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ORIGINAL ARTICLE

A phase II dose-ranging study of mirabegron in patients with overactive bladder

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Abstract
Introduction and hypothesis Mirabegron is a potent and selective β_3-adrenoceptor agonist that may represent an alternative treatment option in place of antimuscarinics for patients with overactive bladder.

Methods Patients completed a single-blinded, 2-week placebo run-in period followed by 12 weeks of randomized (n=928) double-blinded treatment with mirabegron oral controlled absorption system (OCAS) 25, 50, 100, or 200 mg once-daily (QD), placebo or tolterodine extended release (ER) 4 mg QD. The primary endpoint was change from baseline to end-of-treatment in mean number of micturition episodes/24 h. Secondary endpoints included changes in mean volume voided per micturition; mean number of urinary incontinence, urgency urinary incontinence, and urgency episodes/24 h; severity of urgency; nocturia; and quality of life measures. Safety parameters included vital signs, adverse events, laboratory tests, electrocardiogram measurements and post-void residual volume.

Results Mirabegron 25, 50, 100, and 200 mg resulted in dose-dependent reductions (improvements) from baseline to end-of-treatment in micturition frequency of 1.9, 2.1, 2.1, and 2.2 micturitions/24 h respectively, versus 1.4 micturitions/24 h with placebo ($p \leq 0.05$ for the mirabegron 50-, 100-, and 200-mg comparisons). There was a statistically significant improvement with mirabegron compared with placebo for most secondary endpoints including quality of life variables. While there was a significant ($p<0.05$) increase from baseline in pulse rate in the mirabegron 100-mg and 200-mg groups, this was not associated with an increased incidence of cardiovascular adverse events.

Conclusions The favorable efficacy and tolerability of mirabegron in this phase II dose-finding study has led to its successful advancement into a phase III clinical development program.

Keywords β_3-adrenoceptor agonist · Mirabegron · Overactive · Urinary bladder

The members of the DRAGON Investigator Group are listed in the Appendix.

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Introduction

Overactive bladder (OAB), estimated to occur in >50 million people worldwide [1], is characterized by symptoms of urinary urgency, frequency and nocturia, with/without urgency incontinence in the absence of lower urinary tract infection [2]. Antimuscarinic agents are used as first-line pharmacotherapy in the management of OAB; however, patients often discontinue antimuscarinics owing to side effects such as dry mouth, constipation and blurred vision [3], and because of an often insufficient response to treatment [4, 5].

The β-adrenoceptor is classified into β_1, β_2 and β_3 subtypes. The largely post-synaptic β_1-receptors are located primarily in the heart, but also in the salivary glands, platelets, and the gastrointestinal tract. β_2-rceptors are also mainly post-synaptic and can be found in blood vessels, bronchi, skeletal muscle, liver and mast cells, as well as the gastrointestinal tract. The β_3 subtype was first identified in adipose tissue, but has also been identified in bladder smooth muscle tissue (detrusor muscle). In the human bladder, the β_3 subtype promotes detrusor relaxation and urine storage [6–8]. β_3-adrenoceptor mRNA is predominantly expressed in the human urinary bladder, with 97 % of total β-adrenoceptor mRNA expressed by the β_3 subtype and only 1.5 % and 1.4 % expressed by the β_1 and β_2 subtypes respectively [9]. Whereas antimuscarinic agents bind to muscarinic receptors in the bladder and inhibit involuntary bladder contractions, stimulation of the β_3 receptors in the detrusor muscle of the bladder elicits relaxation of the bladder muscle during the storage phase of the micturition cycle [6–8]. Hence β_3-adrenoceptor agonists improve the storage capacity of the bladder without inhibiting bladder voiding. These observations suggest that drugs which act at β_3-adrenoceptors may have therapeutic potential in the treatment of the symptoms of OAB [9, 10].

Mirabegron is a β_3-adrenoceptor agonist whose clinical efficacy was first evaluated in a phase II proof-of-concept study in which patients were randomized to receive mirabegron 100 mg or 150 mg twice-daily (BID), placebo, or tolterodine extended release (ER) 4 mg once-daily (QD) for 4 weeks. As no difference in efficacy was seen between the 100-mg and 150-mg BID doses, it was deduced that the maximum therapeutic dose of mirabegron was a total daily dose of 200 mg. The results of a subsequent phase II, randomized, double-blinded, placebo- and active-controlled clinical study (Clinicaltrials.gov number: NCT00337090) evaluating the efficacy and dose–response relationship of mirabegron utilizing a QD oral controlled absorption system (OCAS) formulation in patients with OAB are presented here. OCAS is a hydrophilic gel-forming matrix tablet that allows more steady absorption of mirabegron than seen with the original, immediate-release formulations, which were associated with high peak-to-trough fluctuations in plasma concentration and a considerable food effect. Tolterodine extended release (ER) is an antimuscarinic agent commonly used to treat the symptoms of OAB; it was included (at a daily dose of 4 mg) as the active control in order to validate the study and to enable the efficacy and safety of mirabegron to be placed in context against a commonly used therapy (although the study was not powered for a head-to-head comparison).

