13. Deschenes MR. Effects of aging on muscle fibre type and size. Sports Med 2004; 34: 809–24.
14. Gray SL, Boudreau RM, Newman AB *et al*. Angiotensin-converting enzyme inhibitor and statin use and incident mobility limitation in community-dwelling older adults: the Health, Aging and Body Composition study. J Am Geriatr Soc 2011; 59: 2226–32.
15. Gray SL, LaCroix AZ, Aragaki AK *et al*. Angiotensin-converting enzyme inhibitor use and incident frailty in women aged 65 and older: prospective findings from the Women's Health Initiative Observational Study. J Am Geriatr Soc 2009; 57: 297–303.
16. Ashfield TA, Syddall HE, Martin HJ, Dennison EM, Cooper CAihie Sayer A. Grip strength and cardiovascular drug use in older people: findings from the Hertfordshire Cohort Study. Age Ageing 2010; 39: 185–91.
17. Syddall HE, Aihie SA, Dennison EM, Martin HJ, Barker DJ, Cooper C. Cohort profile: the Hertfordshire cohort study. Int J Epidemiol 2005; 34: 1234–42.
18. Rose GA, Blackburn H. Cardiovascular Survey Methods. Geneva: WHO, 1968.
19. Prineas RJ, Crow RS, Blackburn H. The Minnesota Code Manual of Electrocardiographic Findings: Standards and Procedures for Measurement and Classification. Boston, MA: John Wright, 1982.
20. Dennison EM, Jameson KA, Syddall HE *et al*. Bone health and deterioration in quality of life among participants from the Hertfordshire cohort study. Osteoporos Int 2010; 21: 1817–24.
21. Williams AG, Rayson MP, Jubb M *et al*. The ACE gene and muscle performance. Nature 2000; 403: 614.
22. Puthucheary Z, Skipworth JR, Rawal J, Loosemore M, Van Someren K, Montgomery HE. The ACE gene and human performance: 12 years on. Sports Med 2011; 41: 433–48.
23. Schellenbaum GD, Smith NL, Heckbert SR *et al*. Weight loss, muscle strength, and angiotensin-converting enzyme inhibitors in older adults with congestive heart failure or hypertension. J Am Geriatr Soc 2005; 53: 1996–2000.
24. Lynch JE, Henderson NR, Ramage L, McMurdo ME, Witham MD. Association between statin medication use and improved outcomes during inpatient rehabilitation in older people. Age Ageing 2012; 41: 260–2.

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The efficacy and tolerability of the β3-adrenoceptor agonist mirabegron for the treatment of symptoms of overactive bladder in older patients

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Abstract

Introduction: mirabegron is a β_3-adrenoceptor agonist developed for the treatment of symptoms of overactive bladder (OAB). As the prevalence of OAB increases with age, a prospective subanalysis of individual and pooled efficacy and

tolerability data from three 12-week, randomised, Phase III trials, and of tolerability data from a 1-year safety trial were conducted in order to evaluate the efficacy and tolerability of mirabegron in subgroups of patients aged ≥65 and ≥75 years.

Methods: primary efficacy outcomes were change from baseline to final visit in the mean number of incontinence episodes/24 h and the mean number of micturitions/24 h. Tolerability was assessed by the incidence of treatment-emergent adverse events (TEAEs).

Results: over 12 weeks mirabegron 25 mg and 50 mg once-daily reduced the mean numbers of incontinence episodes and micturitions/24 h from baseline to final visit in patients aged ≥65 and ≥75 years. Mirabegron was well tolerated: in both age groups, hypertension and urinary tract infection were among the most common TEAEs over 12 weeks and 1 year. The incidence of dry mouth, a typical anticholinergic TEAE, was up to sixfold higher among the older patients randomised to tolterodine than any dose of mirabegron.

Conclusions: these analyses have demonstrated the efficacy of mirabegron over 12 weeks and the tolerability of mirabegron over 12 weeks and 1 year in OAB patients aged ≥65 and ≥75 years, supporting mirabegron as a therapeutic option in older patients with OAB.

Keywords: *older people, overactive bladder, age, mirabegron, tolerability, efficacy*

Introduction

Overactive bladder (OAB) is defined as a condition with characteristic symptoms of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology [1]. It is a particular burden in older people, not only because of its higher prevalence (~15% of people aged ≥65 years [2] and 30–40% of people aged ≥75 years [3]) but also because the impact of its symptoms may be more pronounced due to the increased burden of chronic comorbidities [4]. It is also associated with a significant psychological burden and impairment of quality of life and, if left untreated, can lead to increased risk of falls and fractures [5], sleep disturbances, fear of incontinence and depression [6] all of which may result in more serious outcomes in older patients.

Oral antimuscarinic agents are currently the mainstay of pharmacotherapy for the treatment of OAB. However, these agents are associated with sub-optimal efficacy and burdensome adverse events (AEs), such as dry mouth and constipation [7]. Older patients are known to experience more AEs than younger patients [8], and the AEs they experience with oral antimuscarinic treatment may be more pronounced [7]. Of particular concern are the potentially adverse effects of antimuscarinic medications caused by age-related changes in central cholinergic transmitter systems [9]. Indeed, immediate- and extended-release (ER) formulations of oxybutynin have been associated with cognitive impairment in older people who are cognitively intact [10, 11] although trospium chloride [11], as well as newer antimuscarinics, have been reported to have no adverse effects on cognition in the cognitively intact elderly and those with mild cognitive impairment [12–16]. Nonetheless, the American Geriatric Society has cited oral antimuscarinics as 'potentially inappropriate medications and classes to avoid in older adults' [17].

