Common Drug Review
Clinical Review Report

July 2015

Drug	mirabegron extended-release tablets (Myrbetriq)
Indication	Treatment of overactive bladder (OAB) with symptoms of urgency, urgency incontinence and urinary frequency
Listing request	As a second-line treatment option, in a similar manner to other currently listed second-line drugs for OAB, i.e., for patients who have failed an adequate trial of oxybutynin due to lack of efficacy or unacceptable side effects
Manufacturer	Astellas

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The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
CI	confidence interval
CrI	credible interval
ER	extended release
FAS	full analysis set
HRQoL	health-related quality of life
ICIQ-OAB	International Consultation on Incontinence Questionnaire–OAB
ICIQ-OAB-qol	ICIQ-OAB-quality of life
IR	immediate-release
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KHQ	King's Health Questionnaire
MCID	minimal clinically important difference
MD	mean difference
NICE	National Institute for Health and Care Excellence
OAB	overactive bladder
OAB-q	Overactive Bladder Questionnaire
PPBC	Patient Perception of Bladder Condition
PPIUS	Patient Perception of Intensity of Urgency Scale
PPS	per-protocol analysis set
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
TCCF	The Canadian Continence Foundation
UI	urinary incontinence
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Overactive bladder (OAB) is a chronic condition of the lower urinary tract characterized by symptoms of urinary urgency, with or without urgency incontinence, usually with urinary frequency and nocturia. Mirabegron is selective beta 3-adrenoceptor agonist available as a 25 mg and 50 mg extended-release (ER) tablet. It is approved for the treatment of OAB with symptoms of urgency, urgency incontinence, and urinary frequency. The manufacturer has requested that mirabegron be listed in a manner similar to other second-line OAB drugs. The objective of this report is to perform a systematic review of the beneficial and harmful effects of mirabegron ER (Myrbetriq) for the treatment of OAB.

Indication under review
For the treatment of OAB with symptoms of urgency, urgency incontinence and urinary frequency
Listing criteria requested by sponsor
As a second-line treatment option, in a similar manner to other currently listed second-line drugs for OAB, i.e. for patients who have failed an adequate trial of oxybutynin due to lack of efficacy or unacceptable side effects

Results and Interpretation

Included Studies

Nine manufacturer-sponsored double-blind randomized controlled trials were included in the review. Six trials (SCORPIO, 048, 090, DRAGON, ARIES, and CAPRICORN) were of short duration (12 weeks) and were designed to assess efficacy of mirabegron versus placebo, despite the inclusion of an active comparator (tolterodine) group in four trials. Two additional 12-week trials included solifenacin and were designed to assess the non-inferiority of mirabegron versus solifenacin (BEYOND) or efficacy of mirabegron plus solifenacin compared with solifenacin or placebo. All trials included a mirabegron 50 mg treatment group; three trials (DRAGON, CAPRICORN, and SYMPHONY) included a mirabegron 25 mg group. The primary outcome in seven studies was the change from baseline in number of micturitions per 24 hours at week 12. SCORPIO, ARIES, and CAPRICORN included a co-primary end point, which was change from baseline in number of incontinence episodes per 24 hours at week 12. The primary outcome in SYMPHONY was the change from baseline in the volume voided per micturition. Secondary outcomes of the 12-week trials included changes in episodes of urgency incontinence (also called urge incontinence), urgency, and nocturia, in addition to health-related quality of life and harms. One trial (TAURUS) was 52 weeks in duration and was designed to assess the safety of mirabegron compared with tolterodine; however, no formal statistical analyses of between-treatment differences were planned.

The percentage of patients who had previously received an anticholinergic drug to treat symptoms of OAB ranged from 38% to 65% across included trials, except the BEYOND trial in which all patients were non-responders to anticholinergic therapies. Across studies there was variation in the patient characteristics in terms of race, the proportion of patients with incontinence, and the frequency of incontinence.

Despite the inclusion of solifenacin or tolterodine as an active comparator in seven trials, only the non-inferiority trial was powered for head-to-head comparison of an outcome of interest for this review. Major limitations included the short study duration and substantial withdrawal rates (18% and 23% in two of the trials). The lower dosage of mirabegron ER (25 mg) was studied in only three trials.

It should be noted that, although placebo-controlled trials were included in this review, comparisons of mirabegron with other active comparators are of most interest.

Efficacy

Differences between active treatments in OAB symptom frequency (incontinence, urgency incontinence, micturitions, urgency, and nocturia) were not statistically significant except for the number of micturitions, favouring mirabegron 50 mg versus tolterodine in two 12-week trials; the number of incontinence episodes, favouring tolterodine versus mirabegron 50 mg in the 52-week trial; and the number of micturitions or urgency episodes, favouring mirabegron plus solifenacin versus solifenacin 5 mg, in one 12-week trial. The magnitude of the observed differences was not considered clinically important. Non-inferiority was not met for mirabegron 50 mg versus solifenacin 5 mg in the trial that enrolled patients who had not previously responded to anticholinergic drugs.

Interpretation of between-group differences is challenging because there is no known change value that has been judged to be clinically important. Furthermore, a strong placebo effect is common among studies for OAB.

The available evidence is limited in its ability to address the manufacturer's requested listing (in a manner similar to other second-line OAB drugs). Non-inferiority was not met for mirabegron versus solifenacin in the trial that enrolled non-responders to anticholinergic treatment. All other studies included a mixture of treatment-naive and treatment-experienced patients, but only one trial provided subgroup data based on prior treatment or response to prior treatment. None of the tolterodine-controlled trials were designed to test the non-inferiority of mirabegron versus tolterodine. Thus, despite the lack of statistically significant between-treatment differences for many outcomes, a conclusion of non-inferiority of mirabegron to tolterodine cannot be made. However, the magnitude of the differences for OAB symptoms between mirabegron and tolterodine were of uncertain clinical importance. Finally, in the indirect network meta-analysis, no significant differences were observed between mirabegron 50 mg and the other OAB treatments, except for solifenacin 10 mg which was more effective than mirabegron in reducing the number of micturitions and urge incontinency episodes.

Harms

Overall, the incidence of adverse events, serious adverse events, and withdrawal due to adverse events were similar among placebo, mirabegron, tolterodine, solifenacin, and mirabegron plus solifenacin groups in the 12-week trials, and between mirabegron and tolterodine in the 52-week trial. The incidence of dry mouth was higher in the tolterodine and solifenacin groups than in the mirabegron groups, but the incidence of other anticholinergic adverse events was similar between treatments. Mirabegron may offer an alternative for patients who cannot tolerate anticholinergic medications due to dry mouth or who have contraindications to anticholinergic medications. No increased risk of cardiovascular adverse events was observed for mirabegron versus comparators. Further long-term data are needed to identify potential risks associated with this new therapeutic class of medications.

Pharmacoeconomic Summary

The manufacturer submitted a cost-minimization analysis comparing mirabegron with oxybutynin immediate release (IR), darifenacin ER, fesoterodine ER, solifenacin, tolterodine ER, and trospium chloride over a one-year time horizon.

In the general OAB population (including both treatment-naive and treatment-experienced patients), direct evidence suggests that mirabegron and tolterodine are relatively similar with regard to reductions in urgency, incontinence, or micturition. Results of a manufacturer-funded network meta-analysis,[1] as well as a reanalysis conducted by the National Institute for Health and Care Excellence (NICE) Evidence Review Group,[2] suggest similar efficacy between mirabegron and anticholinergic drugs (darifenacin, fesoterodine ER, oxybutynin IR and ER, tolterodine IR and ER, and trospium chloride IR and ER) with regard to micturition and incontinence, with the exception of solifenacin, which was found to be significantly more effective than mirabegron 50 mg at reducing incontinence in the NICE reanalysis. Both direct and indirect evidence suggest that mirabegron is associated with a lower risk of developing dry mouth compared with anticholinergic drugs. There is limited evidence on the comparative efficacy and safety of mirabegron in the subgroup of patients who have failed an adequate treatment with anticholinergic drugs. The BEYOND trial, which enrolled OAB patients who were non-responders to anticholinergic drugs, failed to demonstrate that mirabegron was non-inferior to solifenacin.

At recommended doses, mirabegron is more expensive than generic oxybutynin IR ($0.20 to $0.30 per day), but less expensive than anticholinergic drugs currently funded by most drug plans as second-line options for the treatment of OAB (cost ranging from $1.50 to $2.28 per day). Mirabegron could save between [redacted] and [redacted] per patient per year, if used as monotherapy, compared with second-line anticholinergic drugs. If mirabegron were used in combination with second-line anticholinergic drugs reimbursed under public drug plans, this would substantially increase treatment costs.

Conclusions

Nine double-blind randomized controlled trials met the inclusion criteria for the systematic review. Non-inferiority was not met for mirabegron versus solifenacin in the trial that enrolled patients who had not responded to previous anticholinergic drug treatment. None of the tolterodine-containing trials, which enrolled a mixture of treatment-naive and treatment-experienced patients, were designed to test the non-inferiority of mirabegron versus tolterodine; however, estimates of treatment effect with regard to reductions in urgency, incontinence, or micturition appeared relatively similar between mirabegron and tolterodine.

The incidence of serious adverse events and premature discontinuation was similar between treatment groups. Dry mouth was reported more frequently by patients who received solifenacin or tolterodine than mirabegron; however, there were no notable differences in the frequency of other anticholinergic adverse events.

TABLE 1: SUMMARY OF RESULTS — EFFICACY FOR ACTIVE COMPARATORS

Bladder Activity — Change From Baseline [a]						
Monotherapy	**Incontinence Episodes per 24 Hours MD (95% CI) Versus TOL**		**Urgency Episodes per 24 Hours MD (95% CI) Versus TOL**		**Micturitions per 24 Hours MD (95% CI) Versus TOL**	
	MIR 25 mg	MIR 50 mg	MIR 25 mg	MIR 50 mg	MIR 25 mg	MIR 50 mg
SCORPIO (12 weeks)		−0.30 (−0.61 to 0.01)		−0.18 (−0.60 to 0.24)		**−0.34 (−0.64 to −0.04)[b]**
Study 048 (12 weeks)		−0.10 (−0.36 to 0.15)		−0.13 (−0.49 to 0.23)		−0.25 (−0.55 to 0.04)
Study 090 (12 weeks)		−0.04 (−0.51 to 0.43)		−0.04 (−0.53 to 0.60)		**−0.60 (−1.07 to −0.13)[b]**
DRAGON (12 weeks)	−0.56 (−1.29 to 0.18)	−0.34 (−1.06 to 0.39)	−0.31 (−1.14 to 0.52)	−0.22 (−1.06 to 0.62)	0. 06 (−0.60 to 0.72)	−0.14 (−0.80 to 0.53)
TAURUS (52 weeks)		**0.25 (0.01 to 0.49) [b]**		0.01 (−0.30 to 0.32)		0.12 (−0.11 to 0.35)
Monotherapy	**Incontinence Episodes per 24 Hours MD (95% CI) Versus SOL 5 mg**		**Urgency Episodes per 24 Hours MD (95% CI) Versus SOL 5 mg**		**Micturitions per 24 Hours MD (95% CI) Versus SOL 5 mg**	
	MIR 25 mg	MIR 50 mg	MIR 25 mg	MIR 50 mg	MIR 25 mg	MIR 50 mg
BEYOND (12 weeks)		[redacted]		[redacted]		0.20 (−0.05 to 0.44)
SYMPHONY (12 weeks)	0.14 (−0.81 to 1.09)	−0.02 (−0.87 to 0.83)	−0.50 (−1.31 to 0.31)	−0.71 (−1.52 to 0.10)	0.06 (−0.66 to 0.78)	−0.02 (−0.73 to 0.69)
Combination Therapy	**Incontinence Episodes per 24 Hours MD (95% CI) Versus SOL 5 mg**		**Urgency Episodes per 24 Hours MD (95% CI) Versus SOL 5 mg**		**Micturitions per 24 Hours MD (95% CI) Versus SOL 5 mg**	
	MIR 25 mg + SOL 5 mg	MIR 50 mg + SOL 5 mg	MIR 25 mg + SOL 5 mg	MIR 50 mg + SOL 5 mg	MIR 25 mg + SOL 5 mg	MIR 50 mg + SOL 5 mg
SYMPHONY (12 weeks)	−0.34 (−1.06 to 0.38)	−0.26 (−1.04 to 0.52)	**−1.13 (−1.80 to −0.46)[b]**	**−1.37 (−2.03 to −0.72)[b]**	−0.02 (−0.62 to 0.58)	**−0.80 (−1.39 to −0.22)[b]**
	MIR 25 mg + SOL 10 mg	MIR 50 mg + SOL 10 mg	MIR 25 mg + SOL 10 mg	MIR 50 mg + SOL 10 mg	MIR 25 mg + SOL 10 mg	MIR 50 mg + SOL 10 mg
SYMPHONY (12 weeks)	0.60 (−0.17 to 1.38)	−0.09 (−0.91 to 0.73)	**−0.98 (−1.78 to −0.18)[b]**	**−1.18 (−1.98 to −0.69)[b]**	**−0.88 (−1.59 to −0.16)[b]**	**−0.98 (−1.68 to −0.27)[b]**

CI = confidence interval; MD = mean difference; MIR = mirabegron; SOL = solifenacin; TOL = tolterodine.
[a] Negative values indicate patients in the treatment group had fewer episodes than control.
[b] Statistically significantly different (in bold).