Materials and methods

Study patients

Enrolled patients were men and women ≥18 years of age experiencing symptoms of OAB for ≥3 months with frequency of micturition on average ≥8 times per 24 h and at least three episodes of urgency (grade 3 or 4) [11], with or without incontinence, during a 3-day micturition diary period at baseline.

Major exclusion criteria at study entry included clinically significant bladder outflow obstruction; significant post-void residual (PVR) volume (>200 ml); incontinence where stress was the predominant factor; indwelling catheters or intermittent self-catheterization; diabetic neuropathy; symptomatic urinary tract infection, interstitial cystitis, bladder stones, previous pelvic radiation therapy or previous or current malignant disease of the pelvic organs; contraindications for anticholinergics; nondrug treatment, including electro-stimulation therapy (although bladder training or pelvic floor exercise programs that had started more than 1 month prior to the start of the study could be continued); use of other urinary incontinence medications; known or suspected hypersensitivity to tolterodine, other anticholinergics, mirabegron, lactose, or any of the excipients; clinically significant cardiovascular (including ECG abnormalities) or cerebrovascular disease; or any other condition making the patient unsuitable for the study (as deemed by the investigator).

Study design and procedures

This was a multinational, multicenter, randomized, double-blind, double-dummy, parallel-group placebo- and active-controlled phase II study. Patients were enrolled into 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: an OCAS formulation of mirabegron QD at a dose of 25, 50, 100 or 200 mg, placebo or tolterodine ER 4 mg QD. There were six study visits: visit 1 (screening); visit 2 (baseline) after placebo run-in; and visits 3, 4, 5, and 6 after 1, 4, 8, and 12 weeks of treatment, respectively.

At visit 1, eligible patients received a micturition diary, used to evaluate mirabegron efficacy, which was to be completed during the 3 days preceding all visits after screening. For each micturition or incontinence episode, patients rated the degree of associated urgency on the five-point Patient's Perception of Intensity of Urgency Scale (0, no urgency; 1, mild urgency; 2, moderate urgency; 3, severe urgency; and 4, urge incontinence) [11]. At visit 2, micturition diary scores were checked against inclusion criteria to confirm study eligibility.

Overactive bladder symptoms and quality of life (QOL) were assessed using the International Consultation on Incontinence Questionnaire-Overactive Bladder (ICIQ-OAB) [12, 13] and ICIQ-OAB QOL (ICIQ-OABqol) [14] questionnaires. Patients' assessment of treatment benefit was also evaluated, starting at visit 2, with the question "has the treatment been of any benefit to you?" (possible responses: "no," "yes, a little," or "yes, very much"). These were assessed at all five study visits after screening.

Observed and spontaneously reported adverse events (AEs) were assessed at all visits, post-screening. Vital signs (heart rate, systolic and diastolic blood pressures) were measured by the investigator at visit 1 (screening) and by the patient in triplicate, twice-daily (BID), during the 3-day diary period preceding each visit in accordance with available guidelines [15]. 12-lead ECGs were performed at visits 1, 2, 3, 4 and 6. Blood and urine samples for safety assessments (hematology, biochemistry, urinalysis and urine culture) were collected by a central laboratory at visits 1, 3, 4, 5, and 6, and PVR was assessed by ultrasonography or bladder scan at visits 1 and 6.

The study was conducted in accordance with the Declaration of Helsinki (1996) and Good Clinical Practice (GCP) guidelines. Institutional Review Board and local Independent Ethics Committee approval for the protocol and amendments was obtained and patients provided written informed consent before any procedures.

Study endpoints

The primary efficacy endpoint was the change from baseline to end-of-treatment in the mean number of micturitions per 24 h. Secondary endpoints included changes in mean volume voided per micturition; mean number of urinary incontinence, urgency urinary incontinence, and urgency episodes per 24 h; severity of urgency; number of nocturia episodes; changes in ICIQ-OAB and ICIQ-OABqol symptom scores, and in patients' perception of treatment benefit. Safety endpoints were incidence and severity of AEs, and changes from baseline to end-of-treatment in vital signs, laboratory tests, ECG parameters, and PVR.

