



# Factors Associated with Improvements in Patient-Reported Outcomes During Mirabegron or Antimuscarinic Treatment of Overactive Bladder Syndrome: A Registry Study (PERSPECTIVE)

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## ABSTRACT

**Introduction:** Patient-reported outcomes (PROs) provide valuable insights about the effectiveness of overactive bladder (OAB) treatments. The aim of PERSPECTIVE (a Prospective,

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non-interventional Registry Study of Patients initiating a Course of drug Therapy for overactive bladder) was to provide real-world evidence from the USA and Canada on patient-perceived effectiveness and safety of mirabegron and antimuscarinics for treating OAB symptoms.

**Methods:** This prospective, non-interventional registry followed adult patients with OAB who were starting treatment with mirabegron or antimuscarinics. All treatment decisions were made at the discretion of the treating healthcare provider with no mandatory visits after enrollment. The primary objective was to identify factors associated with improved treatment effectiveness from a patient perspective mainly using the OAB Questionnaire Short-Form (OAB-q SF). The form was sent to patients via email link at baseline and months 1, 3, 6, and 12. Treatment-emergent adverse event (TEAE) data were collated from investigator reports.

**Results:** Overall, 1514 patients were included (female 73.5%, mean age 62.2 years). Mirabegron was initiated by 613 patients and antimuscarinics by 901 patients. A PRO response rate of approximately 60% was achieved (575 patients did not complete baseline PROs). Similar improvements in OAB-q SF symptom bother score and health-related quality of life (HRQoL) total score were observed for mirabegron and antimuscarinic initiators. Covariate-adjusted models demonstrated that worse baseline PRO score, Hispanic ethnicity,

being treatment naïve, and use of complementary/supportive OAB therapies at baseline were significantly associated with greater improvements in both scores. The most frequent TEAEs were gastrointestinal disorders (dry mouth, constipation, and nausea) and nervous system disorders (headache, somnolence, and dizziness).

**Conclusion:** There are no differences between mirabegron and antimuscarinics in terms of patient-reported OAB symptom bother and HRQoL.

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**Keywords:** Antimuscarinic; Mirabegron; Overactive bladder syndrome; Patient-reported outcomes; Registry; Urology

## PLAIN LANGUAGE SUMMARY

What is overactive bladder (OAB) syndrome?

- People with OAB feel a greater need to urinate and urinate more frequently.
- In the USA and Canada, approximately 1 in 5 people have OAB.
- OAB is often treated with a group of medicines called antimuscarinics or a medicine called mirabegron.

How was the study carried out?

- Men and women with OAB starting treatment with mirabegron or antimuscarinics were followed for 12 months in 91 centers in the USA/Canada.
- Doctors chose which medicine people took: 613 people took mirabegron, 901 people took antimuscarinics.
- People were asked to complete electronic questionnaires about their OAB symptoms and quality-of-life before, during, and after 12 months of treatment.

How well did the medicines work?

- People reported that both medicines improved their symptoms and quality-of-life.
- The level of improvement was similar for mirabegron and antimuscarinics, and seemed to be greater for people who:
  - Had worse questionnaire scores when they started treatment.
  - Were Hispanic.
  - Had not received OAB medication previously.
  - Were using complementary OAB treatments, such as bladder training and pelvic muscle exercises.

What were the side effects?

- Both medicines had side effects.
- Doctors had to report the side effects for mirabegron, but not for other therapies, so the side effects of the medicines cannot be compared directly.
- Approximately 3/10 people taking mirabegron had side effects; the most common were dry mouth, headache, and constipation.

What do the results of this study mean?

- Mirabegron or antimuscarinics both improve OAB symptoms and quality of life to a similar extent.

## INTRODUCTION

Overactive bladder (OAB) syndrome is characterized by urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia, in the absence of other causes [1, 2]. The burden of OAB is significant, with an estimated prevalence in the USA and Canada of approximately 20% and a total economic burden that may exceed 100 billion USD annually in the USA [3–5]. Furthermore, OAB has a significant negative

impact on patients' health-related quality of life (HRQoL) [6, 7].

Antimuscarinics and the  $\beta_3$ -adrenoreceptor agonist mirabegron are recommended as second-line therapies for OAB symptoms after behavioral therapy [8]. Both types of agent are well-established treatments for OAB symptoms [9–11]. Although antimuscarinics are the most widely used pharmacotherapies for OAB symptoms, anticholinergic side effects (including dry mouth, constipation, and blurred vision) are problematic in some patients [12]. Mirabegron represents an alternative to antimuscarinics for the treatment of OAB symptoms, with efficacy demonstrated across numerous studies, including in patients who had an insufficient response or intolerance to antimuscarinics [9, 10]. Furthermore, previous studies have demonstrated that mirabegron is associated with fewer anticholinergic side effects than antimuscarinics [13].

Clinical trials of OAB pharmacotherapies usually focus on objective measures of symptom improvement, such as micturition frequency and volume and the number of incontinence episodes using bladder diaries and/or urodynamic studies [14, 15]. However, there is growing recognition that subjective measures of OAB treatment effectiveness via patient-reported outcomes (PROs) also provide valuable insights. Objective measures of OAB symptom improvement may not fully represent treatment effect from the patients' perspective, which is also impacted by several factors including treatment satisfaction, the effect on HRQoL, and adverse events (AEs) [14, 15]. Furthermore, OAB management in normal clinical practice is usually based on patients reporting their symptoms and previous treatment experiences, so translation of clinical trial efficacy into real-world effectiveness from the patient's perspective is complicated [14].