TABLE 2: SUMMARY OF RESULTS — HARMS FOR ACTIVE COMPARATORS; POOLED BY CADTH WHERE MORE THAN ONE TRIAL

Proportion of Patients with ≥ 1 Event; RR (95% CI)[a]				
	SAE	WDAE	AE	Dry Mouth
Mirabegron Versus Tolterodine				
MIR 25 mg				
12 weeks N trials = 1	0.50 (0.03 to 7.94)	4.53 (0.58 to 35.14)	0.91 (0.69 to 1.20)	0.84 (0.21 to 3.42)
MIR 50 mg				
12 weeks N trials = 4	1.02 (0.57 to 1.82) I^2 = 0%	1.03 (0.69 to 1.54) I^2 = 0%	0.90 (0.84 to 0.96) I^2 = 0%	**0.32 (0.23 to 0.45)[b]** **I^2 = 62%**
52 weeks N trials = 1	0.95 (0.63 to 1.44)	1.04 (0.70 to 1.55)	0.95 (0.88 to 1.03)	**0.33 (0.21 to 0.52)[b]**
Mirabegron Versus Solifenacin 5 mg				
12 weeks				
MIR 25 mg				
N trials = 1	NE[c]	2.03 (0.13 to 31.96)	1.10 (0.83 to 1.46)	**0.23 (0.05 to 0.95)[b]**
MIR 50 mg				
N trials = 2	1.30 (0.65 to 2.60) I^2 = 50%	0.89 (0.45 to 1.73) I^2 = 41%	1.00 (0.88 to 1.13) I^2 = 33%	**0.52 (0.35 to 0.78)[b]** **I^2 = 0%**
MIR 25 mg + SOL 5 mg				
N trials = 1	NE[c]	4.33 (0.49 to 38.32)	1.10 (0.86 to 1.40)	1.26 (0.70 to 2.27)
MIR 25 mg + SOL 10 mg				
N trials = 1	NE[c]	1.93 (0.12 to 30.39)	1.29 (1.00 to 1.67)	1.71 (0.92 to 3.17)
MIR 50 mg + SOL 5 mg				
N trials = 1	NE[c]	1.02 (0.06 to 16.16)	0.98 (0.76 to 1.25)	1.13 (0.62 to 2.06)
MIR 50 mg + SOL 10 mg				
N trials = 1	NE[c]	5.78 (0.61 to 54.66)	**1.32 (1.03 to 1.70)[b]**	1.50 (0.79 to 2.85)

AE = adverse event; CI = confidence interval; MIR = mirabegron; NE = not estimable; RR = relative risk; SAE = serious adverse event; SOL = solifenacin; WDAE = withdrawal due to adverse events.

[a] Calculated by CADTH using Review Manager. values less than 1 indicate that patients in the treatment group had fewer events than those in the control group. Data were pooled using fixed effects model.

[b] Statistically significantly different (in bold).

[c] Zero events in control group.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Overactive bladder (OAB) is a chronic condition of the lower urinary tract defined by the International Continence Society as a symptom syndrome experienced during the storage phase of the bladder. Symptoms include urinary urgency, with or without urgency incontinence, usually with urinary frequency and nocturia.[3-6]

It is estimated that OAB affects 12% to 18% of Canadians, and symptom prevalence and severity tend to increase with age.[7–10] Some studies have reported similar OAB prevalence among men and women; however, OAB with urgency incontinence is more frequently reported in women.[9,10] A true incidence measure of OAB is difficult, since many patients are embarrassed to discuss their symptoms with their physicians or feel that OAB is a normal part of aging and must be accepted.[11,12] OAB therefore often remains underdiagnosed.[11,13]

OAB may affect an individual's psychological and social well-being by leaving sufferers feeling frustrated, anxious, and embarrassed.[12] OAB has been linked to higher levels of depression, higher levels of work impairment (e.g., absenteeism, presenteeism, and decreased productivity), and greater rates of unemployment.[13] Even mild symptoms of urinary incontinence have the potential to affect patient quality of life by negatively affecting everyday participation in a variety of interpersonal, professional, and social activities.[12]

1.2 Standards of Therapy

According to the Canadian Urological Association Guidelines,[9] behavioural and lifestyle modification are recommended for initial treatment of urinary incontinence. Pharmacologic therapies are also used in patients with OAB who do not achieve symptom relief with conservative management. Antimuscarinic drugs are commonly used in OAB patients; treatment options include oxybutynin, tolterodine, trospium chloride, solifenacin, darifenacin, and fesoterodine.[9] A recent systematic review and meta-analysis showed that these medications had comparable benefits and tolerability, with clinically minor differences between drugs.[14] The main safety concerns with these drugs include anticholinergic adverse effects, such as dry mouth, dizziness, blurred vision, constipation, urinary retention, cognitive disorders, confusion, and drowsiness. Antimuscarinic drugs are contraindicated in patients with narrow angle glaucoma, gastric retention, and those at risk for urinary retention. Canadian guidelines state that the choice of antimuscarinic drug may depend on physician experience and preference, formulary coverage, patient preference, and insurance coverage.[9]

1.3 Drug

Mirabegron is a selective beta 3-adrenoceptor agonist that relaxes bladder smooth muscle and enhances urine storage function. Mirabegron is available as 25 mg and 50 mg extended-release (ER) tablets. The recommended dose is 25 mg administered orally, once daily, to a maximum of 50 mg per day.

Indication under review
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Listing criteria requested by sponsor
As a second-line treatment option, in a similar manner to other currently listed second-line drugs for OAB, i.e. for patients who have failed an adequate trial of oxybutynin due to lack of efficacy or unacceptable side effects

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of mirabegron ER (Myrbetriq) for the treatment of OAB in patients with symptoms of urgency, urgency incontinence, and urinary frequency.

2.2 Methods

Studies selected for the systematic review included pivotal trials submitted by the manufacturer in support of the Health Canada indication for which the submission was made (OAB) in addition to trials meeting the selection criteria presented Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients (≥ 18 years old) with OAB with symptoms of urgency, urgency incontinence, and urinary frequency • Subgroups based on prior treatment experience: previously treated with OAB medications versus treatment-naive
Intervention	Mirabegron ER at recommended doses (25 mg or 50 mg once daily)
Comparators[a]	Tolterodine, trospium chloride, darifenacin, solifenacin, oxybutynin, fesoterodine, onabotulinumtoxinA
Outcomes	**Key efficacy outcomes** Bladder activity: • incontinence episodes • urgency incontinence episodes • achievement of continence • micturition frequency • urgency episodes • mocturia episodes. Quality of life: • any validated HRQoL measure (generic or condition-specific instruments). **Harms outcomes** • mortality • SAE • AE • WDAE • cardiovascular and anticholinergic AEs.
Study Design	Published and unpublished DB RCTs, ≥ 12 weeks treatment duration

AE = adverse event; DB = double-blind; ER = extended-release; HRQoL = health-related quality of life; OAB = overactive bladder; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] At Health Canada–approved dosages.

The literature search was performed by an information specialist using a peer-reviewed search strategy (APPENDIX 1: LITERATURE SEARCH STRATEGY).

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid, Embase (1974–) through Ovid, and PubMed.

The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Myrbetriq (mirabegron).

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on May 23, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on October 15, 2014. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, clinical trials and databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Included studies are presented in Table 4; excluded studies (with reasons) are presented in APPENDIX 4: EXCLUDED STUDIES.

Studies were assessed by CADTH for homogeneity in terms of patient, intervention, and study design characteristics and, where appropriate, study data were meta-analyzed using a fixed effects model in Review Manager version 5.3. Pooling was conducted when complete data were available from trials of the same duration (i.e., 12-week trials). Missing between-group data were calculated by CADTH using Excel and Review Manager. Forest plots were generated using Excel.[15]

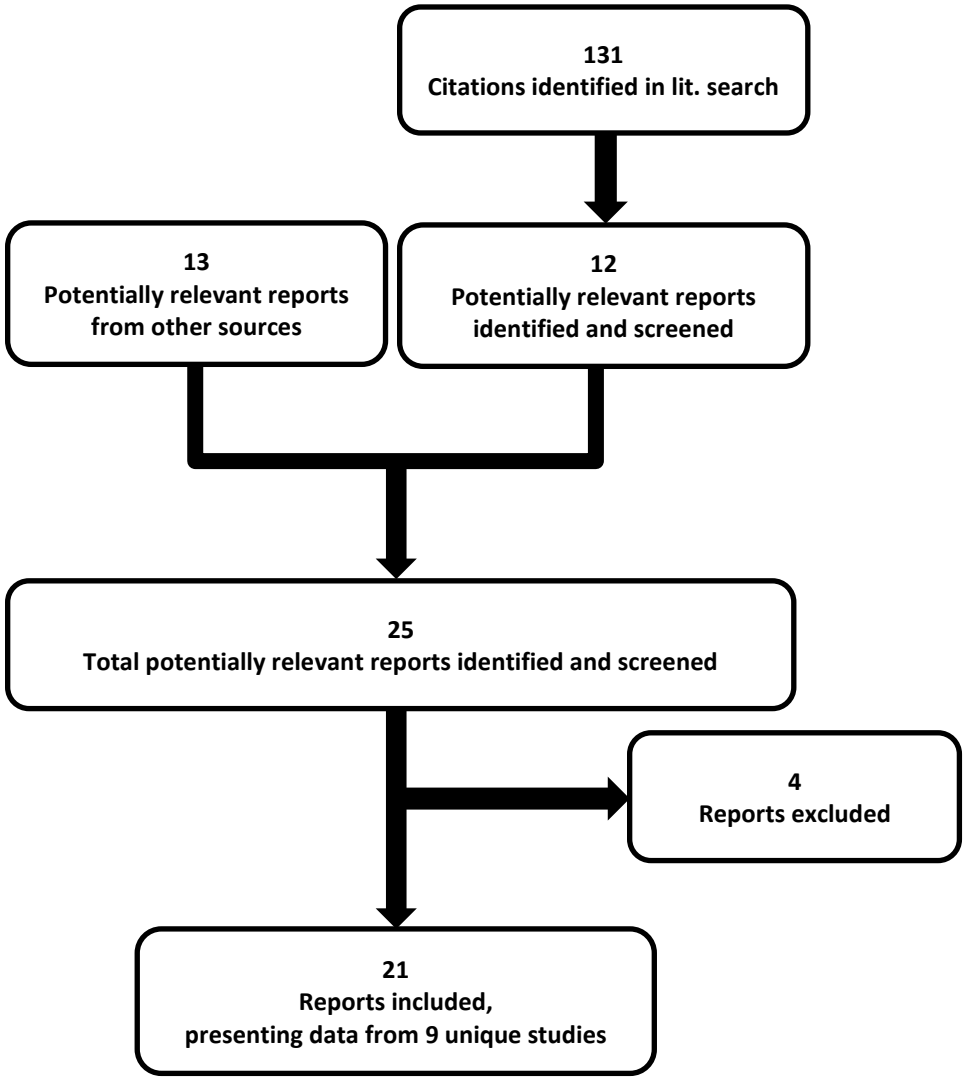
Data for treatment groups utilizing dosages that are consistent with Health Canada recommendations have been extracted and summarized in this review.