Statistical analysis

A primary goal was to ascertain if there was a statistically significant improvement in the mean number of micturitions per 24 h in at least one active treatment group. Assuming a common standard deviation (SD) of 2.7 in the mean number of micturitions per 24 h, the ability to detect with 80 % power at an alpha level of 0.05 and a difference in means characterized by a variance of means of 0.126, it was necessary to recruit 140 patients to each of the five treatment arms (four mirabegron arms and a placebo arm). As tolterodine was included as an active control and was not included in the formal sample size calculation, a group of 70 patients in this arm was expected to be sufficient to establish assay sensitivity in evaluating the efficacy of mirabegron versus tolterodine. The study plan was to have at least 770 evaluable patients.

The primary analysis assessed changes from baseline to end-of-treatment in the mean number of micturitions per 24 h using an analysis of covariance (ANCOVA) model with treatment group (mirabegron dose) and country as fixed factors. The baseline value of the mean number of micturitions per 24 h was included in the models as a covariate. The null hypothesis, that the change in the mean number of micturitions per 24 h from baseline to end-of-treatment was the same for all mirabegron doses and for placebo, was evaluated using a two-sided test with a 0.05 significance level. Pairwise comparisons between each mirabegron group and placebo were performed; p values and 95 % confidence intervals (CIs) were obtained. The tolterodine group was not part of this primary analysis. The analysis described above was also performed for secondary efficacy variables. The percentage of patients showing a response in micturition frequency (defined as a mean of less than eight micturitions per 24 h), incontinence (patients who became dry), urgency, and nocturia episodes per 24 h (no episodes of either at a given visit) were compared between treatment groups using Mantel–Haenszel procedures.

In a secondary analysis, pairwise comparisons between tolterodine and placebo and between tolterodine and each mirabegron group were performed using the ANCOVA model described above.

The sum of scores for the ICIQ-OAB, ICIQ-OABqol, and mean changes from visit 2 to the end-of-treatment were derived for these variables and analyzed using the same ANCOVA model as for the primary variable. Frequencies and percentages for patients' assessment of treatment benefit at end-of-treatment were reported. A responder for treatment benefit was defined by an improvement of at least one category at a visit relative to baseline (i.e., the response changing from "no" to "yes, a little"; from "no" to "yes, very much"; or from "yes, a little" to "yes, very much"). Efficacy data were analyzed using last observation carried forward (LOCF) methodology. Safety variables were analyzed descriptively.

Results

Study patients

A total of 1,108 patients were enrolled and 928 were randomized (Fig. 1); 927 patients received at least one dose of study medication (safety analysis set) and of these, 919 patients had primary efficacy data at baseline and at least one on-treatment visit (full analysis set [FAS]). At least 90 % of patients in each group completed the study. At week 12, data were obtained from a total of 854 subjects; thus, 65 subjects (7 %) without a week 12 measurement were analyzed at endpoint (LOCF). The study groups were well balanced with respect to demographic characteristics, type of OAB and prior drug therapy (Table 1). Approximately 30 % of patients had previously received nondrug therapy; this consisted mostly of exercises, electrical stimulation, behavioral training, and surgery. The mean duration of exposure to study medication ranged from 80 to 84.4 days across groups. Compliance was at least 98.5 % across treatment groups.

Primary efficacy endpoint

The reduction (improvement) from baseline to end-of-treatment in the mean number of micturitions per 24 h increased with mirabegron dose and the improvement relative to placebo was statistically significant ($p \leq 0.05$) for the mirabegron 50-, 100-, and 200-mg groups (Table 2); mirabegron 25, 50, 100, and 200 mg resulted in a mean baseline to end-of-treatment reduction of 1.9, 2.1, 2.1, and 2.2 micturitions per 24 h, respectively, compared with 1.4 micturitions per 24 h with placebo. No statistically significant differences in change in micturition frequency from baseline to end-of-treatment were noted between tolterodine and placebo or between tolterodine ER 4 mg and any mirabegron group.

The percentage of patients classified as responders for micturition frequency at the endpoint (mean of less than eight micturitions per 24 h) were 19.3 % for placebo, 28.7 % for mirabegron 25 mg, and 30.1 % for the mirabegron 200-mg group ($p \leq 0.05$ for all mirabegron dose groups versus placebo). For the tolterodine ER 4-mg group, 18.8 % of patients were classified as responders; the difference relative to placebo was not statistically significant (Table 3).