We herein report the primary findings of PERSPECTIVE (a Prospective, non-interventional Registry Study of PatiEnts initiating a Course of drug Therapy for overactIVE bladder; NCT02386072), a large registry of OAB patients in the USA and Canada designed to provide evidence on the real-world, patient-perceived effectiveness and safety of mirabegron and

antimuscarinics for the treatment of OAB symptoms [16].

## METHODS

The rationale, design, and methodology of PERSPECTIVE have been previously described in detail [16]. In brief, this study was a prospective, multicenter, non-interventional registry, following adult patients in routine clinical practice diagnosed with OAB initiating a new course of treatment with either mirabegron or antimuscarinic medication between January 2015 and August 2017. Patients could be either treatment naïve or switching from a different OAB pharmacotherapy. The primary objective was to identify factors associated with improved effectiveness of pharmacologic therapy for OAB from a patient perspective measured primarily by the OAB Questionnaire Short-Form (OAB-q SF) [17].

This study was conducted in accordance with all applicable laws and regulations, and the ethical principles originating from the Declaration of Helsinki. The protocol and any associated documents were approved by the institutional review board or independent ethics committee at each site prior to enrollment (Table S1). All patients (or their legally authorized representative) provided informed consent before participation in the study.

### Recruitment

Enrollment of 1500 patients with OAB, primarily patients treated by urologists and primary care physicians, was planned from healthcare centers and sites across the USA (85%) and Canada (15%). Of these 1500 patients, it was intended that 600 patients treated with mirabegron and 900 patients treated with an antimuscarinic would be enrolled (as antimuscarinics were anticipated to be prescribed more frequently). Patient access to discounted and free medications varied by healthcare provider (HCP) and location, and initiation of therapy may have been either through prescription or samples. In Canada, except for British Columbia and Quebec, a patient-support program was available that

provided supplemental coverage of up to 100% of the total cost for mirabegron. The program was in place from December 2014 and continued in each province until public reimbursement was initiated in that province. No such program was available in the USA during the study.

### Inclusion/Exclusion Criteria

Patients aged at least 18 years who were diagnosed with OAB (with or without urgency urinary incontinence) by the treating HCP with symptoms for at least 3 months prior to study enrollment and who were initiating a new course of treatment with mirabegron or antimuscarinic medication (including transdermal patch formulations) for OAB were included. Patients had to be willing and able to provide informed consent and complete PRO questionnaires via email link with minimal assistance. Patients were excluded if they were receiving treatment with more than one OAB medication at the time of enrollment or had a history of OAB treatment with onabotulinum toxin A, sacral neuromodulation, percutaneous tibial nerve stimulation, external beam radiation therapy, urinary stents, surgery, or intermittent catheterization prior to or at the time of enrollment; had neurologic conditions associated with OAB symptoms; were pregnant or breastfeeding; or were resident in a nursing home.

### Data Collection

All decisions regarding treatment were made at the discretion of the treating HCP in accordance with their usual practices and all clinical assessments were performed at the time of a routine appointment. Patients were followed for up to 12 months with no mandatory scheduled visits after enrollment.

At baseline (i.e., time of enrollment), patient demographic and clinical OAB characteristics were collected. PROs were sent by email link to patients at baseline (days 0–7), month 1 (days 30–45), month 3 (days 91–125), month 6 (days 182–208), and month 12 (days 336–377) to be

completed electronically in their preferred language (English, French, or Spanish). Responses to baseline PROs were requested within 7 days of enrollment. Patients who failed to complete PROs at a given time point (including at baseline) remained in the study and were not excluded from analysis. PROs included the OAB-q SF [17] and the OAB treatment satisfaction questionnaire (OAB-S) [18].

The OAB-q SF [17] comprises a six-item symptom bother scale and a 13-item HRQoL scale consisting of three subscales (coping, sleep, and emotional/social). Patients rate each item on a six-point Likert scale ranging from “not at all” to “a very great deal” for symptom bother and from “none of the time” to “all of the time” for HRQoL. Scores are generated according to the scoring guidelines [17], with higher symptom bother scores indicating greater symptom bother and higher HRQoL scores indicating better HRQoL. The OAB-S [18] comprises five scales and five single-item overall assessments, including the OAB-S medication tolerability scale which captures bother associated with antimuscarinic AEs (specifically constipation, dry mouth, drowsiness, headache, nausea, and blurred vision).

A treatment-emergent AE (TEAE) was defined as an AE observed after initiation of study drug. TEAE data were based on reports from investigators. Consistent with the requirement for the study sponsor (Astellas Pharma) to report on the safety of its products, all TEAEs for mirabegron and solifenacin initiators (regardless of relationship to study treatment) were monitored and reported throughout the study (mandatory reporting), whereas identification of TEAEs for initiators of any other antimuscarinic was at the discretion of the investigator (discretionary reporting). Investigators were asked to assess the relationship of TEAEs to mirabegron/solifenacin as not related, possible, or probable. In addition, if a patient receiving mirabegron/solifenacin reported bother on the OAB-S medication tolerability scale or reported being hospitalized since the date of the last questionnaire, an email was sent to site staff to alert them to assess the side effect and report the potential TEAE. To establish whether there was differential reporting of TEAEs between the mirabegron and

antimuscarinic treatment groups, reported antimuscarinic TEAEs were cross-validated with their associated bother determined using the OAB-S medication tolerability scale responses.