3. RESULTS

3.1 Findings from the Literature

A total of 131 citations were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 4: EXCLUDED STUDIES.

FIGURE 1: PRISMA FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES



PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

TABLE 4: DETAILS OF INCLUDED STUDIES

	Study Name	SCORPIO 046	Study 048	Study 090	DRAGON 044	TAURUS 049	ARIES 047	CAPRICORN 074	SYMPHONY 100	BEYOND 001
DESIGNS & POPULATIONS	**Study design**	DB RCT	DB RCT	DB RCT	DB RCT	DB RCT	DB RCT	DB RCT	DB RCT	DB RCT Non-inferiority
	Locations	Europe, Australia	Japan	Asia	Europe	Europe, Canada, US, Australia, New Zealand, South Africa	US, Canada	Europe, US, Canada	Europe	Europe, Canada, Middle East
	Randomized (N)	1,987	1,139	1,126	928	2,452	1,329	1,306	1,306	1,870
	Inclusion criteria	Adults (≥ 18 years) with OAB symptoms ≥ 3 months (frequency and urgency with or without incontinence), ≥ 8 micturitions/ day, and ≥ 3 urgency episodes/day	Adults (≥ 20 years) with OAB symptoms ≥ 3 months (frequency and urgency with or without incontinence), ≥ 8 micturitions/ day and ≥ 1 urgency episode/day, or ≥ 1 urgency incontinence episode/day	Adults with OAB symptoms ≥ 3 months (frequency and urgency with or without incontinence), ≥ 8 micturitions/day and ≥ 1 urgency episode/day or ≥ 1 urgency incontinence episode/day	Adults (≥ 18 years) with OAB symptoms ≥ 3 months (frequency and urgency with or without incontinence), ≥ 8 micturitions/day and ≥ 3 urgency episodes/day	Adults (≥ 18 years) with OAB symptoms ≥ 3 months (frequency and urgency with or without incontinence), ≥ 8 micturitions/day and ≥ 3 urgency episodes/day	Adults (≥ 18 years) with OAB symptoms ≥ 3 months (frequency and urgency with or without incontinence), ≥ 8 micturitions/day and ≥ 3 urgency episodes/day	Adults (≥ 18 years) with OAB symptoms ≥ 3 months (frequency and urgency with or without incontinence), ≥ 8 micturitions/day and ≥ 3 urgency episodes/day	Adults (≥ 18 years) with OAB symptoms ≥ 3 months (frequency and urgency with or without incontinence), ≥ 8 micturitions/day and ≥ 1 urgency episode/day or ≥ 1 urgency incontinence episode/day	Adults (≥ 18 years) with OAB symptoms ≥ 3 months (frequency and urgency with or without incontinence), ≥ 8 micturitions/day and ≥ 3 urgency episode/day. Patients also had to be non-responsive (i.e., lack of efficacy) to ≥ 1 anticholinergic drugs
	Exclusion criteria	Stress incontinence, diabetic neuropathy, lower urinary tract pathology, polyuria	Stress incontinence, lower urinary tract pathology, polyuria, TURP within 6 months	Stress incontinence, lower urinary tract pathology, polyuria	Stress incontinence, diabetic neuropathy, lower urinary tract pathology	Stress incontinence, diabetic neuropathy, lower urinary tract pathology, polyuria	Stress incontinence, lower urinary tract pathology, polyuria, diabetic neuropathy	Stress incontinence, lower urinary tract pathology, polyuria, diabetic neuropathy	Stress incontinence, lower urinary tract pathology, diabetic neuropathy	Dissatisfied with anticholinergic drugs due to poor tolerability, stress incontinence, lower urinary tract pathology, diabetic neuropathy
DRUGS	**Intervention**	MIR ER 50 mg daily MIR ER 100 mg daily	MIR ER 50 mg daily	MIR ER 50 mg daily	MIR ER 25 mg daily MIR ER 50 mg daily MIR ER 100 mg daily MIR ER 200 mg daily	MIR ER 50 mg daily MIR ER 100 mg daily	MIR ER 50 mg daily MIR ER 100 mg daily	MIR ER 25 mg daily MIR ER 50 mg daily	MIR ER 25 mg daily MIR ER 50 mg daily	MIR ER 50 mg daily
	Comparator(s)	Tolterodine ER 4 mg daily Placebo daily	Tolterodine ER 4 mg daily Placebo daily	Tolterodine ER 4 mg daily Placebo daily	Tolterodine ER 4 mg daily Placebo daily	Tolterodine ER 4 mg daily	Placebo daily	Placebo daily	Daily treatment with: SOL 2.5 mg SOL 5 mg SOL 10 mg SOL 2.5 mg + MIR	SOL 5 mg daily

	Study Name	SCORPIO 046	Study 048	Study 090	DRAGON 044	TAURUS 049	ARIES 047	CAPRICORN 074	SYMPHONY 100	BEYOND 001
									25 mg SOL 5 mg + MIR 25 mg SOL 10 mg + MIR 25 mg SOL 2.5 mg + MIR 50 mg SOL 5 mg + MIR 50 mg SOL 10 mg + MIR 50 mg, or Placebo daily	
DURATION	**Phase:**	**3**	**3**	**3**	**2**	**3**	**3**	**3**	**2**	**3**
	Run-in	2 weeks	2 weeks	2 weeks	2 weeks	2 weeks	2 weeks	2 weeks	2 weeks	2 weeks
	Double-blind	12 weeks	12 weeks	12 weeks	12 weeks	52 weeks	12 weeks	12 weeks	12 weeks	12 weeks
OUTCOMES	**Primary end point**	Change from baseline: • total incontinence episodes/ 24 hours • micturitions/ 24 hours	Change from baseline: micturitions/ 24 hours	Change from baseline: micturitions/ 24 hours	Change from baseline: micturitions/ 24 hours	Harms	Change from baseline: • total incontinence episodes/24 hours • micturitions/24 hours	Change from baseline: • total incontinence episodes/24 hours • micturitions/ 24 hours	Change from baseline: mean volume voided/ micturition	Change from baseline: micturitions/24 hours
	Other end points	• urgency incontinence episodes/ 24 hours • achievement of continence • urgency episodes/ 24 hours • nocturia • HRQoL • harms	• total incontinence episodes/24 hours • urgency incontinence episodes/24 hours • achievement of continence • urgency episodes/24 hours • nocturia • HRQoL • harms	• total incontinence episodes/24 hours • urgency incontinence episodes/24 hours • achievement of continence • urgency episodes/24 hours • nocturia • HRQoL • harms	• total incontinence episodes/24 hours • urgency incontinence episodes/24 hours • achievement of continence • urgency episodes/24 hours • nocturia • HRQoL • harms	Change from baseline: • total incontinence episodes/24 hours • urgency incontinence episodes/24 hours • achievement of continence • micturitions/24 hours • urgency episodes/24 hours • nocturia • HRQoL	• urgency incontinence episodes/24 hours • achievement of continence • urgency episodes/24 hours • nocturia • HRQoL • harms	• urgency incontinence episodes/24 hours • achievement of continence • urgency episodes/24 hours • nocturia • HRQoL • harms	• total incontinence episodes/24 hours • urgency incontinence episodes/24 hours • achievement of continence • micturitions/ 24 hours • urgency episodes/24 hours • nocturia • HRQoL • harms	• total incontinence episodes/24 hours • urgency incontinence episodes/24 hours • achievement of continence • urgency episodes/24 hours • nocturia • HRQoL • harms

	Study Name	SCORPIO 046	Study 048	Study 090	DRAGON 044	TAURUS 049	ARIES 047	CAPRICORN 074	SYMPHONY 100	BEYOND 001
NOTES	**Publications**	Khullar et al.[16]	Yamaguchi et al.[17]	None	Chapple et al.[18]	Chapple et al.[19]	Nitti et al.[20]	Hershorn et al.[21]	Abrams et al.[22]	None
						81% of enrolled patients had participated in study SCORPIO or ARIES				

DB = double-blind; ER = extended-release; HRQoL = health-related quality of life; MIR = mirabegron; OAB = overactive bladder; RCT = randomized controlled trial; SOL = solifenacin; TURP = transurethral resection of prostate.
Four additional reports (manufacturer's submission binder, Health Canada Reviewer's report, US Food and Drug Administration Medical and Statistical reviews) were included.[23–26]
Source: Clinical Study Report,[27–35] Khullar et al. 2013,[16] Chapple et al. 2013,[19] Chapple et al. 2013,[18] Nitti et al. 2012,[20] Herschorn et al. 2013,[21] Abrams et al. 2014,[22] Yamaguchi et al. 2014,[17] Khullar et al. 2013.[36]

3.2 Included Studies

3.2.1 Description of Studies

Nine double-blind randomized controlled trials (RCTs) met the criteria for inclusion in this systematic review. Studies were similar in terms of design, inclusion criteria, and outcome measures. In all studies, eligible patients underwent a two-week single-blind placebo run-in period, and those who met the inclusion criteria were randomized to treatment groups as described in Table 4.

Eight trials (SCORPIO, 048, 090, DRAGON, ARIES, CAPRICORN, SYMPHONY, and BEYOND) were of short duration (12 weeks). Of these, six trials were designed to examine the efficacy of mirabegron ER versus placebo (SCORPIO, 048, 090, DRAGON, ARIES, and CAPRICORN); four trials also included tolterodine as an active comparator (SCORPIO, 048, 090, and DRAGON). One trial was designed to assess the non-inferiority of mirabegron versus solifenacin (BEYOND), and one trial examined the efficacy of mirabegron as add-on therapy to solifenacin, compared with solifenacin monotherapy (SYMPHONY).

One trial (TAURUS) was 52 weeks in duration and was designed to assess the safety of mirabegron ER versus tolterodine.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

All trials enrolled adults who had OAB symptoms for at least three months (with or without incontinence) and an average of eight or more micturitions per day at baseline. Additional inclusion criteria included three or more urgency episodes per day (SCORPIO, DRAGON, TAURUS, ARIES, CAPRICORN, and BEYOND), or at least one urgency or urgency incontinence episode per day (studies 048, 090, and SYMPHONY).

In the BEYOND study, all patients were either currently or had recently (within past six months) been treated with anticholinergic drugs and were considered non-responsive due to lack of efficacy. In the other eight studies, those who were treatment-naive or who had previously received therapy for OAB (treatment-experienced) were eligible.

In all studies, patients with other bladder disorders, such as stress incontinence, bladder obstruction or stones, urinary tract infection, previous pelvic radiation, or polyuria, or patients who required catheterization, were excluded. In addition, patients with uncontrolled hypertension (blood pressure ≥ 180/110 mm Hg), or severe cardiovascular or cerebrovascular conditions, were excluded.

