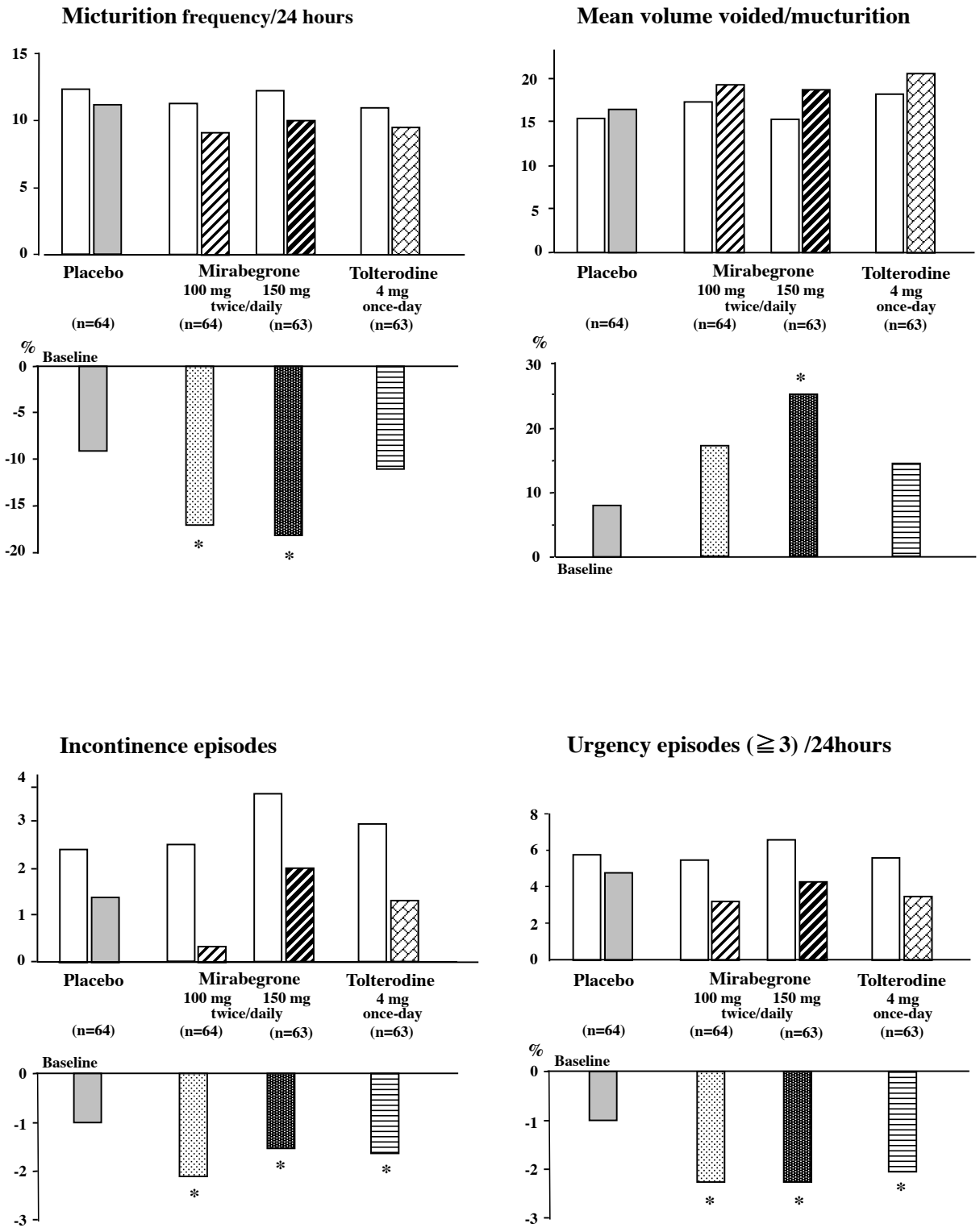


Table 1. Summary data of DRAGON study.
http://dx.doi.org/10.3834/uij.1944-5784.2011.12.03t1