### Statistical Analyses

The analysis population consisted of all enrolled patients who initiated a new course of treatment with either mirabegron or an antimuscarinic. The antimuscarinic data were assessed in terms of the group of therapeutics as a whole. As patients were not excluded from analysis if they failed to complete the PROs at a given time point (including at baseline), the number of patients who completed PROs at each time point varied.

Baseline demographic and clinical OAB characteristics were summarized for mirabegron and antimuscarinic initiators separately.

Analysis of covariance (ANCOVA) models with treatment group, sex, age, and treatment-naïve status as covariates were used to analyze changes from baseline to last reported score for OAB-q SF symptom bother score and HRQoL total score. Changes in the HRQoL coping, sleep, and emotional/social subscales from baseline to month 12 were also examined (data from months 1, 3, and 6 were not included in this analysis).

Univariate generalized linear regression models were used to identify baseline variables that were statistically significant predictors of changes in OAB-q SF symptom bother and HRQoL total scores from baseline to the last reported score in each treatment group. Covariate-adjusted generalized linear regression models were subsequently created which included the significant variables identified in the univariate models together with several predetermined variables (age, sex, baseline PRO score, and initial treatment group). Any co-linear variables (e.g., menopause status and pregnancy were co-linear with female sex) were excluded from the models.

TEAEs were summarized descriptively by treatment group at enrollment using the system organ classes and preferred terms identified through the use of the Medical Dictionary for Regulatory Activities (MedDRA; version 19.0).

## RESULTS

### Patients

A total of 1514 eligible patients were included in PERSPECTIVE, the majority of whom were female (73.5%) and white (87.2%), with a mean age of 62.2 years (Table 1). Mirabegron was initiated by 613 patients and antimuscarinics by 901 patients (Fig. 1). The most frequently initiated antimuscarinics were oxybutynin (46.9% of antimuscarinic initiators), solifenacin (33.1%), and tolterodine (10.0%). A greater proportion of antimuscarinic initiators were treatment naïve (no OAB medication in past 12 months, 81.2%) compared with mirabegron initiators (71.0%, Table 1).

A greater proportion of Canadian patients initiated mirabegron (70.6%) compared with US patients (32.6%). Furthermore, differences in type of drug coverage were apparent between mirabegron and antimuscarinic initiators, with fewer US patients with no coverage initiating mirabegron than antimuscarinics and a lower proportion of US antimuscarinic initiators having private insurance than mirabegron initiators (Table 1). In Canada, fewer mirabegron initiators had provincial health coverage than antimuscarinic initiators.

Most patients were recruited into the study by either primary care clinicians (48.5%) or urologists (43.7%). A greater proportion of mirabegron initiators were enrolled by urologists compared with primary care physicians, whereas the opposite was true for antimuscarinic initiators.

A total of 76.3% of patients were reported as having OAB with incontinence and, among those, 19.9% were reported to have urgency urinary incontinence (not stress or mixed urinary incontinence). A higher rate of OAB with incontinence and a higher mean number of pads used were observed for antimuscarinic initiators (79.8% had OAB with incontinence; 20–21 pads/week) compared with mirabegron initiators (71.1% had OAB with incontinence; 15–16 pads/week). The proportion of patients with OAB with incontinence was higher in the USA (79.2%) than in Canada (65.2%), as was the

**Table 1** Baseline patient demographic and clinical overactive bladder characteristics

	<b>Mirabegron initiators (N = 613)</b>	<b>Antimuscarinic initiators (N = 901)</b>
<b>Demographic characteristics</b>		
Age at enrollment in years		
Mean (SD)	62.6 (14.6)	62.0 (14.3)
Median (min, max)	65.0 (19, 93)	64.0 (18, 93)
Female sex, <i>n</i> (%)	424 (69.2)	689 (76.5)
BMI in kg/m <sup>2</sup> , mean (SD) <sup>a</sup>	30.1 (7.1)	30.4 (7.2)
Country, <i>n</i> (%)		
USA	390 (63.6)	808 (89.7)
Canada	223 (36.4)	93 (10.3)
Race, <i>n</i> (%)		
White	544 (88.7)	776 (86.1)
Black/African American	41 (6.7)	86 (9.5)
Other	19 (3.1)	28 (3.1)
Unknown/not available	9 (1.5)	11 (1.2)
Ethnicity, <i>n</i> (%) <sup>b</sup>		
Non-Hispanic	427 (69.7)	425 (47.2)
Hispanic	93 (15.2)	435 (48.3)
French Canadian	18 (2.9)	11 (1.2)
Unknown/not available	75 (12.2)	30 (3.3)
Employed full-time, <i>n</i> (%)	178 (29.0)	214 (23.8)
US drug coverage, <i>n</i> (%) <sup>c</sup>		
Private	164 (42.1)	222 (27.5)
Medicare	169 (43.3)	375 (46.4)
Medicaid	38 (9.7)	106 (13.1)
No insurance	5 (1.3)	67 (8.3)
Other	14 (3.6)	38 (4.7)
Canadian drug coverage, <i>n</i> (%) <sup>c</sup>		
Private	110 (49.3)	39 (41.9)
Provincial (public)—open coverage	56 (25.1)	12 (12.9)
Provincial (public)—with coverage criteria	40 (17.9)	38 (40.9)
<b>Clinical OAB characteristics</b>		
Time since OAB diagnosis in months		