The β_3-adrenoceptor agonist, mirabegron, is the first in this class of therapeutic agents to have been approved (in the EU, the United States, Canada, Australia and Japan) for the treatment of OAB. Mirabegron is a specific agonist, acting on β_3-adrenoceptors in the human detrusor, stimulation of which leads to active relaxation of the human detrusor in the storage phase, increasing bladder capacity without exerting an effect on voiding [18]. Three large, randomised, placebo-controlled, Phase III trials (Studies 046 [NCT00689104; 19], 047 [NCT00662909; 20] and 074 [NCT00912964; 21]) have demonstrated the efficacy and tolerability of mirabegron, at doses ranging from 25 to 100 mg once-daily, in patients with OAB. (Note that the recommended starting dose for mirabegron is 50 mg in the EU and Japan and is 25 mg in the United States and Canada; the 100 mg dose is not approved for use). A pooled analysis of the mirabegron 50 mg data from these studies demonstrated statistically significant improvements in urinary frequency and incontinence episodes compared with placebo [22]. In addition, mirabegron has demonstrated a favourable safety profile in a 1-year, randomised, double-blind, parallel-group, active-controlled safety trial (Study 049 [NCT00688688]) [23].

Because OAB is a particular problem in older patients, prespecified subanalyses of the efficacy and tolerability data for the mirabegron 25 mg treatment arm of Study 074 (this dose was confined to this study) and the pooled mirabegron 50 mg arms of the three 12-week studies and a pre-specified subanalysis of the 1-year mirabegron 50 mg safety and tolerability data, stratified by age, with age cut-offs of 65 and 75 years were conducted. Tolterodine ER 4 mg once daily was included as an active control arm in one Phase III study (Study 046) and in the 1-year study and for comparison purposes, and subanalysis of these data by age was also conducted.

Materials and methods

Study design and patients

All studies have been described previously [18–20, 22]; but briefly, patients enrolled were men and women aged ≥18 years with OAB symptoms for ≥3 months. Following a 2-week, single-blind, placebo run-in period to determine baseline symptoms and patient eligibility, they were randomised if, during the micturition diary period over the 3 days prior to baseline, they had recorded ≥8 micturitions/24 h and ≥3 urgency episodes with or without urgency incontinence. Stress incontinence or mixed incontinence with stress predominance at screening or an average total daily urine volume of >3,000 ml led to exclusion. Patients who had non-drug treatment including electro-stimulation therapy were excluded from the study, except for patients who had started a bladder training programme or pelvic floor exercises >30 days prior to entry to the study and were continuing their treatment. Treatment arms were: once-daily oral placebo (Studies 046, 047 and 074); mirabegron 25 mg (Study 074), 50 mg (Studies 046, 047 and 074) or 100 mg (Studies 046 and 047) or tolterodine ER 4 mg (active control, Study 046 only). In the 1-year randomised study, treatment arms were mirabegron 50 mg, mirabegron 100 mg or tolterodine ER 4 mg.

Efficacy and tolerability assessments

Efficacy endpoints evaluated in the 12-week studies, and the subject of the subgroup analyses conducted here, were change from baseline to final visit in the mean number of incontinence episodes/24 h and the mean number of micturitions/24 h. These were recorded in a patient micturition diary filled out over the 3 days prior to each clinic visit. Tolerability in all studies was assessed as the incidence of treatment-emergent adverse events (TEAEs) measured by self-report or clinical measurement, as appropriate.

Statistical analyses

The safety analysis set (SAF) comprised all randomised patients who took at least one dose of double-blind study drug. The full analysis set (FAS) comprised SAF patients who had at least one micturition measurement in the baseline micturition diary and at least one diary post-baseline. The FAS-incontinence (FAS-I) population comprised FAS patients who recorded at least one incontinence episode in the 3-day baseline diary. Change from baseline to final visit in the mean number of micturitions/24 h and the mean number of incontinence episodes/24 h in the 12-week studies was evaluated in the FAS and FAS-I populations, respectively. For the pre-specified pooled analysis of the 12-week studies, data from the placebo and mirabegron 50 mg groups of all three studies were pooled. Efficacy and tolerability data for the placebo and mirabegron 25 mg groups of Study 074; the pooled 12-week placebo and mirabegron 50 mg groups; and the placebo and tolterodine groups of Study 046; as well as tolerability data for the mirabegron 50 mg and tolterodine groups of Study 049 were stratified into subgroups by age, with cutoffs of 65 and 75 years. Subgroup analysis of the 12-week efficacy data (whether individual or pooled data) was performed using analysis of covariance (ANCOVA) with treatment group, sex, study (geographical region for Studies 046 and 074), age subgroup and treatment by age (≥65 and ≥75 years) subgroup interaction as fixed factors and baseline as a covariate. Based on the ANCOVA, least-squares mean estimates and two-sided 95% confidence intervals for mean changes from baseline were derived within treatment groups and between mirabegron treatment groups and placebo. Tolerability data were evaluated descriptively.

Results

Study populations

Patient demographics and baseline characteristics [19–21, 23] were comparable across treatment groups and across studies for both the overall populations and for the subgroups of patients aged ≥65 and ≥75 years (Table 1). Across all treatment groups, 36–39% of patients (FAS) were aged ≥65 years and 7–12% were aged ≥75 years (Table 1). The proportion of patients who had received previous OAB medication increased with age group for all treatment arms except the tolterodine treatment arm of the 1-year study; this proportion ranged from 50 to 63% of patients aged ≥65 years and from 61 to 69% of those aged ≥75 years (Table 1). Among patients aged ≥65 years who had received previous antimuscarinic therapy, between 65.8% (pooled placebo group) and 70.7% (mirabegron 25 mg group and pooled 50 mg group) had discontinued their prior therapy due to insufficient clinical effect and between 22.8% (mirabegron 25 mg) and 33.7% (tolterodine ER 4 mg) had discontinued due to intolerability.

Efficacy results

Incontinence frequency

In the subanalysis of the 12-week data, mirabegron 25 mg and 50 mg once-daily, reduced the mean number of incontinence episodes/24 h from baseline to final visit (Figure 1A) in both the ≥65 and ≥75-year subgroups, and improvements were numerically larger than for placebo. The adjusted mean differences versus placebo (treatment effect) for the mirabegron 25 mg and 50 mg doses were similar in all patients and in both age subgroups, and there was little difference with age for either dose of mirabegron. Over a 12-week period the treatment effect of tolterodine ER 4 mg on incontinence frequency in Study 046 was somewhat smaller than with either dose of mirabegron (Figure 1A).