Secondary efficacy endpoints

Urinary symptoms

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);

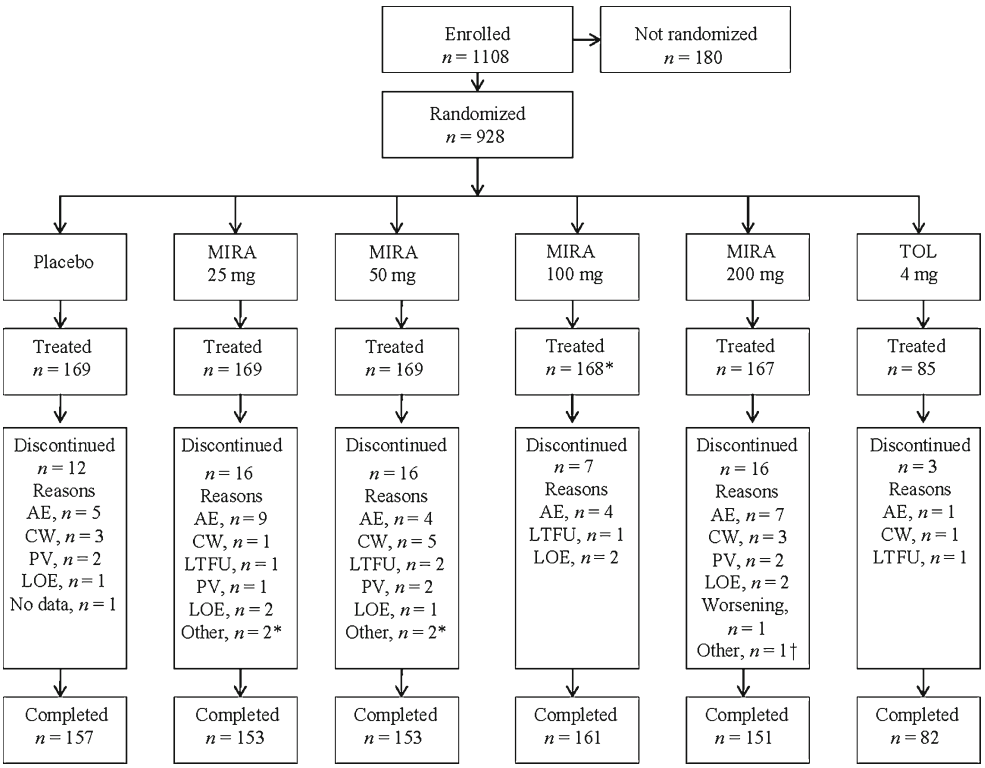

Fig. 1 Disposition of subjects. *MIRA* mirabegron, *TOL* tolterodine, *AE* adverse event, *CW* consent withdrawn, *PV* protocol violation, *LOE* lack of efficacy, *LTFU* lost to follow-up. MIRA and TOL were administered once daily. *Asterisks*: In the mirabegron 100-mg group, 169 patients were randomized and 168 received treatment. *Dagger*: Other reasons for discontinuation included laboratory value out of range and medical advice to stop study drug (25-mg group); noncompliance and patient decision (50-mg group); and a patient stopped taking the study drug during hospitalization for arthroscopy of the knee (200-mg group)

Table 1 Demographic and baseline characteristics (full analysis set)[a]

Characteristic	Placebo	Mirabegron OCAS[c]				Tolterodine ER
	(*n*=166)	25 mg (*n*=167)	50 mg (*n*=167)	100 mg (*n*=168)	200 mg (*n*=166)	4 mg[c] (*n*=85)
Age (years)±SD	57.1±12.9	57.2±12.1	56.9±12.5	57.1±12.5	58.0±13.7	56.6±12.8
Sex, *n* (%)						
Male	15 (9.0)	20 (12.0)	18 (10.8)	17 (10.1)	12 (7.2)	16 (18.8)
Female	151 (91.0)	147 (88.0)	149 (89.2)	151 (89.9)	154 (92.8)	69 (81.2)
Race, *n* (%)						
Asian	0	1 (0.6)	0	1 (0.6)	0	2 (2.4)
Black	0	2 (1.2)	0	0	0	0
White	166 (100)	162 (97.0)	162 (97.0)	167 (99.4)	164 (98.8)	81 (95.3)
Other	0	1 (0.6)	3 (1.8)	0	0	1 (1.2)
Missing	0	1 (0.6)	2 (1.2)	0	2 (1.2)	1 (1.2)
Type of OAB, *n* (%)						
Urge incontinence only	74 (44.6)	79 (47.3)	67 (40.1)	67 (39.9)	63 (38.0)	38 (44.7)
Mixed incontinence[b]	52 (31.3)	41 (24.6)	47 (28.1)	54 (32.1)	63 (38.0)	24 (28.2)
Without incontinence	40 (24.1)	47 (28.1)	53 (31.7)	47 (28.0)	40 (24.1)	23 (27.1)
Prior drug therapy, *n* (%)						
Yes, at least one effective	41 (24.7)	40 (24.0)	39 (23.4)	42 (25.0)	34 (20.5)	19 (22.4)
Yes, none effective	30 (18.1)	42 (25.1)	38 (22.8)	39 (23.2)	38 (22.9)	16 (18.8)
No	95 (57.2)	85 (50.9)	90 (53.9)	87 (51.8)	94 (56.6)	50 (58.8)
Non-drug therapy, *n* (%)	51 (30.7)	57 (34.1)	49 (29.3)	44 (26.2)	40 (24.1)	22 (25.9)