**Table 1** continued

	Mirabegron initiators ( <i>N</i> = 613)	Antimuscarinic initiators ( <i>N</i> = 901)
Mean (SD)	49.3 (73.6)	41.0 (67.7)
Median (min, max)	20.3 (0, 610)	15.0 (0, 579)
Medical specialty of HCP who made OAB diagnosis, <i>n</i> (%)		
Primary care	237 (38.7)	465 (51.6)
Urology	302 (49.3)	352 (39.1)
Gynecology	48 (7.8)	55 (6.1)
Other	26 (4.2)	29 (3.2)
OAB with incontinence, <i>n</i> (%)	436 (71.1)	719 (79.8)
Stress or mixed urinary incontinence, <i>n</i> (%) <sup>d</sup>	314 (72.0)	611 (85.0)
Status of using pads, <i>n</i> (%)		
In the past	27 (4.4)	27 (3.0)
Currently	289 (47.1)	503 (55.8)
Never	264 (43.1)	350 (38.8)
Unknown	33 (5.4)	21 (2.3)
Number of pads used per week <sup>c</sup>		
Mean (SD)	15.9 (11.7)	20.8 (12.1)
Median (min, max)	14.0 (1.0, 84.0)	21.0 (1.0, 70.0)
OAB treatment history, <i>n</i> (%)		
No medication in past 12 months	435 (71.0)	732 (81.2)
≥ 1 medication in past 12 months	178 (29.0)	169 (18.8)
Use of complementary/supportive OAB therapies, <i>n</i> (%)	121 (19.7)	131 (14.5)

*BMI* body mass index, *HCP* healthcare provider, *OAB* overactive bladder, *SD* standard deviation

<sup>a</sup> Not available for one patient in the antimuscarinic initiator group

<sup>b</sup> All categories are mutually exclusive

<sup>c</sup> Percentages calculated among US and Canadian patients separately

<sup>d</sup> Mirabegron initiators, *n* = 436; antimuscarinic initiators, *n* = 719