Incontinence was not a requirement for inclusion in any of the studies; however, all studies identified an incontinent subgroup for the purpose of assessing changes in incontinence-related outcomes.

b) Baseline Characteristics

Baseline characteristics were similar across treatment groups within studies. However, there were a few notable between study differences (Table 6). The mean age per treatment group ranged from 53.4 to 60.3 years, and the percentage of female patients ranged from 64% to 91%.

In study 090, BEYOND, and SYMPHONY, only 40%, 44%, and 22% of patients, respectively, were included in the incontinent subgroup, compared with 59% to 71% of patients in the remaining trials.

The proportion of patients who had received prior treatment for OAB symptoms ranged from 38% to 65% in all studies except BEYOND. In BEYOND, all patients had been treated with one or more

anticholinergic drug for OAB symptoms within the past six months and were dissatisfied due to poor efficacy. The last anticholinergic taken before entering the study is listed in Table 5. Of those enrolled, 57% had previously tried one anticholinergic drug, 28% had tried two, and 15% had received three or more.

In the TAURUS study, 81% patients had previously been enrolled in another mirabegron trial (SCORPIO or ARIES) and had received placebo (22%), mirabegron 50 mg (21%), mirabegron 100 mg (24%), or tolterodine 4 mg per day (14%).

TABLE 5: BEYOND TRIAL — ANTICHOLINERGIC DRUG TAKEN PRIOR TO STUDY ENTRY

Medication	MIR 50 mg [redacted]	SOL 5 mg [redacted]
n (%)		
Trospium chloride		
Tolterodine		
Oxybutynin		
Fesoterodine		
Propiverine		
Darifenacin		
Solifenacin		
Other anticholinergic drug		

MIR = mirabegron; SOL = solifenacin.

TABLE 6A: SUMMARY OF BASELINE CHARACTERISTICS

	SCORPIO			048			090			DRAGON				TAURUS	
Characteristic	**Placebo**	**MIR 50 mg**	**TOL 4 mg**	**Placebo**	**MIR 50 mg**	**TOL 4 mg**	**Placebo**	**MIR 50 mg**	**TOL 4 mg**	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**TOL 4 mg**	**MIR 50 mg**	**TOL 4 mg**
N	**480**	**473**	**478**	**368**	**369**	**368**	**323**	**338**	**333**	**166**	**167**	**167**	**85**	**812**	**812**
Age, mean (SD)	59.3 (12.2)	59.2 (12.2)	59.1 (12.8)	58.2 (14.2)	58.3 (13.9)	58.3 (13.7)	55.3 (13.6)	54.3 (14.2)	53.9 (14.5)	57.1 (12.9)	57.2 (12.1)	56.9 (12.5)	56.6 (12.8)	59.2 (12.6)	59.6 (12.5)
Age ≥ 65 years, N (%)	178 (37)	171 (36)	184 (39)	137 (37)	136 (37)	141 (38)	88 (27)	86 (25)	87 (26)	44 (27)	50 (30)	42 (25)	21 (25)	289 (36)	303 (37)
Female, N (%)	346 (72)	340 (72)	346 (73)	310 (84)	311 (84)	304 (83)	225 (70)	228 (68)	213 (64)	151 (91)	147 (88)	149 (89)	69 (81)	602 (74)	600 (74)
Duration of OAB, mean number of months (SD)	77 (92)	79 (86)	76 (93)	77 (88)	70 (67)	76 (78)	58 (66)	62 (72)	58 (62)	54 (67)[a]	48 (36)[a]	45 (54)[a]	47 (45)[a]	87 (96)	84 (87)
OAB type, N (%)															
Urgency incontinence	201 (42)	192 (41)	184 (39)	236 (64)	230 (62)	235 (64)	136 (42)	124 (37)	136 (41)	74 (45)	79 (47)	67 (40)	38 (45)	296 (37)	317 (39)
Mixed stress/urgency	102 (21)	108 (23)	105 (22)	93 (25)	108 (29)	94 (26)	56 (17)	67 (20)	58 (17)	52 (31)	41 (25)	47 (28)	24 (28)	232 (29)	210 (26)
Frequency	177 (37)	173 (37)	186 (39)	39 (11)	31 (8)	39 (11)	131 (41)	147 (44)	139 (42)	40 (24)	47 (28)	53 (32)	23 (27)	284 (35)	285 (35)
Prior OAB drug use, N (%)	238 (50)	240 (51)	231 (49)	240 (65)	233 (63)	240 (65)	169 (52)	176 (52)	171 (51)	71 (43)[b]	82 (49)[b]	77 (46)[b]	35 (41)[b]	446 (55)	447 (55)
Micturitions/ 24 hours, mean (SD)	11.7 (3.1)	11.7 (3.0)	11.6 (2.8)	11.3 (2.7)	11.2 (2.7)	11.1 (2.6)	12.6 (4.9)	12.1 (4.1)	12.1 (3.7)	11.7 (3.4)	11.9 (2.9)	11.9 (3.3)	12.3 (3.7)	11.1 (2.8)	10.9 (2.7)
Incontinent Subgroup, N (%)	**291 (61)**	**293 (62)**	**300 (63)**	**264 (72)**	**266 (72)**	**240 (65)**	**127 (39)**	**135 (40)**	**137 (41)**	**126 (76)**	**120 (72)**	**114 (68)**	**62 (73)**	**479 (61)**	**488 (62)**
Incontinence episodes/24 hours, mean (SD)	2.7 (2.4)	2.8 (2.8)	2.6 (2.6)	1.9 (1.8)	2.0 (2.1)	1.9 (1.8)	2.4 (2.7)	2.4 (2.5)	2.3 (2.8)	2.5 (2.4)	2.9 (3.2)	2.4 (2.3)	2.9 (2.8)	2.7 (SE 0.12)	2.4 (SE 0.11)

MIR = mirabegron; OAB = overactive bladder; SD = standard deviation; TOL = tolterodine.
[a] The duration of OAB symptoms were reported for 36% of the total enrolled population.
[b] 22% to 25% of patients found prior drug treatment effective for OAB.
Source: Clinical Study Report,[27–35] Chapple et al. 2013,[18] Yamaguchi et al. 2014,[17] Nitti et al. 2012,[20] Herschorn et al. 2013,[21] Abrams et al. 2014.[22]

TABLE 6B: SUMMARY OF BASELINE CHARACTERISTICS (CONTINUED)

	ARIES		CAPRICORN		
Characteristic	Placebo	MIR 50 mg	Placebo	MIR 25 mg	MIR 50 mg
N	**453**	**442**	**433**	**432**	**440**
Age, mean (SD)	60.1 (13.8)	59.2 (13.5)	58.2 (13.7)	58.5 (12.9)	60.3 (12.2)
Age ≥ 65 years, N (%)	180 (40)	168 (38)	160 (37)	154 (36)	168 (38)
Female, N (%)	345 (76)	322 (73)	301 (70)	293 (68)	303 (69)
Duration of OAB, mean months (SD)	92 (109)	84 (95)	91 (96)	97 (115)	94 (99)
OAB type, N (%)	N = 433	N = 425			
Urgency incontinence	124 (29)	135 (32)	117 (28)	156 (38)	164 (39)
Mixed stress/urgency	176 (41)	156 (37)	137 (33)	124 (30)	148 (35)
Frequency	133 (31)	134 (32)	161 (39)	130 (32)	114 (27)
Prior OAB drug use, N (%)	249 (58)	242 (57)	217 (52)	219 (53)	206 (48)
Micturitions/24 hours, mean (SD)	11.5 (3.3)	11.8 (3.5)	11.5 (2.9)	11.7 (3.1)	11.7 (3.2)
Incontinent subgroup, N (%)	**325 (72)**	**312 (71)**	**262 (61)**	**254 (59)**	**257 (58)**
Incontinence episodes/ 24 hours, mean (SD)	3.0 (3.1)	2.8 (2.7)	2.4 (2.3)	2.7 (2.5)	2.5 (2.3)

MIR = mirabegron; OAB = overactive bladder; SD = standard deviation.
Source: Clinical Study Report,[27–35] Chapple et al. 2013,[18] Yamaguchi et al. 2014,[17] Nitti et al. 2012,[20] Herschorn et al. 2013,[21] Abrams et al.2014.[22]

TABLE 6C: SUMMARY OF BASELINE CHARACTERISTICS (CONTINUED)

Characteristic	SYMPHONY									BEYOND	
	Placebo	MIR 25 mg	MIR 50 mg	SOL 5 mg	SOL 10 mg	MIR 25 mg + SOL 5 mg	MIR 25 mg + SOL 10 mg	MIR 50 mg + SOL 5 mg	MIR 50 mg + SOL 10 mg	MIR 50 mg	SOL 5 mg
N	**81**	**77**	**78**	**156**	**78**	**144**	**81**	**153**	**81**	[redacted]	[redacted]
Age, mean (SD)	54.6 (13.4)	55.2 (14.5)	53.4 (14.0)	54.2 (15.5)	55.0 (12.8)	55.0 (14.6)	56.5 (12.3)	54.1 (14.1)	55.5 (13.8)	[redacted]	[redacted]
Age ≥ 65 years, N (%)	22 (27)	21 (27)	20 (26)	43 (28)	21 (27)	39 (27)	24 (30)	41 (27)	23 (28)	[redacted]	[redacted]
Female, N (%)	54 (67)	52 (68)	52 (67)	103 (66)	53 (68)	95 (66)	52 (64)	101 (66)	54 (67)	[redacted]	[redacted]
Duration of OAB, mean months (SD)	49 (39)	61 (69)	57 (67)	63 (80)	54 (57)	56 (85)	66 (102)	58 (82)	58 (80)	[redacted]	[redacted]
OAB type, N (%)											
Urgency incontinence	14 (18)	27 (36)	18 (24)	38 (26)	19 (25)	35 (25)	22 (28)	35 (23)	20 (25)	[redacted]	[redacted]
Mixed stress/urgency	9 (12)	8 (11)	10 (13)	25 (17)	11 (15)	18 (13)	13 (17)	18 (12)	10 (13)	[redacted]	[redacted]
Frequency	55 (71)	40 (53)	48 (63)	86 (58)	46 (61)	88 (62)	43 (55)	97 (65)	49 (62)	[redacted]	[redacted]
Prior OAB drug use, N (%)	40 (50)	42 (55)	38 (49)	70 (47)	29 (38)	64 (45)	42 (54)	71 (47)	40 (50)	[redacted]	[redacted]
Micturitions/	10.4	11.3	10.8	11.4	11.3	10.9	11.1	11.3	11.2 (2.4)	[redacted]	[redacted]

Characteristic	SYMPHONY									BEYOND	
	Placebo	MIR 25 mg	MIR 50 mg	SOL 5 mg	SOL 10 mg	MIR 25 mg + SOL 5 mg	MIR 25 mg + SOL 10 mg	MIR 50 mg + SOL 5 mg	MIR 50 mg + SOL 10 mg	MIR 50 mg	SOL 5 mg
24 hours, mean (SD)	(2.0)	(2.6)	(2.3)	(3.2)	(2.9)	(2.3)	(2.2)	(3.1)		[redacted]	[redacted]
Incontinent subgroup, N (%)	**17 (21)**	**13 (17)**	**18 (23)**	**35 (22)**	**15 (19)**	**32 (22)**	**24 (30)**	**24 (16)**	**20 (25)**	[redacted]	[redacted]
Incontinence episodes/ 24 hours, mean (SD)	0.9 (0.8)	1.9 (1.6)	1.3 (1.0)	1.3 (1.2)	1.4 (1.3)	1.2 (1.1)	1.5 (1.2)	1.2 (1.2)	1.3 (0.9)	[redacted]	[redacted]

MIR = mirabegron; OAB = overactive bladder; SD = standard deviation; SOL = solifenacin.
Source: Clinical Study Report,[27–35] Chapple et al. 2013,[18] Yamaguchi et al. 2014,[17] Nitti et al. 2012,[20] Herschorn et al. 2013,[21] Abrams et al. 2014.[22]

3.2.3 Interventions

All trials used a double-dummy design to maintain blinding to the treatment received. Three trials (DRAGON, CAPRICORN, and SYMPHONY) included mirabegron ER 25 mg daily, and all studies included mirabegron ER 50 mg daily. Five trials included tolterodine ER 4 mg daily (DRAGON, 048, 090, SCORPIO, and TAURUS), one study included solifenacin 5 mg daily (BEYOND), and one study included solifenacin 5 mg or 10 mg, alone or in combination with mirabegron 25 mg or 50 mg (SYMPHONY). All trials except TAURUS and BEYOND also included a placebo group. Treatment duration was 12 weeks except for TAURUS, which was 52 weeks.