Variables (per 24-hour period)	Placebo	Mirabegron (once daily)			
		25 mg	50 mg	100 mg	200 mg
Micturition (primary endpoint)	-1.4	-1.9	-2.1*	-2.1*	-2.2*
Volume void per micturition (ml)	7.3	15.3	27.3*	25.6*	33.3*
Incontinence episodes	-0.5	-1.4*	-1.2*	-1.1	-1.1
Urgency incontinence episodes	-0.4	-1.3*	-1.1	-1.2*	-1.2*
Urgency episodes (grade ≥3)	-1.1	-1.8*	-1.7	-2.3*	-2.5*

* significantly different from placebo, p <0.05

Table 2. Percentage of patients reporting adverse events with antimuscarinic drugs and mirabegron from BLOSSOM and DRAGON studies.
http://dx.doi.org/10.3834/uij.1944-5784.2011.12.03t2

Adverse Events	Mirabegron	Antimuscarinic drugs	Placebo
	(values from 2 clinical trials; %)	(values from meta-analysis; %)	
Any Adverse Events	40.08-45.2	53.4	39.9
Dry mouth	1.8-3.0	29.6	7.9
Constipation	1.8-2.4	7.7	3.9
Dyspepsia	0.6-2.4	4.7	2.1
Nausea	0.6-4.2	3.2	3.1
Headache	6.9	5.9	4.9
Blurred vision	3.6	3.8	2.6
Dizziness/palpitations	0.2-3.6	3.5	2.5
Psychiatric disorders	0.6	1.6	1.8
Drug-related skin reactions	1.5	15.4	5.2
Vascular disorders	1.2-3.6	Not reported	Not reported
Urinary tract infection	14.1	5.0	3.6
Urinary retention	Not reported	1.1	0.2

Data were modified from Tyagi et al.[44-46] and from Chapple et al.[34, 48, 49]

urgency incontinence episodes by 1.1 to 1.3 compared to only 0.4 for a placebo, and decreased urgency episodes by 1.7 to 2.5 compared to only 1.1 for a placebo in a 24-hour period at the end of the treatment period (Table 1). Thus, these studies demonstrated that mirabegron significantly improved the majority of variables compared with a placebo when treating patients with OAB.

SAFETY EVALUATION OF MIRABEGRON

Table 3. Percentage of patients reporting adverse events more than 2% in the Phase III study in Japan.
http://dx.doi.org/10.3834/uij.1944-5784.2011.12.03t3

Adverse events	Placebo	Mirabegron (50 mg once daily)
N	379	379
Dry mouth	2.9%	2.6%
Constipation	2.6%	3.4%
Increase in Serum ALT (GPT)	1.3%	2.4%
Increase in Serum CK (CPK)	3.7%	2.6%
Increase in Serum γ–GTP	2.4%	4.0%
Increase in Serum ALP	2.6%	2.6%

Data were modified from Betanis® Interview Form (in Japanese).[51]