Micturition frequency

In the subanalysis of the 12-week data, mirabegron 25 mg and 50 mg once-daily reduced the mean micturition

Table 1. Demographic and baseline characteristics by treatment group; all patients (FAS) and subgroups of patients aged ≥65 and ≥75 years (SAF)

Studies	12-week studies 046, 047 and 074	074	046, 047 and 074	046	Study 049 (1-year study)	
Treatment group	Placebo[a] (*n* = 1328)	Mirabegron 25 mg (*n* = 410)	Mirabegron 50 mg (*n* = 1324)	Tolterodine ER 4 mg (*n* = 475)	Mirabegron 50 mg (*n* = 789)	Tolterodine ER 4 mg (*n* = 791)
All patients (FAS)						
Female, *n* (%)	966 (72.7)	276 (67.3)	942 (71.1)	346 (72.8)	585 (74.1)	585 (74.0)
Mean age (years) (SD)	59.2 (13.2)	58.8 (12.7)	59.7 (12.6)	59.1 (12.8)	59.2 (12.5)	59.7 (12.4)
Range	20–95	22–85	21–91	18–83	21–87	22–87
Number (%) of patients in subgroups						
≥65 years	504 (38.0)	147 (35.9)	499 (37.7)	184 (38.7)	282 (35.7)	296 (37.4)
≥75 years	154 (11.6)	32 (7.8)	149 (11.3)	33 (6.9)	74 (9.4)	79 (10.0)
Race, *n* (%)						
White	1227 (92.4)	373 (91.0)	1235 (93.3)	472 (99.4)	755 (95.7)	761 (96.2)
Black/African American	80 (6.0)	31 (7.6)	61 (4.6)	2 (0.4)	22 (2.8)	18 (2.3)
Asian	13 (1.0)	5 (1.2)	17 (1.3)	1 (0.2)	8 (1.0)	5 (0.6)
Other	8 (0.6)	1 (0.2)	11 (0.8)	0	4 (0.5)	7 (0.9)
Mean BMI (kg/m^2) (SD)	29.1 (6.3)	29.6 (6.3)	29.0 (6.1)	27.9 (5.0)	28.9 (6.2)	28.5 (5.6)
Range	16–58	18–58	16–60	18–49	18–58	16–53
Type of OAB, *n* (%)						
Urgency incontinence	442 (33.3)	156 (38.0)	491 (37.1)	184 (38.7)	286 (36.2)	311 (39.3)
Mixed stress/urgency incontinence	415 (31.3)	124 (30.2)	412 (31.1)	186 (39.2)	227 (28.8)	203 (25.7)
Frequency/urgency without incontinence	471 (35.5)	130 (31.7)	421 (31.8)	105 (22.1)	276 (35.0)	277 (35.0)
Mean duration of OAB (months) (SD)	86.3 (99.1)	97.4 (115.1)	85.2 (93.1)	76.3 (93.4)	87.8 (95.3)	82.9 (87.0)
Received previous OAB drug, *n* (%)	704 (53.0)	219 (53.4)	688 (52.0)	231 (48.6)	434 (55.0)	435 (55.0)
Discontinued previous OAB drug, *n* (%) because of						
Poor tolerability	185 (26.3)	48 (21.9)	173 (25.1)	56 (24.2)	96 (22.1)	120 (27.6)
Insufficient efficacy	466 (66.2)	149 (68.0)	464 (67.4)	155 (67.1)	288 (66.4)	272 (62.5)
Subgroups aged ≥65 and ≥75 years (SAF)						
≥65 years, *n* (%)	521 (37.8)	154 (35.6)	514 (37.4)	192 (38.8)	289 (35.6)	303 (37.3)
≥75 years, *n* (%)	157 (11.4)	32 (7.4)	154 (11.2)	37 (7.5)	75 (9.2)	83 (10.2)
Female, *n* (%) in						
≥65 year age group	334 (64.1)	95 (61.7)	326 (63.4)	131 (68.2)	203 (70.2)	209 (69.0)
≥75 year age group	99 (63.1)	18 (56.3)	98 (63.6)	26 (70.3)	47 (62.7)	59 (71.1)
Mean age (years) (SD)						
≥65 year age group	72.2 (5.4)	71.4 (4.9)	72.0 (5.3)	70.9 (4.5)	71.5 (4.8)	71.9 (4.8)
≥75 year age group	78.9 (3.5)	78.8 (3.3)	78.7 (3.2)	78.2 (2.1)	78.2 (2.9)	78.1 (2.9)
White, *n* (%)						
≥65 year age group	505 (96.9)	149 (96.8)	501 (97.5)	191 (99.5)	287 (99.3)	298 (98.4)
≥75 year age group	145 (92.4)	31 (96.9)	145 (94.2)	36 (97.3)	74 (98.7)	82 (98.8)
Mean BMI (kg/m^2) (SD)						
≥65 year age group	28.3 (5.4)	29.0 (5.3)	28.3 (5.2)	28.0 (4.4)	28.7 (5.3)	28.3 (4.5)
≥75 year age group	27.9 (5.2)	28.8 (4.6)	27.9 (5.0)	27.3 (4.0)	27.8 (4.7)	27.1 (3.9)
Received previous OAB drug, *n* (%)						
≥65 year age group	292 (56.0)	92 (59.7)	304 (59.1)	95 (49.5)	175 (60.6)	191 (63.0)
≥75 year age group	99 (63.1)	22 (68.8)	96 (62.3)	23 (62.2)	51 (68.0)	51 (61.4)
Discontinued previous OAB drug due to poor tolerability; *n* (%)[b]						
≥65 year age group	88 (30.1)	21 (22.8)	78 (25.7)	32 (33.7)	34 (19.4)	60 (31.4)
≥75 year age group	30 (30.3)	4 (18.2)	21 (21.9)	11 (47.8)	9 (17.6)	18 (35.3)
Discontinued previous OAB drug due to insufficient efficacy, *n* (%)[b]						
≥65 year age group	192 (65.8)	65 (70.7)	215 (70.7)	64 (67.4)	117 (66.9)	119 (62.3)
≥75 year age group	60 (60.6)	15 (68.2)	73 (76.0)	11 (47.8)	38 (74.5)	27 (52.9)
History of						
Hypertension, not taking antihypertensives at baseline *n* (%)						
≥65 year age group	25 (4.8)	13 (8.4)	19 (3.7)	3 (1.6)	5 (1.7)	15 (5.0)
≥75 year age group	10 (6.4)	3 (9.4)	9 (5.8)	1 (2.7)	2 (2.7)	3 (3.6)
Hypertension, taking antihypertensives at baseline, *n* (%)[c]						
≥65 year age group	275 (52.8)	88 (57.1)	277 (53.9)	115 (59.9)	171 (59.2)	176 (58.1)
≥75 year age group	91 (58.0)	18 (56.3)	84 (54.5)	26 (70.3)	47 (62.7)	62 (74.7)
Tachyarrhythmia, *n* (%)						
≥65 year age group	20 (3.8)	5 (3.2)	29. (5.6)	4 (2.1)	9 (3.1)	17 (5.6)
≥75 year age group	9 (5.7)	0	15 (9.7)	3 (8.1)	1 (1.3)	8 (9.6)