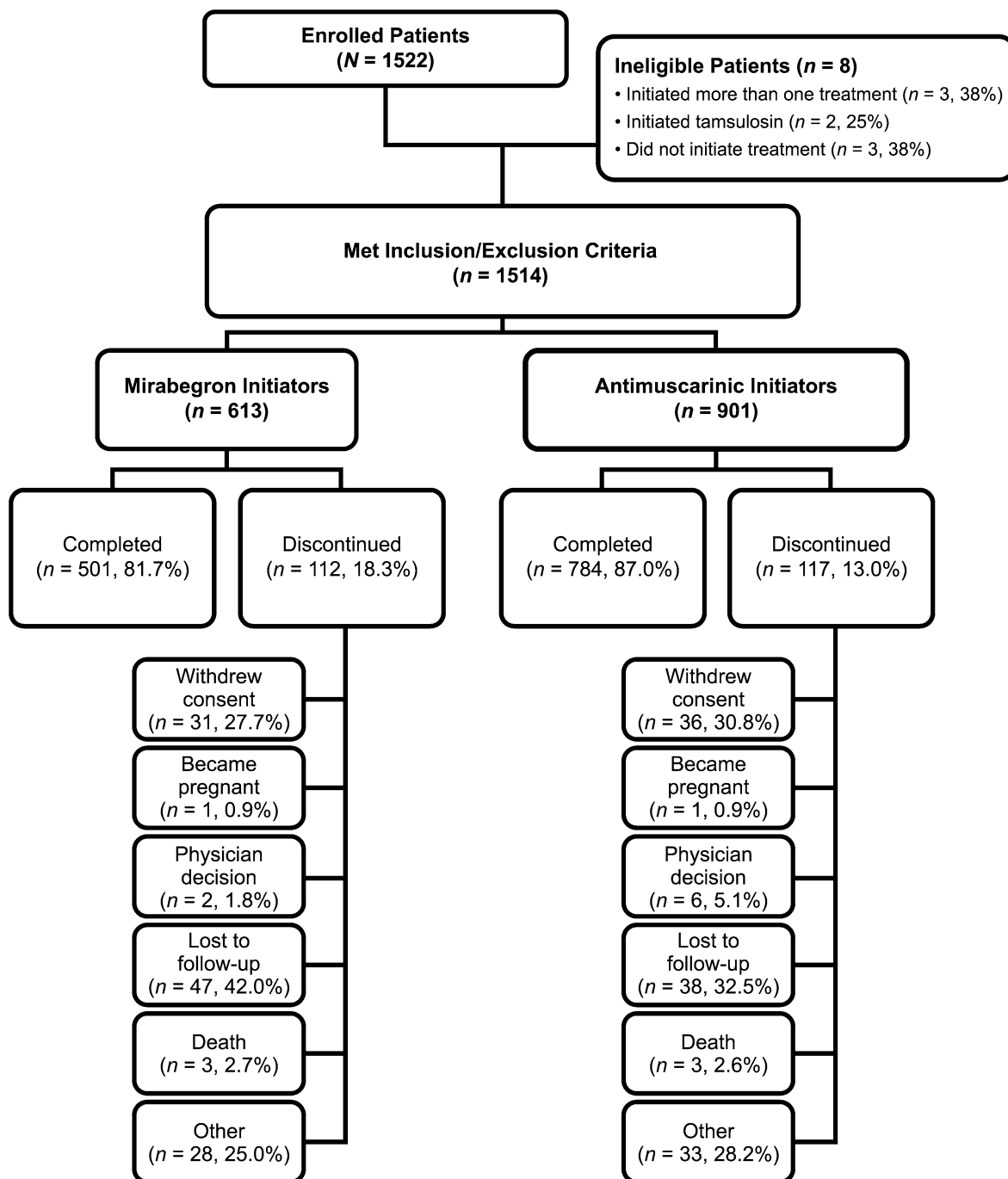
<sup>e</sup> Current pad users only

proportion of patients who currently used pads (55.1% vs. 41.8%, respectively).

### Patient-Reported Outcomes

The PRO response rate was approximately 60%, with 575 patients not completing baseline PROs

(277 [45.2%] mirabegron initiators and 298 [33.1%] antimuscarinic initiators). Mirabegron initiators had slightly less OAB symptom bother and better HRQoL at baseline compared with antimuscarinic initiators (Fig. 2). Mirabegron and antimuscarinic initiators had similar improvements in OAB-q SF symptom bother



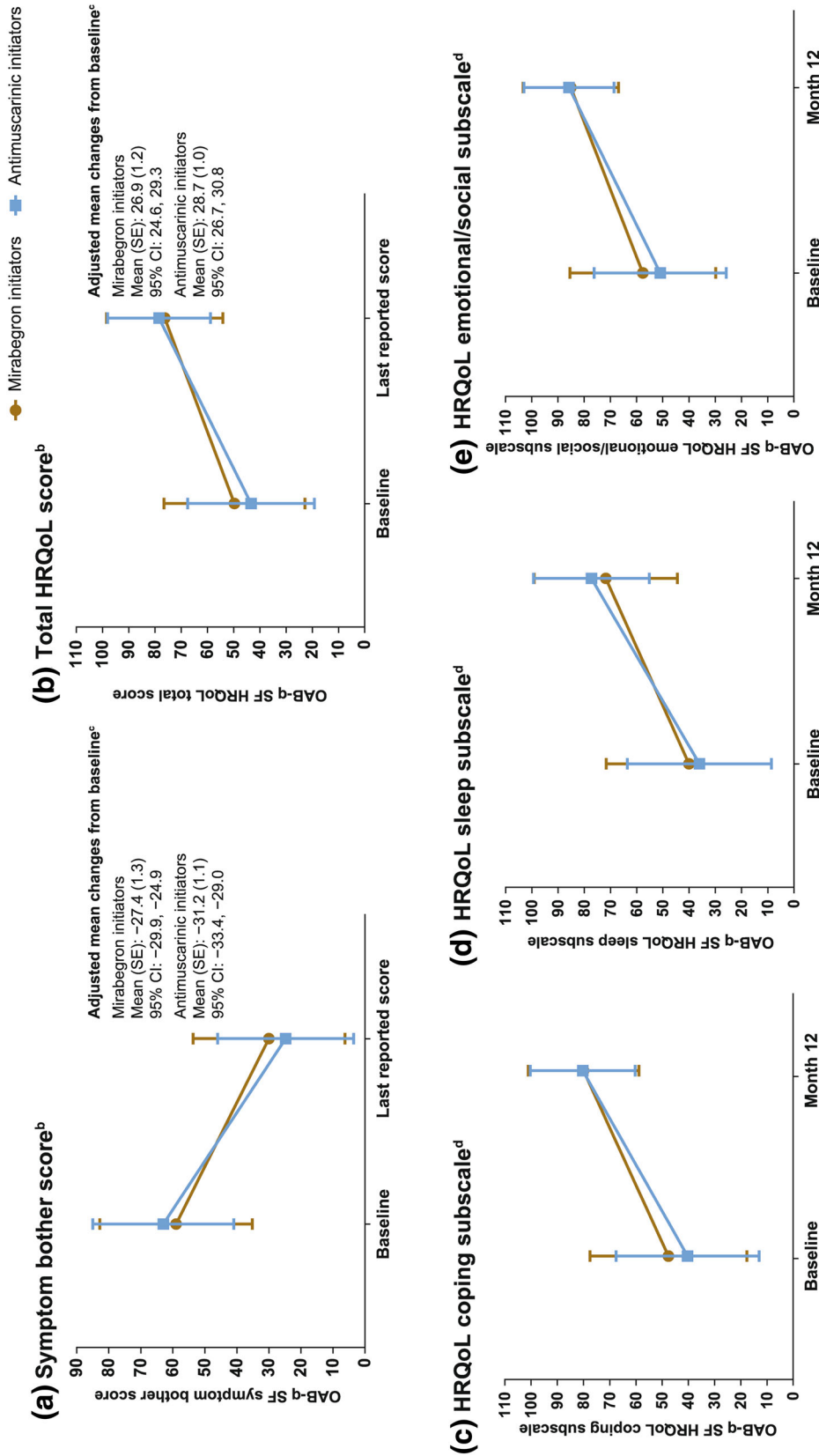
**Fig. 1** Patient disposition

score and HRQoL total score from baseline to the last reported score. Similar improvements were also observed for both groups from baseline to month 12 for the coping, sleep, and emotional/social HRQoL subscales.