The Phase I and II studies for clinical safety for mirabegron are available in the public domain. Four-times daily administration of mirabegron (100 mg) to 28 healthy volunteers for over 2 weeks was only associated with a single occurrence of headache and dysmenorrheal and orthostatic hypotension [49]. The summarized adverse events with mirabegron and antimuscarinics are shown in Table 2 [46]. The rate of the treatment side effects emerging in the BLOSSOM clinical trial for the mirabegron-treated group of patients was 39.2%, which was slightly higher in comparison with the 36.4% observed in the placebo group and lower compared to the 48.4% observed with the active comparator, tolterodine [50]. The most common adverse events associated with mirabegron included headache (6.9%) and gastrointestinal side effects (13.8%). In comparison, the patients treated with tolterodine for the same time period reported headache at a higher rate of 9.4% and gastrointestinal adverse events at 23.4% [50]. In addition, the intensity of adverse events with mirabegron was mostly mild to moderate, except in 2 patients who took the dose of 150 mg mirabegron and reported severe headaches and increased hepatic enzymes [50]. However, there were no reports of acute urinary retention at any dose of mirabegron [50]. On the other hand, treatment-related dizziness and palpitations were noted more frequently with mirabegron treatment compared to placebo and tolterodine treatment. However, mirabegron was associated with a lower incidence of dry mouth compared to reports from clinical experience with antimuscarinics. No specific adverse events led to a discontinuation of more than 1 patient in any treatment group during the double-blind treatment period. However, 3 patients receiving mirabegron (pooled analysis) discontinued prematurely due to a mild or moderate skin reaction (i.e., urticaria, rash, and allergic exanthema). In the DRAGON clinical trial, the incidence of gastrointestinal adverse events (12.1%), infections, and infestations (14.1%) were commonly associated with mirabegron, and most adverse events were of mild or moderate intensity [48]. The adverse events were responsible for the discontinuation in 3% of patients in the placebo group compared to 2.4 to 5.3% in the mirabegron group (50). In the DRAGON clinical trial, dizziness is reported to be 0.6% (1/169), 0% (0/169), 3.6% (6/169), 1.2% (2/168), and 0% (0/167), and cardiac disorder is reported to be 0.6% (1/169), 2.4% (4/169), 1.2% (2/169), 1.2% (2/168), and 3.0% (5/167) in the placebo, with mirabegron treated as a single daily dose of 25, 50, 100, and 200 mg p.o., respectively [48]. In addition, the changes in heart rate after 12 weeks of mirabegron treated with a single daily dose of 50 mg and a placebo were plus 2.74 and plus 0.77 bpm, respectively, in the Phase III studies in Japan [51]. Table 3 shows the incidence of adverse events more than 2% in the Phase III studies in Japan [51]. From these studies, adverse events in mirabegron are quite small. The safety evaluation of mirabegron is well noted and analyzed in the report by Tyagi and associates [46].

CONCLUSION

Mirabegron will be the first β3-adrenoceptor agonist to be released for patients with OAB. Mirabegron has been well tolerated and has a dose-dependent reduction of micturition frequency, episodes of urgency, and nocturia in OAB patients. The increase in these parameters after mirabegron in clinical trials is probably indicative of increased and stabilized

bladder capacity through β3-adrenoceptor activation. The lower propensity of dry mouth and constipation while taking mirabegron may make it an attractive drug candidate for the treatment of OAB symptoms in elderly patients. The long-term safety data, including the risk of drug-related cardiac and vascular events caused by mirabegron in more wide studies, is still awaited.

REFERENCES

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn*. 2002;21(2):167-78. PubMed ; CrossRef

2. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int*. 2001;87(9):760-6. PubMed ; CrossRef

3. Liberman JN, Hunt TL, Stewart WF, Wein A, Zhou Z, Herzog AR, et al. Health-related quality of life among adults with symptoms of overactive bladder: results from a U.S. community-based survey. *Urol*. 2001;57(6):1044-1050. PubMed ; CrossRef

4. Homma Y, Yamaguchi O, Hayashi K. An epidemiological survey of overactive bladder symptoms in Japan. *BJU Int*. 2005;96(9):1314-1318. PubMed ; CrossRef

5. Andersson KE. Antimuscarinic mechanisms and the overactive detrusor: an update. *Eur Urol*. 2011;59(3):377-386. PubMed ; CrossRef

6. Andersson KE, Wein AJ. Pharmacology of the lower urinary tract: basis for current and future treatments of urinary incontinence. *Pharmacol Rev*. 2004;56(4):581-631. PubMed ; CrossRef

7. Yoshimura N, Kaiho Y, Miyazato M, Yunoki T, Tai C, Chancellor MB, et al. Therapeutic receptor targets for lower urinary tract dysfunction. *Naunyn Schmiedebergs Arch Pharmacol*. 2008;377(4-6):437-448. PubMed ; CrossRef