Continued

Table 1. Continued

Studies	12-week studies 046, 047 and 074	074	046, 047 and 074	046	Study 049 (1-year study)	
Treatment group	Placebo[a] (*n* = 1328)	Mirabegron 25 mg (*n* = 410)	Mirabegron 50 mg (*n* = 1324)	Tolterodine ER 4 mg (*n* = 475)	Mirabegron 50 mg (*n* = 789)	Tolterodine ER 4 mg (*n* = 791)
Atrial fibrillation/flutter, *n* (%)						
≥65 year age group	13 (2.5)	5 (3.2)	23 (4.5)	4 (2.1)	3 (1.0)	13 (4.3)
≥75 year age group	8 (5.1)	0	12 (7.8)	3 (8.1)	1 (1.3)	7 (8.4)
Hyperlipidaemia, *n* (%)						
≥65 year age group	195 (37.4)	62 (40.3)	187 (36.4)	42 (21.9)	93 (32.2)	90 (29.7)
≥75 year age group	63 (40.1)	10 (31.3)	68 (44.2)	10 (27.0)	26 (34.7)	24 (28.9)
Atherosclerotic disease, *n* (%)						
≥65 year age group	107 (20.5)	20 (13.0)	95 (18.5)	42 (21.9)	37 (12.8)	61 (20.1)
≥75 year age group	48 (30.6)	6 (18.8)	33 (21.4)	17 (45.9)	15 (20.0)	29 (34.9)
Cardiac failure, *n* (%)						
≥65 year age group	6 (1.2)	1 (0.6)	3 (0.6)	3 (1.6)	1 (0.3)	3 (1.0)
≥75 year age group	3 (1.9)	1 (3.1)	3 (1.9)	0	0	0
Diabetes mellitus, *n* (%)						
≥65 year age group	57 (10.9)	23 (14.9)	50 (9.7)	18 (9.4)	33 (11.4)	30 (9.9)
≥75 year age group	17 (10.8)	7 (21.9)	15 (9.7)	5 (13.5)	4 (5.3)	9 (10.8)
Benign prostatic hyperplasia (males only), *n* (%)[d]						
≥65 year age group	103 (55.1)	29 (49.2)	84 (44.7)	32 (52.5)	48 (55.8)	45 (47.9)
≥75 year age group	35 (60.3)	7 (50.0)	31 (55.4)	7 (63.6)	15 (53.6)	15 (62.5)
Glaucoma, *n* (%)						
≥65 year age group	22 (4.2)	8 (5.2)	16 (3.1)	1 (0.5)	5 (1.7)	16 (5.3)
≥75 year age group	10 (6.4)	3 (9.4)	6 (3.9)	1 (2.7)	2 (2.7)	7 (8.4)
Malignant disease, *n* (%)						
≥65 year age group	59 (11.3)	16 (10.4)	62 (12.1)	16 (8.3)	20 (6.9)	33 (10.9)
≥75 year age group	21 (13.4)	6 (18.6)	24 (15.6)	2 (5.4)	3 (4.0)	13 (15.7)

BMI, body mass index; FAS, full analysis set; OAB, overactive bladder; SAF, safety analysis set; SD, standard deviation.
[a]Demographic and baseline characteristics of the placebo groups of Study 046 (*n* = 497) and Study 074 (*n* = 433) are not shown separately (although efficacy data for these placebo groups are presented in this paper) as these placebo groups are included in the pooled placebo group shown; demographic and baseline characteristics of individual placebo groups were similar to those shown here for the pooled placebo group.
[b]Percentages are based on patients who had taken previous OAB medication. Patients could choose more than one reason for discontinuation.
[c]Based on medical history and medication history.
[d]Percentage of total number of males in group.

frequency from baseline to final visit in both subgroups of older patients and improvements were numerically greater than for placebo (Figure 1B). The largest treatment effect was seen with the mirabegron 25 mg dose in the ≥65-year subgroup. With mirabegron 50 mg the magnitude of the treatment effect was independent of subgroup age category. The adjusted change from baseline in micturition frequency over a 12-week period with tolterodine ER 4 mg in Study 046 was smaller than with either dose of mirabegron in all patients and both age subgroups. The treatment effect of tolterodine relative to placebo was likewise smaller than with either dose of mirabegron (Figure 1B).

Safety and tolerability

In the subanalysis of the 12-week data (both individual and pooled treatment arms), between 49% (pooled placebo group) and 55% (mirabegron 25 mg group of Study 074) of patients aged ≥65 years experienced a TEAE (Table 2). The overall incidence of TEAEs was more variable in the ≥75-year subgroup than in the ≥65-year subgroup (ranging from 49% [pooled placebo group] to 63% [mirabegron 25 mg group of Study 074]) and was higher over 1 year (65 and 68% of patients aged ≥65 and ≥75 years, respectively, who had been randomised to mirabegron 50 mg and 64% of patients in both age subgroups who had been randomised to tolterodine) than over 12 weeks.