**Factors Associated with Changes in OAB-q SF Scores**

Significant predictors of OAB-q SF symptom bother score improvement as examined by





**Fig. 2** Mean (SD) changes in OAB-q SF questionnaire symptom bother score (a), total HRQoL score (b), and coping (c), sleep (d), and emotional/social (e) subscales<sup>a</sup>. CI confidence interval, HRQoL health-related quality of life, OAB overactive bladder, OAB-q SF OAB Questionnaire Short-Form, SD standard deviation, SE standard error. <sup>a</sup>All scores are transformed scores. If < 50% of the scale items were missing, the scale was retained with the mean score of the items present used to impute a score for the missing items. Higher symptom bother scores indicate greater symptom bother. Higher HRQoL subscale and total scores indicate better HRQoL. If  $\geq 50\%$  of the items were missing, no scale score was calculated. <sup>b</sup>Baseline: mirabegron initiators,  $n = 336$ ; antimuscarinic initiators,  $n = 602$ . Last reported score: mirabegron initiators,  $n = 335$ ; antimuscarinic initiators,  $n = 603$ . <sup>c</sup>Generated from an analysis of covariance (ANCOVA) model with treatment group, sex, age, and treatment-naïve status as covariates. <sup>d</sup>Changes in the HRQoL subscales were assessed from baseline to month 12, not last reported score. Baseline: mirabegron initiators,  $n = 336$ ; antimuscarinic initiators,  $n = 602$ . Month 12: mirabegron initiators,  $n = 310$ ; antimuscarinic initiators,  $n = 548$

univariate generalized linear regression analysis were sex, ethnicity, country, medical insurance, history of prostate disease, history of urinary tract infection (UTI), number of pregnancies, type of OAB, presence of incontinence, treatment-naïve status, use of complementary/supportive OAB therapies at baseline, and use of concomitant medications at baseline. Covariate-adjusted models demonstrated that patients had statistically significantly greater improvement in OAB-q SF symptom bother score if they had a higher (worse) baseline score, were Hispanic, were treatment naïve, or used complementary/supportive OAB therapies at baseline. Whether patients initiated mirabegron or antimuscarinics was not statistically significantly associated with degree of change in OAB-q SF symptom bother score.

Significant predictors of OAB-q SF HRQoL total score improvement from baseline as examined by univariate generalized linear regression analysis, and included in covariate-adjusted models, were sex, ethnicity, country, medical insurance, prostate disease, history of UTI, type of OAB, treatment-naïve status, use of complementary/supportive OAB therapies at baseline and use of concomitant medications at baseline. Covariate-adjusted models demonstrated that patients had statistically significantly greater improvement in OAB-q SF HRQoL total score if they had a lower (worse) baseline score, were Hispanic, were treatment naïve, or used complementary/supportive therapies at baseline. Whether patients initiated mirabegron or antimuscarinics was not statistically significantly associated with degree of change in HRQoL total score.

### Safety

A total of 529 TEAEs were reported in 203 (33.1%) patients who initiated mirabegron (mandatory reporting) and 394 TEAEs in 152 (16.9%) patients who initiated antimuscarinics (mandatory reporting for solifenacin, otherwise discretionary). The most frequent TEAEs were gastrointestinal disorders (dry mouth, constipation, and nausea) and nervous system disorders (headache, somnolence, and dizziness)

(Table 2). Serious TEAEs were reported in 25 (4.1%) of mirabegron initiators and 16 (1.8%) antimuscarinic initiators. The most frequent serious TEAEs were respiratory, thoracic, and mediastinal disorders in mirabegron initiators and benign, malignant, and unspecified neoplasms in antimuscarinic initiators. There were eight fatal TEAEs (none deemed to be related to study drug); three among mirabegron initiators (metastatic neoplasm, dyspnea, lung infiltration) and five among antimuscarinic initiators (anemia, cardiac arrest, myocardial infarction, toxicity to various agents, small cell lung cancer).

An imbalance in TEAE reporting was evident from the OAB-S medication tolerability reporting (Table 3). Using the most frequent TEAE, dry mouth, as an example, the proportion of patients who had reported the symptom as a TEAE at the month 1 assessment was lower for patients who initiated antimuscarinics and reported medication-related symptom bother (2.5%, 4/161) compared with mirabegron initiators who reported symptom bother (7.0%, 6/86) (Table 3). A similar pattern was observed at month 3 (2.2% [4/184] vs. 6.4% [7/110] for antimuscarinics and mirabegron, respectively). There were too few TEAEs reported at the month 6 and 12 assessments to permit further comparisons.

## DISCUSSION

PERSPECTIVE represents the first prospective, observational study conducted in North America involving patients with OAB initiating a new course of pharmacotherapy.