In all trials, concomitant drug or non-drug therapies for OAB were not allowed during the study period. However, bladder training programs or pelvic floor exercises could be continued, provided they were started more than 30 days before study entry.

In seven trials (SCORPIO, TAURUS, study 090, ARIES, CAPRICORN, SYMPHONY and BEYOND) the use of alpha blockers or 5-alpha reductase inhibitors was permitted if they had been initiated before enrolment and the dosage was stable in the previous four weeks. In study 048 and DRAGON, use of alpha blockers or therapies for lower urinary tract obstructive disease were not permitted.

3.2.4 Outcomes

Bladder function outcomes were captured through a micturition diary completed by patients for three days at baseline (during placebo run-in) and before each follow-up assessment visit (e.g., weeks 4, 8, and 12). All studies measured total incontinence episodes (any involuntary leakage of urine), urgency incontinence episodes (also described as urge incontinence; the involuntary leakage of urine accompanied by symptoms of urgency), micturitions, nocturia, and urgency episodes for the three days and averaged scores to obtain the number of episodes per 24 hours. In SCORPIO, ARIES, and CAPRICORN, the co-primary outcomes were the change from baseline in mean number of incontinence episodes and micturitions per 24 hours at week 12. The primary outcomes in study 048, study 090, DRAGON, and BEYOND were the change from baseline in mean number of micturitions per 24 hours at week 12. The primary outcome in SYMPHONY was the change from baseline in the mean volume voided per micturition at week 12. The primary outcomes in TAURUS were harms at week 52.

Different symptom rating scales and health-related quality of life (HRQoL) scales were used in the trials.

In the SCORPIO, DRAGON, TAURUS, ARIES, CAPRICORN, SYMPHONY, and BEYOND studies, the intensity of urgency was assessed using the Patient Perception of Intensity of Urgency Scale (PPIUS), a five-point categorical scale with responses including no urgency; mild, moderate, or severe urgency; or urgency incontinence. Severe (grade 3) urgency is described as "I could not postpone voiding, but had to rush to the toilet in order not to wet myself," and urgency incontinence (grade 4) as "I leaked before arriving at the toilet."[37] The scale has demonstrated content validity and good test-retest reliability among patients with stable symptoms.[37]

Patient Perception of Bladder Condition (PPBC) scale is a global measure of the patient's subjective impression of his or her current urinary problem. It consists of a six-point Likert scale ranging from 1 "no problems at all" to 6 "many severe problems" due to bladder condition.[38]

The Overactive Bladder Questionnaire (OAB-q) consists of a symptom bother scale, four HRQoL subscales (coping behaviour, concern, sleep, and social interaction), and a total HRQoL score.[39] Each subscale is transformed to a 0 to 100 score, with higher symptom bother scores indicating worse symptom severity and lower HRQoL subscale scores reflecting greater effect of OAB on HRQoL. The minimal clinically important difference (MCID) is considered to be 10 points.[39]

The King's Health Questionnaire (KHQ) is a 21-item HRQoL measure for patients with lower urinary tract symptoms.[38] It consists of nine domains (general health perceptions, incontinence impact, role limitations, physical limitations, social limitations, personal relationships, emotions, sleep/energy, and severity) which are scored from 0 (best) to 100 (worst).[38] An MCID for each domain score of five points has been reported.[40,41]

Treatment-emergent adverse events were defined as any adverse event starting or worsening from the first double-blind study drug intake until the end of follow-up. Serious adverse events were events that were fatal or life-threatening; that required hospitalization or prolonged an existing hospitalization; that resulted in persistent or significant disability, a congenital anomaly, or a birth defect; or that were an important medical event.

3.2.5 Statistical Analysis

Six trials (SCORPIO, DRAGON, ARIES, CAPRICORN, and studies 048 and 090) were powered to test the superiority of mirabegron versus placebo for the primary outcome of micturitions per day. In addition, four trials of the above (SCORPIO, ARIES, CAPRICORN, and study 048) were also powered to detect differences in incontinence episodes (co-primary outcome in SCORPIO, ARIES, CAPRICORN; secondary outcome in study 048). Although four studies (SCORPIO, DRAGON, and studies 048 and 090) also included an active comparator group (tolterodine), the studies were not powered to test for differences between mirabegron and tolterodine.

TAURUS was a 52-week study designed to assess safety of mirabegron versus tolterodine. No formal power calculations were completed for TAURUS. The study used a repeated-measures model and an analysis of covariance (ANCOVA) model (with covariates treatment group, baseline value, previous RCT participant history, sex, and geographic region) to analyze change from baseline in efficacy outcomes. However, there was no statistical testing of between-group differences.

The SYMPHONY study was powered to detect a difference between mirabegron plus solifenacin combination therapy and solifenacin 5 mg monotherapy or placebo for the change from baseline in the mean volume voided per micturition. The secondary objective of the study was to explore the dose–

response relationship and safety compared with placebo or monotherapy. The study was not powered for secondary efficacy outcomes.

The BEYOND study was powered to test the non-inferiority of mirabegron versus solifenacin for the primary outcome of micturitions per day. A non-inferiority margin of –0.20 was set. The non-inferiority margin was based on [redacted].

Seven studies used ANCOVA models (SCORPIO, DRAGON, 090, ARIES, CAPRICORN, SYMPHONY, and BEYOND) for the analysis of continuous efficacy outcomes. Models included treatment group, baseline outcome value, and the following covariates:

- DRAGON: country
- SCORPIO: sex, geographic region
- Study 090: geographic region
- ARIES: sex, geographic region
- CAPRICORN: sex, geographic region
- SYMPHONY: sex, age group, geographic region
- BEYOND: sex, age < 65 or ≥ 65 years, number of prior anticholinergic drugs (one drug or two or more drugs), geographic region.

The primary analyses in study 048 used a *t*-test or Wilcoxon rank sum test to test for differences between mirabegron and placebo, with a secondary analysis using an analysis of variance model with baseline value as a covariate. In studies 048 and 090, SCORPIO, ARIES, CAPRICORN, and BEYOND, the between-group differences for number of incontinence episodes were tested using non-parametric tests.

SCORPIO, DRAGON, TAURUS, study 090, ARIES, CAPRICORN, SYMPHONY, and BEYOND used the last observation carried forward method for missing data. In study 048, there was no mention of methods to handle missing data.

SCORPIO, CAPRICORN, and ARIES used the Hochberg procedure and a stepwise parallel gatekeeping procedure control for multiple comparison testing. No methods to control for multiple outcome testing were used in DRAGON, 048, 090, SYMPHONY, and BEYOND.

The DRAGON study used the Mantel-Haenszel test, and the SCORPIO, ARIES, CAPRICORN, SYMPHONY, and BEYOND studies used logistic regression to test for differences in the proportion of patients who were continent at the end of the trials. No statistical testing of this outcome was performed in studies 090 and 048.

a) Analysis Populations

In all trials, the full analysis set (FAS) included all patients who received at least one dose of study medication and had a baseline and one post-baseline outcome measure. The FAS population was used for analyses of change in micturition and urgency episodes. However, for outcomes related to incontinence (including incontinence episodes, urgency incontinence episodes, and proportion of patients achieving continence), analyses were restricted to the proportion of the FAS population that reported at least one incontinence episode at baseline. Similarly, for the outcome of nocturia, the

analysis was restricted to those patients who had a least one episode of nocturia at baseline in all studies.

In the SYMPHONY study, the per-protocol analysis set (PPS) was used for primary outcome assessment of non-inferiority. This PPS included all patients in the FAS who had no major protocol violations.

The safety population included all patients who received at least one dose of study medication.

3.3 Patient Disposition

The disposition of participants in the included studies is presented Table 7a: Patient Disposition.

The proportion of patients who withdrew from the trials was similar across treatment groups within trials, but some differences were noted between trials. The proportion of patients who withdrew was higher for study 090 (18%) and TAURUS (23%) compared with the other trials (5% to 14%). In study 090 and TAURUS, the reasons for withdrawal were similar across treatment groups. The reasons for withdrawal are described in Table 7a: Patient Disposition.

TABLE 7A: PATIENT DISPOSITION

	SCORPIO			048			090			DRAGON				TAURUS		ARIES	
	PL	MIR 50 mg	TOL 4 mg	PL	MIR 50 mg	PL	PL	MIR 50 mg	TOL 4 mg	PL	MIR 25 mg	MIR 50 mg	TOL 4 mg	MIR 50 mg	TOL 4 mg	PL	MIR 50 mg
Screened, N	2,437			1,381			1,547			1,108				2,849		2,342	
Entered placebo run-in, N	2,397			1,332			1,506			NR				2,801		2,149	
Randomized total N (%)	1,987 (83%)			1,139 (86%)			1,126 (75%)			928 (NR)				2,452 (88%)		1,329 (62%)	
Randomized, N	497	497	495	381	380	378	377	372	377	169	169	169	85	815	813	454	442
Withdrawal, N (%)	44 (9)	57 (11)	50 (10)	31 (8)	31 (8)	23 (6)	77 (20)	61 (16)	67 (18)	12 (7)	16 (9)	16 (9)	3 (4)	186 (23)	192 (24)	69 (15)	59 (13)
Reasons for WD																	
Unmet inclusion criteria	5 (1)	8 (2)	0	0	0	0	23 (6)	18 (5)	17 (5)	0	0	0	0	7 (1)	10 (1)	0	0
WDAE	13 (3)	25 (5)	24 (5)	9 (2)	15 (4)	13 (3)	14 (4)	9 (2)	15 (4)	5 (3)	9 (5)	4 (2)	1 (1)	52 (6)	49 (6)	17 (4)	18 (4)
Lack of efficacy	5 (1)	6 (1)	3 (1)	3 (1)	4 (1)	2 (< 1)	7 (2)	4 (1)	2 (1)	1 (< 1)	2 (1)	1 (< 1)	0	34 (4)	45 (6)	9 (2)	1 (< 1)
Withdrew consent	11 (2)	9 (2)	9 (2)	12 (3)	8 (2)	1 (< 1)	21 (6)	21 (6)	24 (6)	3 (2)	1 (< 1)	5 (3)	1 (1)	65 (9)	64 (8)	29 (6)	22 (5)
Lost to follow-up	4 (1)	3 (1)	5 (1)	0	0	0	6 (2)	3 (1)	7 (2)	0	1 (< 1)	2 (1)	1 (1)	14 (2)	7 (1)	2 (< 1)	9 (2)
Protocol violation	2 (< 1)	3 (1)	3 (1)	5 (1)	3 (1)	2 (< 1)	2 (1)	4 (1)	0	2 (1)	1 (< 1)	2 (1)	0	6 (0.7)	11 (1)	7 (2)	4 (1)
Never received study drug	2 (< 1)	1 (< 1)	0	0	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (< 1)	0
Other	2 (< 1)	2 (< 1)	2 (< 1)	2 (1)	1 (< 1)	5 (1)	4 (1)	2 (1)	2 (1)	1 (< 1)	2 (1)	2 (1)	0	7 (0.9)	6 (1)	4 (1)	5 (1)
FAS, N[a]	480	473	475	368	369	368	323	338	333	166	167	167	85	789	791	433	425
FAS-Incontinent, N[b]	291	293	300	264	266	240	127	135	137	106	99	108	53	479	488	325	312
Safety, N[c]	494	493	495	379	379	375	366	366	371	169	169	169	85	812	812	453	442
PPS, N[d]	425	417	426	356	358	357	261	258	258	146	141	142	73	–	–	380	372

FAS = full analysis set; MIR = mirabegron; NR = not reported; PL = placebo; PPS = per-protocol set; TOL = tolterodine; WDAE = withdrawal due to adverse event.