OCAS oral controlled absorption system, *ER* extended release, *OAB* overactive bladder, *SD* standard deviation

[a] Full analysis set means all patients with primary efficacy data at baseline and at least one on-treatment visit

[b] Urge was the predominant factor

[c] Mirabegron and tolterodine were administered once daily (QD)

and nocturia episodes (at a dose of 50 mg) ($p<0.05$ for all comparisons; Table 2).

A statistically significant difference ($p<0.01$) between tolterodine and placebo was noted for mean volume voided per micturition, but not for other secondary endpoints. Statistically significant differences ($p\leq0.05$) favoring the mirabegron 200-mg group relative to tolterodine were noted for grade at ≥3 urgency episodes (and level of urgency).

The percentage of patients classified as responders for incontinence episodes at the end of treatment (patients who became dry) was 36.8 % for placebo; 41.7–55.9 % across the four mirabegron groups ($p\leq0.05$ for all mirabegron groups versus placebo); and 35.8 % for tolterodine. At the end of treatment, more patients in the mirabegron than in the placebo group were responders with respect to urgency (grade ≥3) and nocturia episodes (no episodes of either at the end of treatment), although differences between groups were not statistically significant. The responder levels for urgency and nocturia episodes for the tolterodine ER 4-mg group were similar to those seen for placebo (Table 3).

Quality of life

The positive effect of mirabegron on QOL scores (a reduction in ICIQ-OAB score indicated improvement) increased with mirabegron dose (Table 2); moreover, the change from baseline to the end of treatment for all mirabegron groups was statistically significant versus placebo ($p\leq0.05$). Improvements from baseline to the end of treatment were also observed with the ICIQ-OABqol questionnaire, although only the comparison between the mirabegron 200-mg group and placebo was statistically significant (−22.19 versus −16.11, $p\leq0.05$; Table 2).

No statistically significant differences between tolterodine ER 4 mg and placebo were noted for the QOL scores obtained on both the ICIQ-OAB and ICIQ-OABqol. A statistically significant treatment effect favoring mirabegron 200 mg compared with tolterodine ER 4 mg (−3.05 versus −2.21, $p<0.05$) was seen on the ICIQ-OAB.

The percentage of patients classified as "responders" in patient perception of treatment benefit (improvement of ≥1 category from baseline) at the end of treatment was 59.0 %, 65.0 %. 65.8 % and 70.8 % for the mirabegron 25-mg,

Table 2 Adjusted changes from baseline to endpoint and estimated differences versus placebo for efficacy variables by treatment group (full analysis set)