8. Mutoh S, Latifpour J, Saito M, Weiss RM. Evidence for the presence of regional differences in the subtype specificity of muscarinic receptors in rabbit lower urinary tract. *J Urol*. 1997;157(2):717-721. CrossRef

9. de Groat WC, Yoshimura N. Pharmacology of the lower urinary tract. *Annu Rev Pharmacol Toxicol*. 2001;41:691-721. PubMed ; CrossRef

10. Yoshimura N, Chancellor MB. Neurophysiology of lower urinary tract function and dysfunction. *Rev Urol*. 2003;5 (suppl 8):S3-S10.

11. Nomiya M, Yamaguchi O. A quantitative analysis of mRNA expression of alpha 1 and beta-adrenoceptor subtypes and their functional roles in human normal and obstructed bladders. *J Urol*. 2003;170(2, pt 1):649-653. PubMed ; CrossRef

12. Johnson M. The beta-adrenoceptor. *Am J Respir Crit Care Med*. 1998;158(5, pt 3):S146-153. PubMed

13. Koike K, Takayanagi I. Beta3-adrenoceptor mechanisms in guinea-pig taenia caecum. *Life Sci*. 1998;62(17-18):1503-1507. CrossRef

14. Nagatomo T, Koike K. Recent advances in structure, binding sites with ligands and pharmacological function of beta-adrenoceptors obtained by molecular biology and molecular modeling. *Life Sci*. 2000;66(25):2419-2426. PubMed ; CrossRef

15. Tanaka Y, Yamashita Y, Yamaki F, Horinouchi T, Shigenobu K, Koike K. Evidence for a significant role of a Gs-triggered mechanism unrelated to the activation of adenylyl cyclase in the cyclic AMP-independent relaxant response of guinea-pig tracheal smooth muscle. *Naunyn Schmiedebergs Arch Pharmacol*. 2003;368(5):437-441. PubMed ; CrossRef

16. Fujimura T, Tamura K, Tsutsumi T, Yamamoto T, Nakamura K, Koibuchi Y, et al. Expression and possible functional role of the beta3-adrenoceptor in human and rat detrusor muscle. *J Urol*. 1999;161(2):680-685. PubMed ; CrossRef

17. Igawa Y, Yamazaki Y, Takeda H, Hayakawa K, Akahane M, Ajisawa Y, et al. Functional and molecular biological evidence for a possible beta3-adrenoceptor in the human detrusor muscle. *Br J Pharmacol*. 1999;126(3):819-825. PubMed ; CrossRef

18. Li G, Li K, Li Z, Wang P. Age-dependent changes in beta-adrenoceptor function in human detrusors and possible mechanisms. *Chin Med J* (Engl). 2003;116(10):1511-1514.

19. Takeda M, Obara K, Mizusawa T, Tomita Y, Arai K, Tsutsui T, et al. Evidence for beta3-adrenoceptor subtypes in relaxation of the human urinary bladder detrusor: analysis by molecular biological and pharmacological methods. *J Pharmacol Exp Ther*. 1999;288(3):1367-1373. PubMed

20. Goepel M, Wittmann A, Rübben H, Michel MC. Comparison of adrenoceptor subtype expression in porcine and human bladder and prostate. *Urol Res*. 1997;25(3):199-206. PubMed ; CrossRef

21. Levin RM, Ruggieri MR, Wein AJ. Identification of receptor subtypes in the rabbit and human urinary bladder by selective radio-ligand binding. *J Urol*. 1988;139(4):844-848. PubMed

22. Morita T, Iizuka H, Iwata T, Kondo S. Function and distribution of beta3-adrenoceptors in rat, rabbit and human urinary bladder and external urethral sphincter. *J Smooth Muscle Res*. 2000;36(1):21-32. PubMed ; CrossRef