[a] All patients who received at least one dose of study medication and had a baseline and one post-baseline outcome measure.

[b] All patients in FAS analysis who reported at least one incontinence episode at baseline.

[c] All patients who received at least one dose of study medication.

[d] All FAS patients without major protocol violations: the main analysis set for the primary end point testing non-inferiority in BEYOND.

Source: Clinical Study Report,[27–32,35] Chapple et al. 2013,[18] Nitti et al. 2012,[20] Herschorn et al. 2013,[21] Abrams et al.[22]

TABLE 7B: PATIENT DISPOSITION (CONTINUED)

	CAPRICORN			SYMPHONY									BEYOND	
	PL	MIR 25 mg	MIR 50 mg	PL	MIR 25 mg	MIR 50 mg	SOL 5 mg	SOL 10 mg	MIR 25 mg + SOL 5 mg	MIR 25 mg + SOL 10 mg	MIR 50 mg + SOL 5 mg	MIR 50 mg + SOL 10 mg	MIR 50 mg	SOL 5 mg
Screened, N	2,201			2,092									2,586	
Entered placebo run-in, N	2,030			1,658									2,487	
Randomized total N (%)	1,306 (64%)			1,306 (79%)									1,887 (76%)	
Randomized, N	433	433	440	81	78	79	156	78	144	81	152	81	[redacted]	[redacted]
Withdrawal, N (%)	66 (15)	46 (11)	54 (12)	5 (6)	7 (9)	3 (4)	10 (6)	4 (5)	8 (6)	2 (3)	6 (4)	4 (5)	[redacted]	[redacted]
Reasons for WD														
Unmet inclusion criteria	1 (< 1)	1 (< 1)	0	0	0	0	0	0	0	0	0	0	[redacted]	[redacted]
WDAE	15 (4)	17 (4)	12 (3)	0	1 (1)	2 (3)	1 (< 1)	2 (3)	1 (< 1)	1 (1)	1 (< 1)	3 (4)	[redacted]	[redacted]
Lack of efficacy	11 (3)	4 (1)	3 (1)	0	0	0	0	0	1 (< 1)	0	0	0	[redacted]	[redacted]
Withdrew consent	20 (5)	12 (3)	18 (4)	4 (5)	3 (4)	1 (1)	3 (2)	2 (3)	4 (3)	0	2 (1)	1 (1)	[redacted]	[redacted]
Lost to follow-up	4 (1)	3 (1)	3 (1)	0	1 (1)	0	0	0	0	0	1 (< 1)	0	[redacted]	[redacted]
Protocol violation	5 (1)	3 (1)	8 (2)	1 (1)	2 (3)	0	6 (4)	0	1 (< 1)	0	2 (1)	0	[redacted]	[redacted]
Never received study drug	0	1 (< 1)	0	0	0	0	0	0	0	0	0	0	[redacted]	[redacted]
Other	10 (2)	5 (1)	10 (2)	0	0	0	0	0	0	1 (1)	0	0	[redacted]	[redacted]
FAS, N[a]	415	410	426	80	76	77	150	76	141	78	150	80	[redacted]	[redacted]
FAS-Incontinent, N[b]	262	254	257	17	13	18	35	15	32	24	24	20	[redacted]	[redacted]
Safety, N[c]	433	432	440	81	78	78	156	78	144	81	152	81	[redacted]	[redacted]
PPS, N[d]	367	385	388	72	64	67	131	68	128	69	125	70	[redacted]	[redacted]

FAS = full analysis set; MIR = mirabegron; PL = placebo; PPS = per-protocol set; SOL = solifenacin; WD = withdrawal.

[a] All patients who received at least one dose of study medication and had a baseline and one post-baseline outcome measure.

[b] All patients in FAS analysis who reported at least one incontinence episode at baseline.

[c] All patients who received at least one dose of study medication.

[d] All FAS patients without major protocol violations: the main analysis set for the primary end point testing non-inferiority in BEYOND.

Source: Clinical Study Report,[27–32,35] Chapple et al. 2013,[18] Nitti et al. 2012,[20] Herschorn et al. 2013,[21] Abrams et al.[22]

3.4 Exposure to Study Treatments

Mean drug exposure was similar across treatment groups and across the 12-week trials (SCORPIO, 048, DRAGON, 090, ARIES, CAPRICORN, SYMPHONY, and BEYOND), ranging from 76 days to 84 days. In the TAURUS study, the mean exposure was 311 and 309 days in the mirabegron 50 mg and tolterodine groups, respectively.

3.5 Critical Appraisal

3.5.1 Internal Validity

- Eight studies used central computerized randomization to assign patients to treatment groups; the methods reported for study 048 were not explicitly stated.
- All studies used a double-dummy design to maintain double blinding. Some unblinding may have occurred among patients previously treated with antimuscarinic drugs, as these patients may be familiar with the side effect profile of these drugs.
- The proportion of withdrawals was high in study 090 (18%) and TAURUS (23%), which could threaten the validity of the results despite a similar frequency of withdrawal across treatment groups. Within all studies the reasons for withdrawal were fairly consistent between treatment groups.
- In the 52-week TAURUS trial, 81% of patients had previously participated in another manufacturer-sponsored mirabegron study. The results of the comparison of mirabegron with tolterodine in the TAURUS study may be subject to recruitment bias.
- Incontinence subgroup analysis may be subject to bias. Although the analysis was pre-planned, the randomization was not stratified by the presence of incontinence at baseline. Thus, the benefit of randomization may not have been maintained. This may be a more significant issue for studies in which the incontinent subgroup accounted for a smaller percentage of the total patient population (i.e., study 090, SYMPHONY, and BEYOND).
- Only the SCORPIO study reported results for the intention to treat population, but as a secondary analysis. All trials used the FAS population (patients who took the study drug and had a baseline and post-baseline outcome measure). In addition, some analyses were further restricted to patients who had a specific symptom at baseline (e.g., nocturia or urgency episodes).

3.5.2 External Validity

- OAB symptoms, prevalence, and severity tend to increase with advancing age. However, the study populations were, on average, 50 to 60 years of age, with elderly patient populations greater than 65 years old under-represented.
- The duration of treatment effect and long-term safety beyond 12 weeks remain uncertain. Although there was a 12-month study to assess safety, results from this trial are subject to bias, as a large proportion of patients entering the trial had participated in earlier mirabegron trials.
- All trials included Health Canada–approved doses of mirabegron at the maximum daily dosage of 50 mg; however, the recommended initial dose of mirabegron 25 mg per day was included in only three trials. The dose of active comparator was consistent with Health Canada recommendations (tolterodine 4 mg, solifenacin 5 mg or 10 mg), although the SYMPHONY trial also included low-dose solifenacin (2.5 mg daily; these data were not included in this review).
- The non-inferiority study enrolled patients who had experienced poor response to prior anticholinergic drugs and thus were receiving solifenacin or mirabegron as second-line therapy.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Table 3 in Section 2.2). See APPENDIX 3: DETAILED OUTCOME DATA for detailed efficacy data.

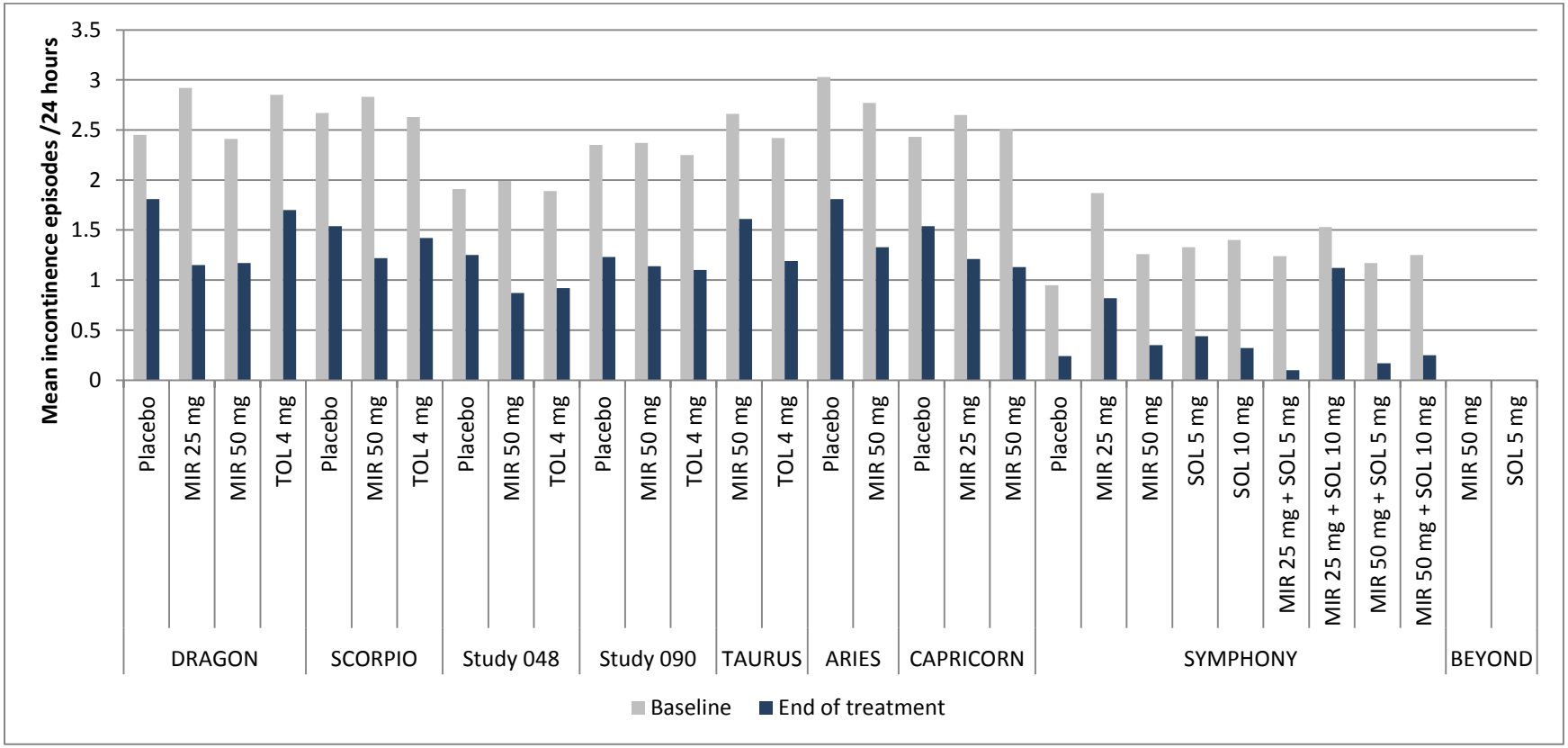
In addition, data were pooled by the CADTH Common Drug Review (CDR) when complete data were available from trials of the same duration (i.e., data from the 12-week trials were pooled where possible). For most efficacy outcomes, it was not possible to pool data because of missing variance on the change from baseline data in study 048 and DRAGON.

The results for mirabegron versus placebo are reported, but the focus of the review is comparisons between mirabegron and active drugs. Results for treatment groups employing non–Health Canada–approved doses have not been included in this report.