The three most common TEAEs over 12 weeks in patients aged ≥65 years randomised to mirabegron 50 mg were hypertension, nasopharyngitis and UTI (9.9, 4.1 and 3.1%, respectively; Table 2). In patients randomised to mirabegron 50 mg in the ≥75-year subgroup, these were also among the most common TEAEs in the 12-week analysis but headache, dry mouth and pain in extremity (each 2.6%) were more common than UTI (1.9%). In both older subgroups, hypertension and UTI were still the most common TEAEs with mirabegron 50 mg over the 1-year period. In the ≥65-year subgroup, over 12 weeks, the incidence of the most common TEAEs was similar for both doses of mirabegron and placebo, except for hypertension, UTI and dizziness, which occurred with a higher incidence in the mirabegron 25 mg group than the placebo or mirabegron 50 mg groups. Over 12 weeks, in the ≥75-year subgroup, the incidence of hypertension with tolterodine ER 4 mg was

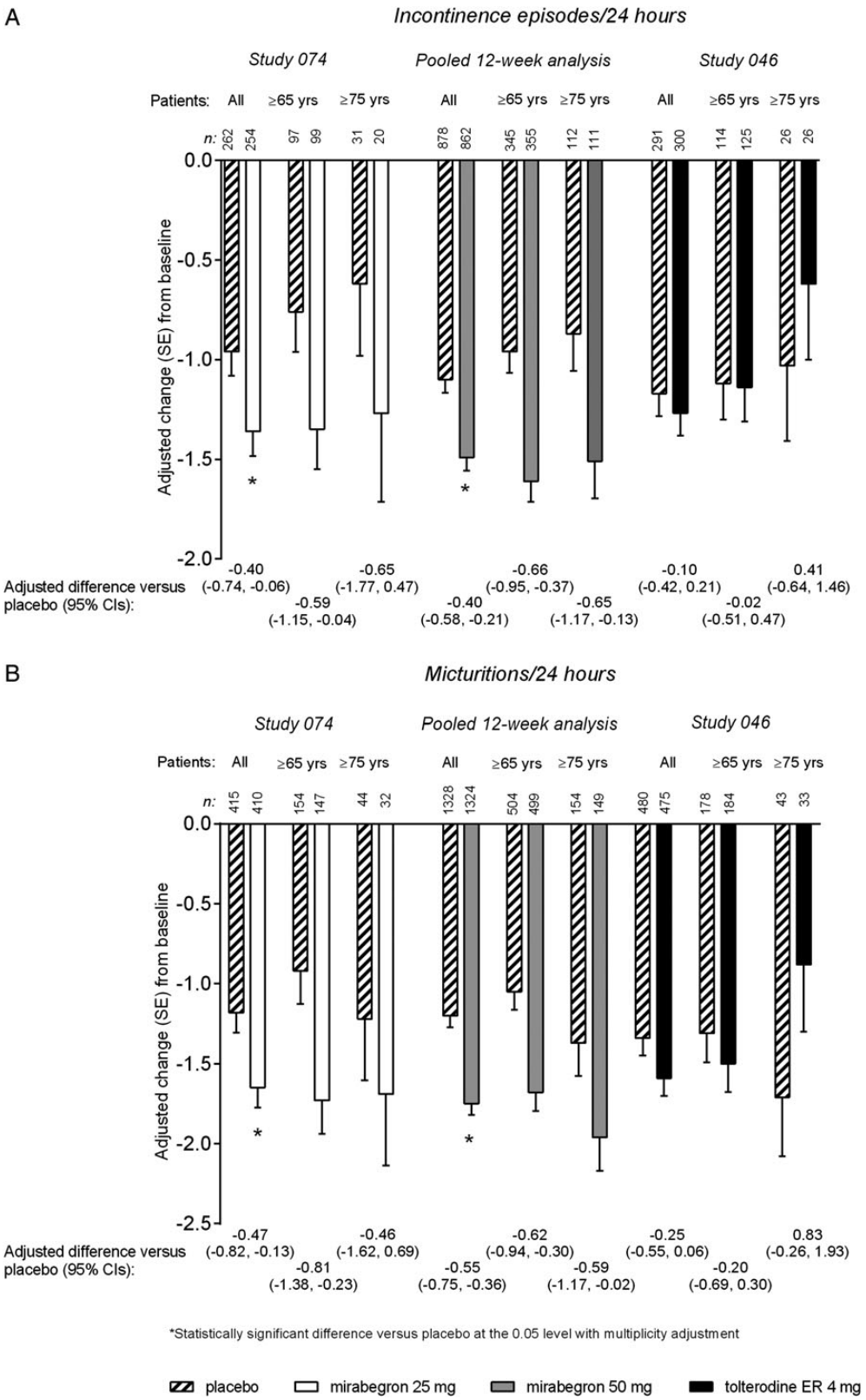

Figure 1. Adjusted mean change from baseline to final visit (SE) in (A) mean number of incontinence episodes/24 h (FAS-I) and (B) mean number of micturitions/24 h (FAS) over 12 weeks with mirabegron 25 mg (Study 074), mirabegron 50 mg (Studies 046, 047 and 074 pooled) and tolterodine ER 4 mg (Study 046) versus placebo; all patients and subpopulations of patients aged ≥65 and ≥75 years.

Table 2. TEAEs by preferred term; 12-week and 1-year analyses (SAF)