Both mirabegron and antimuscarinics resulted in similar, statistically significant improvements in OAB-q SF symptom bother and HRQoL total scores. This finding is consistent with the improvements in symptom bother and HRQoL that were observed in a prospective, observational study of 862 patients with OAB prescribed mirabegron during routine clinical practice in Europe (BELIEVE) [19]. Other studies have compared PROs for mirabegron and antimuscarinics in the clinical trial setting [20–23]. PRO results from a phase 3 trial

**Table 2** Treatment-emergent adverse events

System organ class <sup>a</sup> Preferred term <sup>b</sup>	Number of patients with TEAE, <i>n</i> (%)	
	Mirabegron initiators ( <i>N</i> = 613) <sup>c</sup>	Antimuscarinic initiators ( <i>N</i> = 901) <sup>d</sup>
Any TEAE	203 (33.1)	152 (16.9)
Gastrointestinal disorders	116 (18.9)	77 (8.5)
Dry mouth	78 (12.7)	57 (6.3)
Constipation	48 (7.8)	39 (4.3)
Nausea	19 (3.1)	11 (1.2)
Nervous system disorders	74 (12.1)	35 (3.9)
Headache	54 (8.8)	19 (2.1)
Somnolence	30 (4.9)	17 (1.9)
Dizziness	5 (0.8)	2 (0.2)
Any serious TEAE	25 (4.1)	16 (1.8)
Respiratory, thoracic, and mediastinal disorders	7 (1.1)	3 (0.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	4 (0.7)	6 (0.7)

TEAE treatment-emergent adverse event

<sup>a</sup> System organ class TEAEs reported in > 5% and serious TEAEs reported in > 0.5% of total population

<sup>b</sup> Most frequent preferred term TEAEs

<sup>c</sup> All TEAEs for mirabegron initiators (regardless of relationship to study treatment) were monitored and reported to the study sponsor throughout the study (mandatory reporting)

<sup>d</sup> Identification of TEAEs for antimuscarinic initiators was at the discretion of the investigator (discretionary reporting). The only exception was for solifenacin where mandatory reporting of TEAEs was required

**Table 3** Treatment-emergent adverse event reporting among patients who reported symptom bother on the OAB-S medication tolerability scale at month 1

OAB-S medication tolerability scale TEAE	Patients reporting symptom bother on the OAB-S medication tolerability scale who had reported the symptom as a TEAE, <i>n/N</i> (%)	
	Mirabegron initiators	Antimuscarinic initiators
Dry mouth	6/86 (7.0)	4/161 (2.5)
Constipation	6/72 (8.3)	6/93 (6.5)
Headache	9/78 (11.5)	0/67 (0)
Drowsiness	2/65 (3.1)	3/67 (4.5)
Blurred vision	5/42 (11.9)	5/53 (9.4)
Nausea	1/34 (2.9)	1/38 (2.6)

OAB overactive bladder, OAB-S OAB treatment satisfaction questionnaire, TEAE treatment-emergent adverse event

demonstrated significant improvements for mirabegron over placebo in OAB-q coping, concern, and HRQoL total score, whereas no significant difference was reported for tolterodine compared with placebo [20]. A two-period crossover study (PREFER), during which patients were randomized to receive mirabegron or tolterodine in one of four sequences (mirabegron–tolterodine, tolterodine–mirabegron, mirabegron–mirabegron, or tolterodine–tolterodine), reported similar mean OAB-q SF improvements for each of the treatments. However, patients were more likely to achieve clinically relevant improvements in HRQoL during mirabegron treatment [21]. Moreover, the PREFER study demonstrated improved tolerability for mirabegron compared with tolterodine. In addition, in the phase 2 (SYMPHONY) and phase 3 (SYNERGY) trials, which involved mirabegron and solifenacin in combination, the changes in OAB-q symptom bother and HRQoL total scores were similar in the mirabegron and solifenacin monotherapy groups [22, 23]. However, in the present study, patients were grouped according to the treatment initiated at enrollment; they may have added, switched, or discontinued treatment during the study period. As such, the final PRO score during follow-up may not reflect patient experiences on the initial treatment.

Baseline PRO score, being treatment naïve, use of complementary/supportive OAB therapies at baseline, and Hispanic ethnicity were consistently associated with greater OAB-q SF symptom bother and HRQoL total score improvements. Higher (worse) OAB-q SF symptom bother score at baseline and lower (worse) HRQoL score at baseline were associated with greater score improvement, indicating that patients with more symptomatic OAB at baseline experienced greater treatment benefit. The treatment-experienced patients enrolled in this study may represent a more difficult-to-treat group, particularly if they had previously discontinued pharmacotherapy because of insufficient efficacy, which may explain the better response in treatment-naïve patients. The use of complementary therapies is consistent with American Urological Association/Society of Urodynamics, Female Pelvic Medicine, and

Urogenital Reconstruction (AUA/SUFU) treatment guidelines which recommend behavioral therapies as first-line treatments [8]. As such, it is not surprising that patients who added on pharmacotherapy to behavioral therapies had greater perceived symptom and HRQoL improvements. It is notable that Hispanic ethnicity was also associated with greater OAB-q SF symptom bother and HRQoL total score improvements. This is the first study to show that ethnicity may impact OAB treatment response, which warrants further exploration.