23. Hoffmann C, Leitz MR, Oberdorf-Maass S, Lohse MJ, Klotz KN. Comparative pharmacology of human beta-adrenergic receptor subtypes–characterization of stably transfected receptors in CHO cells. *Naunyn Schmiedebergs Arch Pharmacol*. 2004;369(2):151-159. PubMed ; CrossRef

24. Michel MC, Vrydag W. Alpha1-, alpha2- and beta-adrenoceptors in the urinary bladder, urethra and prostate. *Br J Pharmacol*. 2006;147(suppl 2):S88-119. PubMed ; CrossRef

25. Nergardh A, Boreus LO, Naglo AS. Characterization of the adrenergic beta-receptor in the urinary bladder of man and cat. *Acta Pharmacol Toxicol* (Copenh). 1977;40(1):14-21. CrossRef

26. Badawi JK, Uecelehan H, Hatzinger M, Michel MS, Haferkamp A, Bross S. Relaxant effects of beta-adrenergic agonists on porcine and human detrusor muscle. *Acta Physiol Scand*. 2005;185(2):151-159. PubMed ; CrossRef

27. Kaidoh K, Igawa Y, Takeda H, Yamazaki Y, Akahane S, Miyata H, et al. Effects of selective beta2 and beta3-adrenoceptor agonists on detrusor hyperreflexia in conscious cerebral infarcted rats. *J Urol*. 2002;168(3):1247-1252. PubMed ; CrossRef

28. Woods M, Carson N, Norton NW, Sheldon JH, Argentieri TM. Efficacy of the beta3-adrenergic receptor agonist CL-316243 on experimental bladder hyperreflexia and detrusor instability in the rat. *J Urol*. 2001;166(3):1142-1147. PubMed ; CrossRef

29. Furuta A, Thomas CA, Higaki M, Chancellor MB, Yoshimura N, Yamaguchi O. The promise of beta3-adrenoceptor agonists to treat the overactive bladder. *Urol Clin North Am*. 2006;33(4):539-543. PubMed ; CrossRef

30. Murakami S, Chapple CR, Akino H, Sellers DJ, Chess-Williams R. The role of the urothelium in mediating bladder responses to isoprenaline. *BJU Int*. 2007;99(3):669-673. PubMed ; CrossRef

31. Otsuka A, Shinbo H, Matsumoto R, Kurita Y, Ozono S. Expression and functional role of beta-adrenoceptors in the human urinary bladder urothelium. *Naunyn Schmiedebergs Arch Pharmacol*. 2008;377(4-6):473-481. PubMed ; CrossRef

32. Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. *Eur Urol*. 2008;54(3):543-562. PubMed ; CrossRef

33. Sellers DJ, McKay N. Developments in the pharmacotherapy of the overactive bladder. *Curr Opin Urol*. 2007;17(4):223-230. PubMed ; CrossRef

34. Chess-Williams R, Chapple CR, Yamanishi T, Yasuda K, Sellers DJ. The minor population of M3-receptors mediate contraction of human detrusor muscle in vitro. *J Auton Pharmacol*. 2001;21(5-6):243-248. PubMed ; CrossRef

35. Fetscher C, Fleichman M, Schmidt M, Krege S, Michel MC. M(3) muscarinic receptors mediate contraction of human urinary bladder. *Br J Pharmacol*. 2002;136(5):641-643. PubMed ; CrossRef

36. Hawthorn MH, Chapple CR, Cock M, Chess-Williams R. Urothelium-derived inhibitory factor(s) influences on detrusor muscle contractility in vitro. *Br J Pharmacol*. 2000;129(3):416-419. PubMed ; CrossRef

37. Ruggieri MR, al. e. Which muscarinic receptor subtype mediates contraction of human urinary bladder? *Neurourol Urodyn*. 2006;25:61.