	Placebo	Mirabegron OCAS[b]				Tolterodine ER[c]
		25 mg	50 mg	100 mg	200 mg	4 mg
Micturitions/24 h	*n*=166	*n*=167	*n*=167	*n*=168	*n*=166	*n*=85
Adjusted mean CFB	−1.44	−1.88	−2.08	−2.12	−2.24	−1.99
Estimated difference from placebo		−0.45	−0.64*	−0.68*	−0.80**	−0.52
95 % CIs		−0.99, 0.10	−1.19 , −0.10	−1.22, −0.13	−1.34, −0.25	−1.18, 0.15
Mean volume voided/micturition (ml)	*n*=165	*n*=167	*n*=167	*n*=168	*n*=166	*n*=85
Adjusted mean CFB	7.29	15.32	27.34	25.56	33.34	23.86
Estimated difference from placebo		8.03	20.05***	18.28***	26.06***	16.81*
95 % CIs		−1.54, 17.60	10.48, 29.63	8.66, 27.89	16.49, 35.62	5.09, 28.5
Incontinence episodes/24 h	*n*=106	*n*=99	*n*=108	*n*=111	*n*=110	*n*=53
Adjusted mean CFB	−0.53	−1.36	−1.15	−1.06	−1.10	−0.81
Estimated difference from placebo		−0.84**	−0.62*	−0.53	−0.58	−0.28
95 % CIs		−1.45, −0.23	−1.22, −0.02	−1.12, 0.06	−1.16, 0.01	−1.01, 0.45
Nocturia episodes/24 h	*n*=144	*n*=145	*n*=142	*n*=141	*n*=147	*n=72*
Adjusted mean CFB	−0.38	−0.52	−0.60	−0.42	−0.59	−0.59
Estimated difference from placebo		−0.15	−0.22*	−0.04	−0.21	−0.21
95 % CIs		−0.36, 0.07	−0.44, −0.01	−0.26, 0.17	−0.43, 0.00	−0.47, 0.05
Urgency incontinence episodes[a]/24 h	*n*=106	*n*=93	*n*=106	*n*=107	*n*=108	*n=52*
Adjusted mean CFB	−0.44	−1.31	−1.13	−1.18	−1.24	−0.76
Estimated difference from placebo		−0.86**	−0.69**	−0.74**	−0.80**	−0.31
95 % CIs		−1.38, −0.35	−1.18, −0.19	−1.23, −0.25	−1.29, −0.31	−0.92, 0.30
Urgency episodes/24 h (severity ≥3)	*n*=165	*n*=167	*n*=166	*n*=168	*n*=165	*n=85*
Adjusted mean CFB	−1.07	−1.77	−1.67	−2.28	−2.48	−1.46
Estimated difference from placebo		−0.70*	−0.60	−1.21***	−1.42***	−0.37
95 % CIs		−1.38, −0.01	−1.29, 0.08	−1.90, −0.52	−2.10, −0.73	−1.21, 0.47
Level of urgency/24 h	*n*=166	*n*=166	*n*=166	*n*=168	*n*=166	*n*=85
Adjusted mean CFB	−0.10	−0.21	−0.18	−0.29	−0.38	−0.14
Estimated difference from placebo		−0.12	−0.08	−0.19**	−0.28***	−0.04
95 % CIs		−0.25, 0.02	−0.22, 0.05	−0.33, −0.06	−0.41, −0.15	−0.21, 0.12
ICIQ-OAB	*n*=166	*n*=167	*n*=166	*n*=168	*n*=166	*n*=85
Adjusted mean CFB	−1.82	−2.40	−2.51	−2.72	−3.02	−2.21
Estimated difference from placebo		−0.58*	−0.69*	−0.90**	−1.20***	−0.37
95 % CIs		−1.13, −0.02	−1.24, −0.13	−1.45, −0.34	−1.76, −0.65	−1.05, 0.31
ICIQ-OABqol	*n*=162	*n*=163	*n*=165	*n*=163	*n*=162	*n*=84
Adjusted mean CFB	−16.11	−17.09	−20.36	−20.57	−22.19	−17.42
Estimated difference from placebo		−0.98	−4.25	−4.46	−6.08*	−1.32
95 % CIs		−5.88, 3.92	−9.13, 0.62	−9.37, 0.46	−11.0, −1.19	−7.32, 4.69

OCAS oral controlled absorption system, *CFB* change from baseline, *CI* confidence interval, *ICIQ* International Consultation on Incontinence Questionnaire, *OAB* overactive bladder, *qol* quality of life

*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$

[a] Urgency incontinence (incontinence with urgency) is a subset of incontinence (with or without urgency)

[b] Mirabegron was administered once daily (QD)

[c] The statistics for values given in the placebo and mirabegron columns come from the primary analysis, in which treatment group was included as a fixed factor in the ANCOVA model; pairwise comparisons between each mirabegron group and placebo were performed; the tolterodine group was excluded. The statistics for values in the tolterodine column come from the secondary analysis in which tolterodine was also included as a fixed factor; in this analysis, pairwise comparisons between tolterodine and placebo and between tolterodine and each mirabegron group were performed

Table 3 Number (%) of responders[a] for selected efficacy variables at the study endpoint (full analysis set)

	Placebo	Mirabegron OCAS[b]				Tolterodine ER[b]
		25 mg	50 mg	100 mg	200 mg	4 mg
Patients, *n* (%)[c]						
Micturitions/24 h*	*n*=166	*n*=167	*n*=167	*n*=168	*n*=166	*n*=85
	32 (19.3)	48 (28.7)	46 (27.5)	55 (32.7)	50 (30.1)	16 (18.8)
Incontinence episodes/24 h*	*n*=106	*n*=99	*n*=108	*n*=111	*n*=110	*n*=53
	39 (36.8)	42 (42.4)	45 (41.7)	62 (55.9)	53 (48.2)	19 (35.8)
Urgency episodes (grade ≥3)/24 h	*n*=165	*n*=167	*n*=166	*n*=168	*n*=165	*n*=85
	25 (15.2)	27 (16.2)	24 (14.5)	33 (19.6)	36 (21.8)	13 (15.3)
Nocturia episodes/24 h	*n*=144	*n*=145	*n*=142	*n*=141	*n*=147	*n*=72
	21 (14.6)	34 (23.4)	34 (23.9)	20 (14.2)	34 (23.1)	13 (18.1)