3.6.1 Incontinence

The mean number of incontinence episodes at baseline was similar across treatment groups in eight studies (DRAGON, 048, 090, SCORPIO, TAURUS, ARIES, CAPRICORN, and BEYOND) and ranged from 1.9 to 3.0 events per day, whereas in the SYMPHONY trial, fewer incontinence episodes were reported at baseline (median 1.3 episodes per day) for the subgroup of patients who reported at least one incontinence episode during the placebo run-in period (Figure 2 and Table 10, Table 11, and Table 12 in Appendix 3). All treatment groups showed a reduction from baseline to the end of treatment in mean number of incontinence episodes per 24 hours. Reductions ranged from 0.5 to 1.2 fewer episodes for placebo, 0.7 to 1.6, for mirabegron, 0.8 to 1.3, for tolterodine, 0.9 to 1.6, for solifenacin, and 0.3 to 1.2, for mirabegron plus solifenacin combination therapy.

FIGURE 2: INCONTINENCE EPISODES



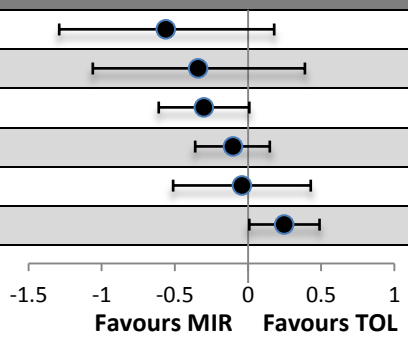
MIR = mirabegron; SOL = solifenacin; TOL = tolterodine.

The mean change from baseline in incontinence frequency was statistically significantly different for mirabegron 25 mg and mirabegron 50 mg versus placebo in SCORPIO, 048, DRAGON, ARIES, and CAPRICORN, and not significantly different in study 090 (mean difference [MD] –0.11 to –0.84) (Table 10 in Appendix 3). In the SYMPHONY trial, none of the active treatment groups (monotherapy or combination therapy) was statistically significantly different than placebo for the mean change from baseline in incontinence frequency (Table 12 in Appendix 3).

Mean changes from baseline were not statistically significantly different between mirabegron 25 mg or 50 mg and tolterodine in studies 048, 090, DRAGON, and SCORPIO (Figure 3). Tolterodine showed a statistically greater reduction in incontinence episodes than mirabegron 50 mg in the 52-week TAURUS study.

FIGURE 3: INCONTINENCE EPISODES PER 24 HOURS — MIRABEGRON VERSUS TOLTERODINE

Duration	MIR Dose	Study	Adjusted MD (95% CI) [ab]	
12 weeks	25 mg	DRAGON	–0.56 (–1.29 to 0.18)	
	50 mg	DRAGON	–0.34 (–1.06 to 0.39)	
	50 mg	SCORPIO	–0.3 (–0.61 to 0.01)	
	50 mg	Study 048	–0.1 (–0.36 to 0.15)	
	50 mg	Study 090	–0.04 (–0.51 to 0.43)	
52 weeks	50 mg	TAURUS	0.25 (0.01 to 0.49)	

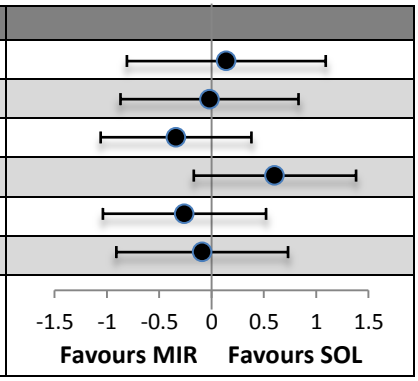


CI = confidence interval; MD = mean difference; MIR = mirabegron; TOL = tolterodine.
[a] SCORPIO and TAURUS data calculated by CADTH.
[b] Negative values indicate the MIR group had a greater reduction in incontinence episodes than the TOL group.

Mean changes from baseline were not statistically significantly different for mirabegron 25 mg or 50 mg monotherapy, or for combination therapy with solifenacin (5 mg or 10 mg), compared with solifenacin 5 mg in the BEYOND and SYMPHONY studies (Figure 4).

FIGURE 4: INCONTINENCE EPISODES PER 24 HOURS — MIRABEGRON MONOTHERAPY VERSUS SOLIFENACIN 5 MG, AND MIRABEGRON PLUS SOLIFENACIN VERSUS SOLIFENACIN 5 MG

Duration	Dose	Study	Adjusted MD (95% CI)[a]	
12 weeks	MIR 50 mg[b]	BEYOND	[redacted]	
	MIR 25 mg[c]	SYMPHONY	0.14 (–0.81 to 1.09)	
	MIR 50 mg[c]	SYMPHONY	–0.02 (–0.87 to 0.83)	
	MIR 25 mg + SOL 5 mg	SYMPHONY	–0.34 (–1.06 to 0.38)	
	MIR 25 mg + SOL 10 mg	SYMPHONY	0.60 (–0.17 to 1.38)	
	MIR 50 mg + SOL 5 mg	SYMPHONY	–0.26 (–1.04 to 0.52)	
	MIR 50 mg + SOL 10 mg	SYMPHONY	–0.09 (–0.91 to 0.73)	



CI = confidence interval; MD = mean difference; MIR = mirabegron; SOL = solifenacin.
[a] Negative values indicate the MIR group had a greater reduction in the number of micturitions than the SOL group.
[b] Full analysis set population.
[c] Calculated by CADTH.

Subgroup data by previous treatment with antimuscarinic drugs for OAB were available for the SCORPIO study (Table 26 in Appendix 3). The difference between mirabegron and tolterodine (calculated by CADTH) in incontinence episodes per day was not significantly different for either subgroup (previous treatment: MD –0.38 [95% confidence interval, –0.80 to 0.04]; no previous treatment: MD –0.22 [confidence interval –0.68 to 0.24]). However, results were generally consistent with the results for the entire population. Of note, the results from BEYOND reflect a patient population considered unresponsive to prior anticholinergic treatment.

3.6.2 Urgency Incontinence

The results for urgency incontinence (i.e., incontinence accompanied by urgency) were similar to those for any incontinence episode, and no studies showed statistically significant differences between mirabegron and tolterodine (Table 13 in Appendix 3) or mirabegron (monotherapy or combination therapy) and solifenacin (Table 11 and Table 12 in Appendix 3). The differences between mirabegron and placebo were statistically significant in SCORPIO, 048, DRAGON, ARIES, and CAPRICORN, but not in study 090 or SYMPHONY (Table 12 and Table 13 in Appendix 3).

3.6.3 Achievement of Continence

Among the subgroup of patients with incontinence at baseline, the proportion of patients who were continent at the end of treatment ranged from 34% to 82% for placebo, 41% to 67% for mirabegron, 36% to 54% for tolterodine, 53% to 69% for solifenacin, and 54% to 88% for mirabegron plus solifenacin (Table 11, Table 12, and Table 14 in Appendix 3).

Pooled data for the 12-week placebo-controlled studies suggest that patients who received mirabegron 50 mg were statistically significantly more likely to achieve continence than placebo; however, for mirabegron 25 mg, the difference versus placebo did not achieve statistical significance (Table 8). Absolute differences in the proportion of continent patients for mirabegron 25 mg or 50 mg versus tolterodine 4 mg or solifenacin 5 mg were not statistically significant (Table 8).

As a result of the lower baseline frequency of incontinence episodes, data from SYMPHONY were not included in the meta-analysis. In SYMPHONY, comparisons between active treatment groups and the placebo group were not statistically significantly different except for the mirabegron 25 mg group, in which patients less likely to achieve continence than those in the placebo group (Table 12 in Appendix 3). Patients who received mirabegron 25 mg or 50 mg in combination with solifenacin 5 mg were statistically significantly more likely to achieve continence than those who received solifenacin 5 mg monotherapy. The mirabegron monotherapy, or mirabegron plus solifenacin 10 mg combination therapy groups were not statistically significantly different from solifenacin 5 mg monotherapy (Table 8). Of note, the number of patients included in the incontinent subgroup was limited (13 to 35 patients per treatment group), and the baseline rate of incontinence was low (median 1.3 episodes per day). Thus, the findings of the incontinence subgroup should be interpreted with caution.

TABLE 8: META-ANALYSIS — PROPORTION OF PATIENTS ACHIEVING CONTINENCE

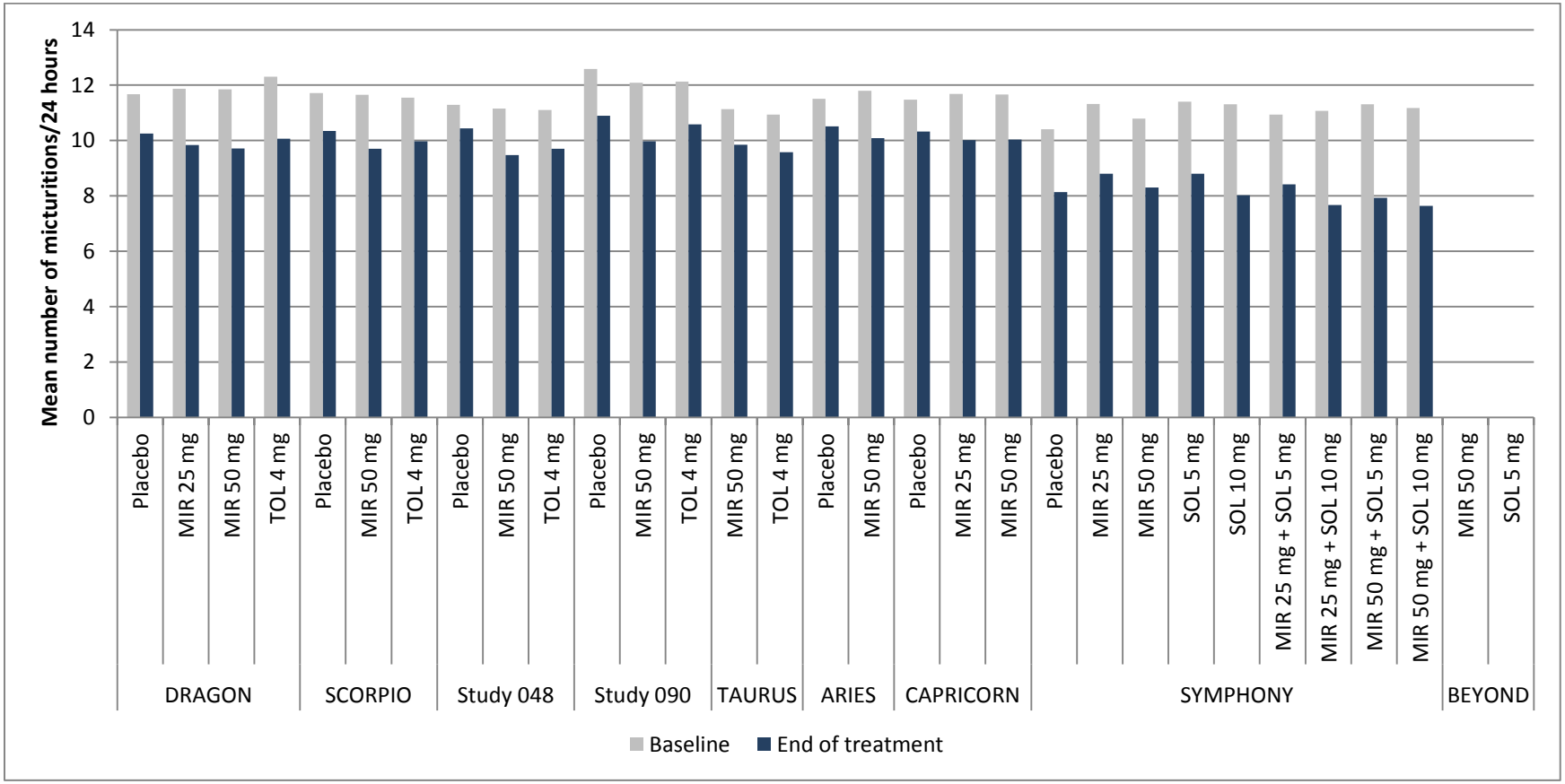
Study Duration	12-Week Trials		52-Week Trial
Mirabegron versus Placebo			
Intervention	MIR 25 mg	MIR 50 mg	–
N studies	2	6	
ARD (95% CI) MIR versus placebo[a]	6% (–1% to 13%)[b]	6% (2% to 9%)[b]	
P value	0.11	0.002	
Mirabegron Versus Tolterodine 4 mg			
Intervention	MIR 25 mg	MIR 50 mg	MIR 50 mg
N studies	1	4	1
ARD (95% CI) MIR versus TOL[a]	7% (–10% to 23%)	0% (–5% to 5%)	–2% (–8% to 5%)
P value	0.43	0.94	0.60
Mirabegron Monotherapy Versus Solifenacin 5 mg			
Intervention	MIR 25 mg	MIR 50 mg	
N studies	1	1	–
ARD (95% CI) MIR versus SOL[a]	14% (–45% to 18%)	–1% (–8% to 5%)[b]	
P value	0.39	0.71	
Mirabegron Combination Therapy Versus Solifenacin 5 mg			
Intervention	MIR 25 mg + SOL 5 mg	MIR 50 mg + SOL 5 mg	
N studies	1	1	–
ARD (95% CI) MIR+SOL versus SOL	28% (8% to 47%)	28% (7% to 48%)	
P value	NR	NR	
Intervention	MIR 25 mg + SOL 10 mg	MIR 50 mg + SOL 10 mg	
N studies	1	1	–
ARD (95% CI) MIR+SOL versus SOL	19% (–4% to 42%)	15% (–10% to 40%)	
P value	NR	NR	