38. Kullmann FA, Artim D, Beckel J, Barrick S, de Groat WC, Birder LA. Heterogeneity of muscarinic receptor-mediated Ca2+ responses in cultured urothelial cells from rat. *Am J Physiol Renal Physiol*. 2008;294(4):F971-981. PubMed

39. Kullmann FA, Artim DE, Birder LA, de Groat WC. Activation of muscarinic receptors in rat bladder sensory pathways alters reflex bladder activity. *J Neurosci*. 2008;28(8):1977-1987. PubMed ; CrossRef

40. Takasu T, Ukai M, Sato S, Matsui T, Nagase I, Maruyama T, et al. Effect of (R)-2-(2-aminothiazol-4-yl)-4'-{2-[(2-hydroxy-2-phenylethyl)amino]ethyl} acetanilide (YM178), a novel selective beta3-adrenoceptor agonist, on bladder function. *J Pharmacol Exp Ther*. 2007;321(2):642-647. PubMed ; CrossRef

41. Noguchi Y, Someya A, Ukai M, Nakata M, Ohtake A, Suzuki M, et al. Effects of mirabegron (YM178) on non-micturition contractions in the bladder of conscious rats with bladder outlet obstraction (BOO). *J Urol*. 2009;181:10. CrossRef

42. Ukai M, Someya A, Nakata M, Ohtake A, Ueshima K, Suzuki M, et al. Effects of mirabegron (YM178), a novel β3-adrenoceptor agonist, on non-micturition bladder contractions in conscious rats with bladder outlet obstruction (BOO). *J Pharmacol Sci*. 2010;112:155.

43. Someya A, Ukai K, Yanai H, Watanabe M, Ohtake A, Ueshima K, et al. Mirabegron (YM178), a novel β3-adrenoceptor (AR) agonist increased functional bladder capacity and decreased micturition frequency in conscious water-loaded cynomolgus. *Eur Urol Suppl*. 2010;9:111. CrossRef

44. van Gelderen EM, Li Q, Meijer J, Schaddelee MP, Takusagawa S, Sugawara, et al. An exploratory comparison of the single dose pharmacokinetics of the beta 3-adrenoceptor agonist mirabegron in healthy CYP2D6 poor and extensive metabolizers. *Clin Pharmacol Ther*. 2009;85:S88.

45. Tyagi P, Tyagi V. Mirabegron, a beta3-adrenoceptor agonist for the potential treatment of urinary frequency, urinary incontinence or urgency associated with overactive bladder. *IDrugs*. 2010;13(10):713-722. PubMed

46. Tyagi P, Tyagi V, Chancellor M. Mirabegron: a safety review. *Expert Opin Drug Saf*. 2011;10(2):287-294. PubMed ; CrossRef

47. Tyagi P, Tyagi V, Yoshimura N, Chancellor M. β3-adrenoceptor agonists for the treatment of overactive bladder. *Drugs Future*. 2009;34:635-640.

48. Chapple C, Wyndaele JJ, van Kerrebroeck P, Radziszewski P, Dvorak V, Boerriggter P. Dose-ranging of once-daily mirabegron (YM178), a novel selective β3-adrenoceptor agonist, in patients with overactive bladder (OAB). *Eur Urol Suppl*. 2010;9:249. CrossRef

49. Krauwinkel WJ, van Gelderen EM, Groen MJ, editors. An open-label, once-sequence crossover study to evaluate the effect of multiple doses of mirabegron on the pharmacokinetics of the CYP2D6 substrate desipramine in healthy subjects. American Society for Clinical Pharmacology and Therapeutics Annual Meeting; March 17-20, 2010; Atlanta, GA.

50. Chapple CR, Yamaguchi O, Ridder A, Liehne J, Carl S, Mattiasson A, et al. Clinical proof of concept study (BLOSSOM) shows novel β3-adrenoceptor agonist YM178 is effective and well tolerated in the treatment of symptoms of overactive bladder. *Eur Urol Suppl*. 2008;7:239. CrossRef

51. Betanis® interview form (in Japanese). Available from: http://www.info.pmda.go.jp/go/pack/2590014F1021_1_01/@Generic__BookView.