OCAS oral controlled absorption system, *ER* extended release

*$p \leq 0.05$ based on a Mantel–Haenszel test to compare all treatment groups, except tolterodine

[a] Responder definitions: micturitions, <8 micturitions/24 h; incontinence episodes, no episodes (patient became dry); urgency and nocturia episodes, no episodes of either

[b] Mirabegron and tolterodine were administered once daily (QD)

[c] Percentages are based on the number of patients with available data at the endpoint

50-mg, 100-mg, and 200-mg groups, respectively, compared with 51 % for placebo. Approximately 55 % of the tolterodine ER 4-mg patients were classified as responders on this measure.

Safety

The incidence of treatment-related AEs was comparable for the mirabegron and placebo groups (Table 4). Dry mouth was more common with tolterodine ER 4 mg (3.5 %) than with mirabegron (1.8 % to 3.0 % depending on dose). Discontinuation owing to AEs was low at 3.0 % (placebo), 2.4–5.3 % (mirabegron groups), and 1.2 % (tolterodine). Serious adverse events were reported in <2 % of patients across treatment groups; two events, one of pneumonia and one of hypothyroidism, were considered to be possibly related to mirabegron.

A statistically significant increase in pulse rate from baseline was seen with mirabegron 100 and 200 mg versus placebo. In addition, pulse rate was seen to increase in a dose-related manner. The adjusted mean change in morning pulse rate from baseline was 0.51 bpm for placebo, 2.15 bpm for mirabegron 100 mg ($p \leq 0.05$), and 4.66 bpm for mirabegron 200 mg ($p \leq 0.001$). Similarly, the adjusted mean change in afternoon pulse rate from baseline was –0.04 bpm for placebo, 2.71 bpm for mirabegron 100 mg ($p \leq 0.001$), and 4.63 bpm for mirabegron 200 mg ($p \leq 0.001$). However, this was not associated with a clinically significant increase in cardiovascular AEs (for example, atrial fibrillation or palpitations), the incidence of which was comparable to that seen with tolterodine. Morning and afternoon pulse rate increases from baseline for the mirabegron 25-mg (0.34 and 0.44 bpm, respectively) and 50-mg (1.64 and 1.12 bpm, respectively) groups were not statistically significant compared with placebo. By comparison, the adjusted mean changes from baseline in the morning and afternoon pulse rates seen with tolterodine were 1.50 and 2.50, respectively. No drug effect on systolic or diastolic blood pressure was observed; the net changes in morning and afternoon blood pressure from baseline in all mirabegron groups were <2 mm Hg and comparable to placebo. No differences between treatment groups were observed with respect to ECG parameters, including QTcF. Mean changes in PVR were small, at –4.6 ml for placebo; –4.7, –4.3, 0.6, and –3.0 mL for mirabegron 25, 50, 100, and 200 mg, respectively; and –1.3 for tolterodine ER 4 mg. There were no clinically relevant changes in laboratory parameters.

Discussion

In this study, mirabegron OCAS was effective and well tolerated with clear dose-dependent efficacy above 50 mg. The difference in response versus placebo was evident after 1 week of treatment and a maximum effect was achieved and sustained from 8 to 12 weeks, as seen in previous studies evaluating antimuscarinic therapy for OAB [16]. Approximately half of the incontinent patients in each mirabegron treatment group (from 41.7 % of the mirabegron 50-mg group to 55.9 % of the mirabegron 100-mg group) were dry at the end of treatment. Thus, mirabegron exhibited considerable clinical benefit as

Table 4 Treatment-related AEs reported during treatment (safety populations)[a]