12-week analysis								
Age category	≥65 years				≥75 years			
	Placebo[a]	Mirabegron		Tolterodine ER 4 mg	Placebo[a]	Mirabegron		Tolterodine ER 4 mg
	(*n* = 521)	25 mg (*n* = 154)	50 mg (*n* = 514)	(*n* = 192)	(*n* = 157)	25 mg (*n* = 32)	50 mg (*n* = 154)	(*n* = 37)
Studies	046, 047, 074	074	046, 047, 074	046	046, 047, 074	074	046, 047, 074	046
Any TEAE, *n* (%)	254 (48.8)	84 (54.5)	258 (50.2)	95 (49.5)	77 (49.0)	20 (62.5)	77 (50.0)	22 (59.5)
TEAEs reported by ≥3% of patients in any treatment group in the ≥65-year subgroup (by preferred term), *n* (%)								
Hypertension	44 (8.4)	21 (13.6)	51 (9.9)	23 (12.0)	15 (9.6)	6 (18.8)	21 (13.6)	8 (21.6)
Nasopharyngitis	13 (2.5)	7 (4.5)	21 (4.1)	7 (3.6)	2 (1.3)	0	4 (2.6)	2 (5.4)
UTI	15 (2.9)	10 (6.5)	16 (3.1)	3 (1.6)	3 (1.9)	5 (15.6)	3 (1.9)	0
Headache	9 (1.7)	4 (2.6)	14 (2.7)	9 (4.7)	0	2 (6.3)	4 (2.6)	1 (2.7)
Dry mouth	8 (1.5)	3 (1.9)	9 (1.8)	21 (10.9)	0	0	4 (2.6)	4 (10.8)
Dizziness	8 (1.5)	7 (4.5)	9 (1.8)	3 (1.6)	1 (0.6)	1 (3.1)	2 (1.3)	0
Constipation	8 (1.5)	4 (2.6)	7 (1.4)	6 (3.1)	5 (3.2)	1 (3.1)	2 (1.3)	1 (2.7)
Pain in extremity	8 (1.5)	5 (3.2)	7 (1.4)	0	1 (0.6)	1 (3.1)	4 (2.6)	0
Any TEAE leading to discontinuation, *n* (%)	26 (5.0)	7 (4.5)	29 (5.6)	14 (7.3)	6 (3.8)	1 (3.1)	12 (7.8)	6 (16.2)
Any SAE, *n* (%)	15 (2.9)	2 (1.3)	14 (2.7)	8 (4.2)	3 (1.9)	0	5 (3.2)	4 (10.8)
1 year study								
			(*n* = 289)	(*n* = 303)			(*n* = 75)	(*n* = 83)
Any TEAE, *n* (%)			188 (65.1)	195 (64.4)			51 (68.0)	53 (63.9)
TEAEs reported by ≥3% of patients in any treatment group in the ≥65-year subgroup (by preferred term), *n* (%)								
Hypertension			30 (10.4)	39 (12.9)			7 (9.3)	12 (14.5)
UTI			23 (8.0)	25 (8.3)			7 (9.3)	9 (10.8)
Dizziness			14 (4.8)	11 (3.6)			2 (2.7)	5 (6.0)
Constipation			12 (4.2)	10 (3.3)			3 (4.0)	5 (6.0)
Influenza			12 (4.2)	7 (2.3)			5 (6.7)	2 (2.4)
Back pain			10 (3.5)	5 (1.7)			4 (5.3)	1 (1.2)
Nasopharyngitis			9 (3.1)	6 (2.0)			2 (2.7)	1 (1.2)
Dry mouth			9 (3.1)	31 (10.2)			0	8 (9.6)
Bronchitis			9 (3.1)	10 (3.3)			1 (1.3)	2 (2.4)
Diarrhoea			8 (2.8)	9 (3.0)			3 (4.0)	4 (4.8)
Cystitis			8 (2.8)	14 (4.6)			2 (2.7)	4 (4.8)
Fatigue			5 (1.7)	9 (3.0)			1 (1.3)	3 (3.6)
Headache			4 (1.4)	9 (3.0)			2 (2.7)	2 (2.4)
Any TEAE leading to discontinuation, *n* (%)			20 (6.9)	23 (7.6)			6 (8.0)	6 (7.2)
Any SAE, *n* (%)			18 (6.2)	22 (7.3)			9 (12.0)	8 (9.6)

AE, adverse event; SAE, serious adverse event; SAF, safety analysis set; TEAE, treatment-emergent adverse event; UTI, urinary tract infection.

[a]Tolerability data for the placebo groups of Study 046 and Study 074 are not shown separately (although efficacy data for these placebo groups are presented in this paper) as these placebo groups are included in the pooled placebo group shown; tolerability data for individual placebo groups were similar to those shown here for the pooled placebo group.

seen to be higher (21.6%) than with either dose of mirabegron (18.8 and 13.6% for the 25 and 50 mg doses, respectively) or placebo (9.6%). The incidence of hypertension in the oldest patients was also higher with tolterodine (14.5%) than mirabegron 50 mg (9.3%) over a 1-year period (Table 2).

Dry mouth and constipation are AEs of particular interest as these are typically associated with the use of antimuscarinics. There was no evidence of a mirabegron dose–response relationship in the incidence of any of these AEs over a 12-week period and their incidence was similar to that seen with placebo. The largest difference between treatment groups in AE incidence was seen for dry mouth. In the ≥65-year subgroup, dry mouth occurred with a sixfold higher incidence with tolterodine than mirabegron 25 mg or 50 mg over 12 weeks and a threefold higher incidence with tolterodine than mirabegron 50 mg over 1 year. In the ≥75-year subgroup, dry mouth occurred with a fourfold higher incidence with tolterodine than mirabegron 50 mg over 12 weeks (there were no cases of dry mouth with mirabegron 25 mg over 12 weeks or with mirabegron 50 mg over 1 year).

The incidence of serious AEs (SAEs) and TEAEs that led to discontinuation was low and comparable across treatment groups in both age subgroups over 1 year. Constipation was the only TEAE that resulted in permanent discontinuation of the 1-year study by ≥2% of older patients in any treatment group: one patient (0.3%) aged ≥65 years in the tolterodine group and two patients (2.7%) aged ≥75 years in the mirabegron 50 mg group. Over 12 weeks, the overall incidence of SAEs and TEAEs leading to permanent discontinuation of study drug was higher with tolterodine than with either dose of mirabegron or placebo in both older subgroups (Table 2). Hypertension led to study discontinuation by two patients aged ≥65 years in each of the placebo (0.4%), mirabegron 25 mg (1.3%) and mirabegron 50 mg (0.4%) groups (none were aged ≥75 years), and by one patient (2.7%) aged ≥75 years in the tolterodine group. Constipation led to study discontinuation by two patients (0.4%) aged ≥65 years in the placebo group and by one patient aged ≥75 years in each of the placebo (0.6%), mirabegron 25 mg (3.1%), mirabegron 50 mg (0.6%) and tolterodine (2.7%) groups. The only other TEAE that resulted in discontinuation of a 12-week study by a mirabegron-treated patient was pruritic rash (one patient [0.6%] in the mirabegron 25 mg group).