The safety data from this study are difficult to interpret because of imbalanced reporting of TEAEs in patients initiating mirabegron/solifenacin (mandatory reporting) and any other antimuscarinic (discretionary reporting), which prevents meaningful comparisons between the treatment groups. Pharmacovigilance requirements necessitate mandatory reporting of all AEs associated with pharmacotherapies manufactured by the sponsor [24]. Hence, physicians were obliged to report the AEs for mirabegron and solifenacin (manufactured by the sponsor, Astellas Pharma), but not the AEs associated with other treatments. The imbalance was evident when examining the proportions of patients who reported bother on the OAB-S medication tolerability scale and how often it was reported as a TEAE. As reporting of bother on the OAB-S medication tolerability scale for mirabegron/solifenacin initiators resulted in an alert for site staff to assess the side effect as a potential TEAE, symptom bother was more likely to be reported as a TEAE in mirabegron initiators than in antimuscarinic initiators. This yielded results that are inconsistent with data from the large patient population (> 10,000) who received mirabegron during the clinical development studies and that are contradictory with the mechanisms of action of the two drug classes [9, 10, 25]. In particular, the results of the present study indicate that anticholinergic TEAEs were more frequent with mirabegron than antimuscarinics, which is inconsistent with previously reported data [9, 10, 13] as well as the known pharmacodynamic properties of these agents. Furthermore, the frequency of TEAEs in the present study is considerably higher than the number of

adverse drug reactions reported in two real-world Japanese surveillance studies [26, 27].

Consistent with observations from another real-world study [28], fewer mirabegron initiators were treatment naïve compared with antimuscarinic initiators; the greater proportion of mirabegron initiators who were treatment experienced may suggest more frequent use of mirabegron as a second-line pharmacotherapy. Differences were also noted between mirabegron and antimuscarinic initiators with regards to the HCP specialty who made the OAB diagnosis, as well as by country and drug coverage. However, interpretation of these findings is complicated by the confounding influences of differences in patient access to discounted/free medications. These observations highlight the complex interplay of factors affecting OAB treatment choice. Of all the treatment-seeking patients in this study, 76.3% had OAB with incontinence, despite the notion that OAB without incontinence is the more prevalent form [29]. This may be due to the high proportion of women recruited, who are more likely to have incontinence than men [30–33], or the possibility that incontinence may motivate patients to seek OAB treatment, as has been suggested by other studies [34, 35].

The strengths of this study include the generation of real-world data across a large, diverse patient group, with inclusion criteria more closely representing patients receiving OAB treatment in routine clinical practice than those enrolled according to the more restrictive requirements of a randomized clinical trial (RCT). Furthermore, the use of PROs to reflect patients' perception of treatment effect provides insights relevant to routine patient management. Some limitations should be noted. As participation was voluntary for patients and doctors, the representativeness of the enrolled study sample with the general population is unknown. However, as it was based on both primary care and specialty sites, and enrollment was for patients in whom a decision had already been made to start a medication, it is probable that the present study was more representative of the real-world situation with OAB patients than RCTs. Although the demographics of the patients appear similar to other studies

involving patients with OAB and a wide age range of patients were enrolled, the need for the patients to complete the PROs by email link may have introduced selection bias into this study. In addition, the number of patients who did not complete PROs or who were lost to follow-up may have reduced the strength of the study findings and also led to potential bias in the results. Although baseline characteristics were generally similar between patients who did/did not complete the study, patients who did not complete the study were more likely to be non-Hispanic, employed full-time, and have private insurance. Baseline characteristics were also generally similar between patients who did/did not complete any PROs, although patients who did not complete any PROs were more likely to be Hispanic, employed full-time, have private insurance, have OAB with incontinence, and be using pads. Furthermore, a greater proportion of mirabegron initiators discontinued the study compared with antimuscarinic initiators (18.3% vs. 13.0%), mostly prior to completion of the first PRO. In addition, the requirement for electronic completion of PROs and the 7-day time scale for completing baseline PROs may have been challenging for patients. The high level of mirabegron prescribing in Canada, combined with a high dropout rate before completion of the first PRO, may reflect lack of patient engagement in the patient-support program that may have resulted in study discontinuation. The response rate was lower than in the non-interventional BELIEVE study, which included scheduled follow-up visits [19]. The lack of scheduled follow-up visits was intended to interfere as little as possible with routine care, but likely contributed to the loss of information from both treatment groups and incomplete patient-reported information such as OAB medication usage and compliance. As for all observational studies, unmeasured variables related to mirabegron and antimuscarinic use and outcomes have the potential to confound the study results. In addition, antimuscarinic data were assessed for the entire group of therapeutics and analyses by individual agent were not conducted. Finally, TEAEs were not systematically collected for both mirabegron and antimuscarinic initiators, resulting

in imbalanced reporting that prevented meaningful comparisons between the treatment groups and provided results inconsistent with previously reported studies [9, 10, 13].

## CONCLUSION

The results from PERSPECTIVE affirm that mirabegron and antimuscarinics offer patients multiple medication options that are associated with clinically important improvements in patient-reported OAB symptom bother and HRQoL.

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**Compliance with Ethics Guidelines.** This study was conducted in accordance with all applicable laws and regulations, and the ethical principles originating from the Declaration of Helsinki. The protocol and any associated documents were approved by the institutional review board or independent ethics committee at each site prior to enrollment (Table S1). All patients (or their legally authorized representative) provided informed consent before participation in the study.

**Data Availability.** Access to anonymized individual participant level data will not be provided for this trial as it meets one or more of the exceptions described on <http://www.clinicalstudydatarequest.com> under “Sponsor Specific Details for Astellas”.

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