System organ class preferred term	Placebo (*n*=169)	Mirabegron OCAS 25 mg[b] (*n*=169)	Mirabegron OCAS 50 mg (*n*=169)	Mirabegron OCAS 100 mg (*n*=168)	Mirabegron OCAS 200 mg (*n*=167)	Tolterodine ER 4 mg (*n*=85)
Patients, *n* (%)						
Overall	26 (15.4)	34 (20.1)	38 (22.5)	36 (21.4)	37 (22.2)	13 (15.3)
Cardiac disorders	1 (0.6)	4 (2.4)	7 (4.1)	2 (1.2)	5 (3.0)	1 (1.2)
Eye disorders	3 (1.8)	3 (1.8)	2 (1.2)	1 (0.6)	6 (3.6)	0 (0.0)
Gastrointestinal disorders	9 (5.3)	14 (8.3)	14 (8.3)	16 (9.5)	12 (7.2)	7 (8.2)
Constipation	2 (1.2)	2 (1.2)	4 (2.4)	3 (1.8)	3 (1.8)	1 (1.2)
Dry mouth	3 (1.8)	5 (3.0)	3 (1.8)	5 (3.0)	3 (1.8)	3 (3.5)
Dyspepsia	1 (0.6)	1 (0.6)	1 (0.6)	0 (0.0)	4 (2.4)	0 (0.0)
Nausea	2 (1.2)	2 (1.2)	2 (1.2)	7 (4.2)	1 (0.6)	1 (1.2)
General disorders and administration site conditions	2 (1.2)	3 (1.8)	6 (3.6)	3 (1.8)	1 (0.6)	1 (1.2)
Investigations	9 (5.3)	10 (5.9)	4 (2.4)	6 (3.6)	7 (4.2)	1 (1.2)
Gamma-glutamyl transferase increased	2 (1.2)	4 (2.4)	0 (0.0)	2 (1.2)	2 (1.2)	0 (0.0)
Nervous system disorders	6 (3.6)	7 (4.1)	10 (5.9)	7 (4.2)	6 (3.6)	1 (1.2)
Dizziness	1 (0.6)	0 (0.0)	6 (3.6)	2 (1.2)	0 (0.0)	0 (0.0)
Headache	4 (2.4)	6 (3.6)	5 (3.0)	4 (2.4)	3 (1.8)	1 (1.2)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	2 (2.4)
Vascular disorders	4 (2.4)	4 (2.4)	4 (2.4)	6 (3.6)	2 (1.2)	0 (0.0)

OCAS oral controlled absorption system, *ER* extended release

[a] The AEs listed were reported in ≥2 % of the patients in either treatment group

[b] Mirabegron and tolterodine were administered once daily (QD)

demonstrated by consistently improved symptoms of OAB and associated QOL measures.

The mirabegron doses of 25, 50, 100, and 200 mg QD used in this study were based on the results of a proof-of-concept study in which total daily doses of 200 and 300 mg (100 and 150 mg BID, respectively) were investigated. Notably, a QD OCAS formulation was utilized in this study. In the proof-of-concept study, no difference in efficacy was seen between the 100-mg and 150-mg BID doses, leading to the conclusion that a total daily dose of 200 mg provides maximum therapeutic efficacy. Hence, this was the highest dose investigated in the current study.

Tolterodine is a licensed antimuscarinic antagonist for OAB that was used as an active control for mirabegron in this study in order to give context to the efficacy and safety results seen with mirabegron. Hence, it is notable that the magnitude of improvements in efficacy outcomes in the mirabegron groups were within the same range as those of the tolterodine ER 4-mg group, further suggesting that mirabegron is a potentially effective treatment for the management of patients with OAB. However, one limitation of this study is that it was not powered to detect differences between mirabegron and tolterodine for which head-to-head comparison studies are required. In addition, the short duration of this study could also be perceived as a limitation, as it allows no insight into the long-term effects of mirabegron, notably whether its favorable efficacy and tolerability profile is maintained over a prolonged period and whether it leads to improved compliance. However, this was a phase II study, designed as a dose-finding study, and its design and conduct are usual and adequate for that purpose. It is worth noting too that between 24.6 % and 38.0 % of the patients across treatment groups had urge-predominant mixed incontinence at baseline.

Mirabegron was found to be well tolerated with a low incidence of AEs, between that seen with placebo and tolterodine. Dry mouth is the most common, and most bothersome side effect of antimuscarinic treatment [16–19]. Thus, the low incidence of dry mouth seen with mirabegron and the observation that its incidence was lower with mirabegron than with tolterodine may be an important benefit of mirabegron treatment. The small mean increase in pulse rate from baseline observed with mirabegron was less pronounced than that reported in other studies [20, 21] and was not associated with a clinically significant increase in cardiovascular AEs. There was no evidence of a dose–response relationship for these events and none of

the patients discontinued the study because of symptoms associated with increased heart rate.

The favorable efficacy and tolerability profile of mirabegron, the first in this new class of compounds to be approved for the treatment of the symptoms of OAB, in once-daily doses ranging from 25 to 200 mg OCAS, has led to its successful advancement into a phase III clinical development program at doses of 25, 50, and 100 mg.

Conclusions

The satisfactory balance between efficacy and tolerability observed in this study of mirabegron in OAB patients may result in improved compliance compared with that seen with currently available antimuscarinics, whose use is hampered by bothersome side effects and insufficient efficacy.

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