Discussion

This study showed that mirabegron 25 mg and 50 mg once-daily reduced the mean number of incontinence episodes and micturitions/24 h from baseline to final visit in two groups of older OAB patients (those aged ≥65 or ≥75 years) with no loss of efficacy. Darifenacin, fesoterodine, solifenacin and tolterodine have previously been shown to be efficacious in patients aged ≥65 years [23–30], although one study [31] found that greater age was associated with a slight, but statistically significant, decrease in the efficacy of tolterodine. In the analysis presented here, tolterodine showed a lesser treatment effect relative to placebo with increasing age for both incontinence and micturition frequency over 12 weeks.

Mirabegron was well tolerated in older OAB patients, with no difference in tolerability with age over a 1-year period. Over 12 weeks, the incidence of TEAEs, overall and individually, was more variable in the oldest subgroup; however, this may be attributed to the smaller number of patients, particularly in the treatment groups derived from single studies (mirabegron 25 mg in Study 074 and tolterodine ER 4 mg in Study 046). The incidence of TEAEs, TEAEs leading to permanent discontinuation of study drug, and SAEs was higher among patients aged ≥65 years in both the mirabegron 50 mg and tolterodine ER 4 mg groups of the 1-year study compared with the 12-week analyses, as expected given the longer duration of exposure. As reported previously for the total pooled population [22], hypertension and UTI were among the most common TEAEs with mirabegron in older patients over both 12 weeks and 1 year and, in the 12-week analysis, in patients aged ≥65 years, their incidence in the mirabegron 50 mg group was comparable with that seen with placebo and tolterodine. For patients aged ≥65 years, it is difficult to draw a meaningful inference from this single descriptive analysis given the variability of these data, and the underlying limitations of sample size. Over 12 weeks and 1 year, the incidence of hypertension with tolterodine ER 4 mg was higher than that seen with mirabegron 50 mg. Dry mouth and constipation, which are often cited as AEs leading to discontinuation with antimuscarinics and which may be particularly troubling in older patients, occurred with a similar incidence with either dose of mirabegron compared with placebo in the ≥65-year subgroup over 12 weeks. Dry mouth occurred with an incidence that was as much as sixfold higher among older patients (whether ≥65 or ≥75 years) randomised to tolterodine compared with any dose of mirabegron. A previously reported study has established ocular safety in healthy volunteers [32].

These analyses demonstrate that mirabegron is efficacious in the treatment of the symptoms of OAB in older adults. In short-term studies, there appears to be no loss of efficacy with age. However, there remains a need for longer-term, prospective studies to assess the efficacy of mirabegron in older patients, either in the form of interventional or in the form of observational studies. A low incidence of typical antimuscarinic AEs that often lead to poor long-term adherence to treatment [33] may be a particular advantage for community dwelling older patients and those clinicians treating them. The lack of age-related differences in the tolerability of mirabegron simplifies management for the treating physician. Hence, mirabegron may be a more suitable first line option than antimuscarinics for the treatment of symptoms of OAB in community dwelling older patients.

Key points

- Mirabegron (25 mg and 50 mg once-daily) reduced the frequency of incontinence episodes and micturitions in older patients over 12 weeks.
- Mirabegron was well tolerated, regardless of age, over 12-week and 1-year study periods.
- The incidence of TEAEs was similar with mirabegron and placebo in the pooled 12-week analysis.
- The incidence of dry mouth was as much as sixfold higher with tolterodine than mirabegron in patients aged 65 years or older.

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Conflicts of interest

A.W. has acted as a consultant to Pfizer, Astellas, SCA and Watson Pharma; he, and his institution, have received payment for lectures including service on speakers bureaus from Astellas, Pfizer and SCA; and his institution has received grants or has grants for research pending from Pfizer and Astellas L.C. has, during the last year, received funding for research, lecturing and/or advice/consultancies from the following organisations: Astellas (as member of Global Advisory Board for solifenacin, co-chairman of the European OAB forum, principal investigator for the SUNRISE study and speaker at satellite symposia) and Pfizer (as member of Global Advisory Board for fesoterodine and as a participant in a multi-centre research study). She has also been reimbursed by Allergan, Astellas, Ethicon, Merck, Pfizer and Teva for research consultancy and/or advisory work. V.N. has received grants from Astellas, Allergan and Coloplast; has received consulting fees or honoraria from Astellas, Allergan, Ipsen, Ono, Pfizer and Teva; payment for lectures including service on speakers' bureaus from Allergan; and has received support for travel to meetings in regard to the work presented here from Astellas. D.C.-D. has been reimbursed by Astellas for expert testimony and by Astellas, AMS and Eli Lilly for the development of educational presentations. S.A. has received consulting fees or honoraria for serving on medical advisory boards for Astellas, Allergan, Auxilium, Eli Lilly and Sophiris-Bio; and his institution has received grants from Allergan, Astellas, Auxilium, Eli Lilly, HEB, Serenity and Sophiris-Bio for conducting clinical trials; M.B.B. and E.S. are employees of the study sponsor.

References

1. Abrams P, Cardozo L, Fall M *et al*. The standardization of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002; 21: 167–78.
2. Milsom I, Irwin DE. A cross-sectional, population-based, multinational study of the prevalence of overactive bladder and lower urinary tract symptoms: results from the EPIC study. Eur Urol 2007; 6(Suppl 1): 4–9.
3. Stewart WF, Van Rooyen JB, Cundiff GW *et al*. Prevalence and burden of overactive bladder in the United States. World J Urol 2003; 20: 327–36.
4. Macdiarmid SA. Maximizing the treatment of overactive bladder in the elderly. Rev Urol 2008 Winter; 10: 6–13.
5. Brown JS, McGhan WF, Chokroverty S. Comorbidities associated with overactive bladder. Am J Manag Care 2000; 6(11 Suppl): S574–79.
6. McGhan WF. Cost effectiveness and quality of life considerations in the treatment of patients with overactive bladder. Am J Manag Care 2001; 7(2 Suppl): S62–75.
7. Buser N, Ivic S, Kessler TM, Kessels AG, Bachmann LM. Efficacy and adverse events of antimuscarinics for treating overactive bladder: network meta-analyses. Eur Urol 2012; 62: 1040–60.
8. Wagg A. Treating overactive bladder in the elderly. Can Urol Assoc J 2011; 5(2 Suppl): S149–51.
9. Kay GG, Granville LJ. Antimuscarinic agents: implications and concerns in the management of overactive bladder in the elderly. Clin Ther 2005; 27: 127–38.
10. Katz IR, Sands LP, Bilker W *et al*. Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride. J Am Geriatr Soc 1998; 46: 8–13.
11. Staskin D, Kay G, Tannenbaum C *et al*. Trospium chloride has no effect on memory testing and is assay undetectable in the central nervous system of older patients with overactive bladder. Int J Clin Pract 2010; 64: 1294–300.
12. Kay G, Crook T, Rekeda L *et al*. Differential effects of the antimuscarinic agents darifenacin and oxybutynin ER on memory in older subjects. Eur Urol 2006; 50: 317–26.
13. Lipton RB, Kolodner K, Wesnes K. Assessment of cognitive function of the elderly population: effects of darifenacin. J Urol 2005; 173: 493–8.
14. Kay GG, Maruff P, Scholfield D *et al*. Evaluation of cognitive function in healthy older subjects treated with fesoterodine. Postgrad Med 2012; 124: 7–15.
15. Wesnes KA, Edgar C, Tretter RN, Bolodeoku J. Exploratory pilot study assessing the risk of cognitive impairment or sedation in the elderly following single doses of solifenacin 10 mg. Expert Opin Drug Saf 2009; 8: 615–26.
16. Wagg A, Dale M, Tretter R *et al*. Randomised, multicentre, placebo-controlled, double-blind crossover study investigating the effect of solifenacin and oxybutynin in elderly people with mild cognitive impairment: the SENIOR study. Eur Urol 2013; 64: 74–81.
17. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2012; 60: 616–31.
18. Imran M, Najmi AK, Tabrez S. Mirabegron for overactive bladder: a novel, first-in-class β3- agonist therapy. Urol J 2013; 10: 935–40.

19. Khullar V, Amarenco G, Angulo J *et al*. The efficacy and tolerability of mirabegron, a ß3-adrenoceptor agonist, in patients with overactive bladder: results from a randomized European–Australian phase 3 trial. Eur Urol 2013; 63: 283–95.
20. Nitti V, Auerbach S, Martin N, Calhoun A, Lee M, Herschorn S. Results of a randomized phase III trial of mirabegron in patients with overactive bladder. J Urol 2013; 189: 1388–95.
21. Herschorn S, Barkin J, Castro-Diaz D *et al*. A phase III, randomized, double-blind, parallel-group, placebo-controlled, multicenter study to assess the efficacy and safety of the beta-3 agonist mirabegron in patients with symptoms of overactive bladder. Urology 2013; 82: 313–20.
22. Nitti V, Herschorn S, Khullar V *et al*. Mirabegron for the treatment of overactive bladder: a prespecified pooled efficacy analysis and pooled safety analysis of three randomised, double-blind, placebo-controlled, phase III studies. Int J Clin Pract 2013; 67: 619–32. doi: 10.1111/ijcp.12194.
23. Chapple C, Kaplan S, Mitcheson D *et al*. Randomized, double-blind, active-controlled phase III study to assess 12-month safety and efficacy of mirabegron, a B3 adrenoceptor agonist in overactive bladder (OAB). Eur Urol 2013; 63: 296–305.
24. Chapple C, DuBeau C, Ebinger U, Rekeda L, Viegas A. Darifenacin treatment of patients > or =65 years with overactive bladder: results of a randomized, controlled, 12-week trial. Curr Med Res Opin 2007; 23: 2347–58.
25. Malone-Lee JG, Walsh JB, Maugourd MF. Tolterodine: a safe and effective treatment for older patients with overactive bladder. J Am Geriatr Soc 2001; 49: 700–5.
26. Zinner NR, Mattiasson A, Stanton SL. Efficacy, safety, and tolerability of extended-release once-daily tolterodine treatment for overactive bladder in older versus younger patients. J Am Geriatr Soc 2002; 50: 799–807.
27. Wagg A, Wyndaele JJ, Sieber P. Efficacy and tolerability of solifenacin in elderly subjects with overactive bladder syndrome: a pooled analysis. Am J Geriatr Pharmacother 2006; 4: 14–24.
28. Wagg A, Khullar V, Marschall-Kehrel D *et al*. Flexible-dose fesoterodine in elderly adults with overactive bladder: results of the randomized, double-blind, placebo-controlled study of fesoterodine in an aging population trial. JAGS 2013; 61: 185–93.
29. Dubeau CE, Morrow JD, Kraus SR, Creanga D, Bavendam T. Efficacy and tolerability of fesoterodine versus tolterodine in older and younger subjects with overactive bladder: A post hoc, pooled analysis from two placebo-controlled trials. Neurourol Urodyn 2012; 31: 1258–65.
30. Sand PK, Heesakkers J, Kraus SR, Carlsson M, Guan Z, Berriman S. Long-term safety, tolerability and efficacy of fesoterodine in subjects with overactive bladder symptoms stratified by age: pooled analysis of two open-label extension studies. Drugs Aging 2012; 29: 119–31.
31. Michel MC, Schneider T, Krege S, Goepel M. Does gender or age affect the efficacy and safety of tolterodine? J Urol 2002; 168: 1027–31.
32. Novack GD, Lewis RA, Vogel R, Sheth N, Swearingen D, Rasmussen S, Hantsbarger G, Martin NE. Randomized, double-masked, placebo-controlled study to assess the ocular safety of mirabegron in healthy volunteers. J Ocul Pharmacol Ther 2013; 29: 674–80.
33. Wagg A, Compion G, Fahey A, Siddiqui E. Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. BJU Int 2012; 110: 1767–7.

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