ARD = absolute risk difference; CI = confidence interval; MIR = mirabegron; NR = not reported; SOL = solifenacin; TOL = tolterodine.
[a] Calculated by CADTH using Review Manager, fixed effects model; positive numbers indicate that more patients in the MIR group achieved continence than in the TOL or SOL groups.
[b] Analyses excluded SYMPHONY trial due to heterogeneity.

3.6.4 Micturition Frequency

At baseline, the mean number of micturitions per 24 hours ranged from 10.3 to 12.6 and was similar within and between studies (Figure 5 and Table 15, Table 16, and Table 17 in Appendix 3). All treatment groups reported a reduction in the mean number of micturitions per 24 hours at the end of treatment (placebo 0.8 to 2.4, mirabegron 1.3 to 2.6, tolterodine 1.4 to 2.0, solifenacin 2.4 to 3.2, mirabegron plus solifenacin 2.6 to 3.5).

FIGURE 5: MICTURITION FREQUENCY



MIR = mirabegron; SOL = solifenacin; TOL = tolterodine.

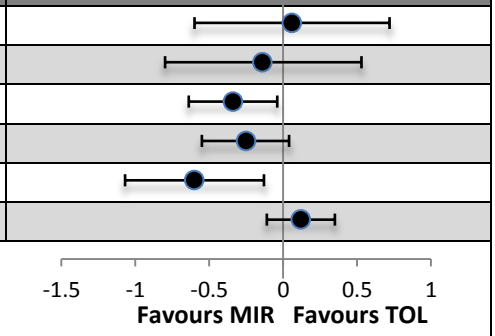
The mean change from baseline in micturition frequency was statistically significant, favouring mirabegron versus placebo in SCORPIO, 048, 090, DRAGON, ARIES and CAPRICORN, except in the mirabegron 25 mg dosage group in DRAGON (Table 15 in Appendix 3). Mean changes from baseline were statistically significant, favouring mirabegron 50 mg compared with tolterodine in SCORPIO and study 090 only (Figure 6). The BEYOND trial, which enrolled patients who were dissatisfied with prior anticholinergic drug treatment due to lack of efficacy, failed to demonstrate the non-inferiority of mirabegron 50 mg compared with solifenacin 5 mg for the primary outcome of micturition frequency (non-inferiority margin 0.2; MD PPS 0.18; 95% confidence interval [CI], –0.06 to 0.42) (Table 16 in Appendix 3).

In the SYMPHONY trial, no statistically significant differences in micturition frequency were detected between mirabegron 25 mg or 50 mg and solifenacin 5 mg or placebo. However, combination therapy (excepting the lowest combination dose of mirabegron 25 mg plus solifenacin 5 mg) showed statistically significant differences from solifenacin 5 mg (Figure 7) or placebo (Table 17 in Appendix 3). Patients who received mirabegron 50 mg plus solifenacin 5 mg reported an average of 0.8 or 0.9 fewer micturitions per day, compared with those treated with solifenacin 5 mg or placebo, respectively.

Subgroup data for patients with and without previous anticholinergic therapy for OAB were available for the SCORPIO study (Table 26 in Appendix 3). The difference in micturition frequency between mirabegron versus tolterodine (calculated by CADTH) was statistically significantly different (favouring mirabegron) for the previous OAB treatment subgroup (MD –0.48; 95% CI, –0.91 to –0.05, *P* = 0.03), but not the subgroup with no previous OAB therapy (MD –0.23; 95% CI, –0.66 to 0.20). As stated above, the BEYOND study exclusively enrolled patients that were unresponsive to prior anticholinergic therapy and this trial failed to demonstrate non-inferiority of mirabegron 50 mg compared with solifenacin 5 mg.

FIGURE 6: MICTURITIONS PER 24 HOURS — MIRABEGRON VERSUS TOLTERODINE

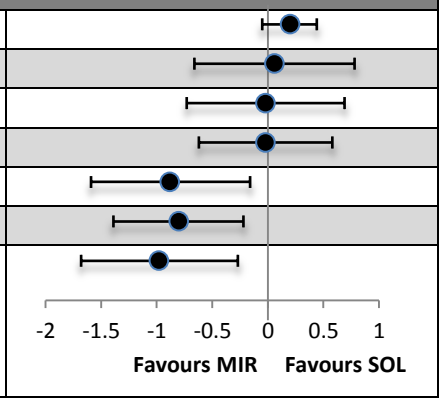
Duration	MIR Dose	Study	Adjusted MD (95% CI)[ab]
12 weeks	25 mg	DRAGON	0.06 (–0.60, 0.72)
	50 mg	DRAGON	–0.14 (–0.80, 0.53)
	50 mg	SCORPIO	–0.34 (–0.64 to –0.04)
	50 mg	study 048	–0.25 (–0.55 to 0.04)
	50 mg	study 090	–0.60 (–1.07 to –0.13)
52 weeks	50 mg	TAURUS	0.12 (–0.11 to 0.35)



CI = confidence interval; MD = mean difference; MIR = mirabegron; TOL = tolterodine.
[a] SCORPIO and TAURUS data calculated by CADTH.
[b] Negative values indicate the MIR group had a greater reduction in micturitions than the TOL group.

FIGURE 7: MICTURITIONS PER 24 HOURS — MIRABEGRON MONOTHERAPY AND MIRABEGRON PLUS SOLIFENACIN COMBINATION THERAPY, VERSUS SOLIFENACIN 5 MG

Duration	Dose	Study	Adjusted MD (95% CI)[a]	
12 wks	MIR 50 mg[b]	BEYOND	0.20 (–0.05 to 0.44)	
	MIR 25 mg[c]	SYMPHONY	0.06 (–0.66 to 0.78)	
	MIR 50 mg[c]	SYMPHONY	–0.02 (–0.73 to 0.69)	
	MIR 25 mg + SOL 5 mg	SYMPHONY	–0.02 (–0.62 to 0.58)	
	MIR 25 mg + SOL 10 mg	SYMPHONY	–0.88 (–1.59 to –0.16)	
	MIR 50 mg + SOL 5 mg	SYMPHONY	–0.80 (–1.39 to –0.22)	
	MIR 50 mg + SOL 10 mg	SYMPHONY	–0.98 (–1.68 to –0.27)	



CI = confidence interval; MD = mean difference; MIR = mirabegron; SOL = solifenacin; wks = weeks.
[a] Negative values indicate the MIR group had a greater reduction in the number of micturitions than SOL group.
[b] Full analysis set population.
[c] Calculated by CADTH.

3.6.5 Urgency

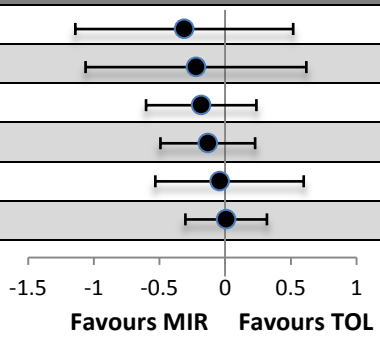
In SCORPIO, DRAGON, TAURUS, ARIES, CAPRICORN, SYMPHONY, and BEYOND, urgency was defined based on the PPIUS instrument that recorded the number of severe urgency or urgency incontinence (grade 3 or 4) episodes. In studies 048 and 090, it was unclear how urgency, a subjective outcome, was defined and measured.

At baseline, patients in the SCORPIO, study 048, study 090, DRAGON, TAURUS, ARIES, and CAPRICORN studies reported on average 4.1 to 5.8 urgency episodes per 24 hours. In the solifenacin-controlled studies (BEYOND and SYMPHONY), patients reported on average 5.3 to 7.7 urgency episodes per 24 hours. At the end of treatment, all groups reported a reduction in the mean number of urgency episodes per 24 hours (placebo 0.8 to 3.5, mirabegron 1.6 to 4.6, tolterodine 1.5 to 2.4, solifenacin 2.7 to 4.8, mirabegron plus solifenacin 3.2 to 4.1) (Table 16, Table 17, and Table 18 in Appendix 3). The differences between mirabegron versus placebo were statistically significant, favouring mirabegron 25 mg in DRAGON, and mirabegron 50 mg in SCORPIO, study 048, ARIES and CAPRICORN; other comparisons with placebo did not reach statistical significance (Table 18 in Appendix 3). Mean changes from baseline were not statistically significantly different between mirabegron and tolterodine in any studies (Figure 8).

In SYMPHONY, comparisons between mirabegron monotherapy or mirabegron plus solifenacin and placebo were not statistically significantly different for urgency frequency (Table 17 in Appendix 3). Differences between mirabegron 50 mg and solifenacin 5 mg were not statistically significant in either BEYOND or SYMPHONY. In SYMPHONY, combination therapy with mirabegron plus solifenacin showed statistically significant reductions in urgency episodes compared with solifenacin 5 mg monotherapy (Figure 9).

FIGURE 8: URGENCY EPISODES PER 24 HOURS — MIRABEGRON VERSUS TOLTERODINE

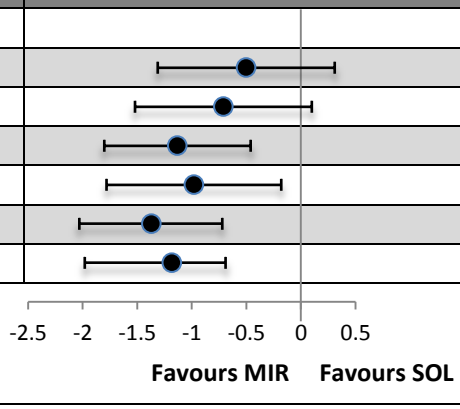
Duration	MIR Dose	Study	Adjusted MD (95% CI) [ab]	
12 weeks	25 mg	DRAGON	–0.31 (–1.14 to 0.52)	
	50 mg	DRAGON	–0.22 (–1.06 to 0.62)	
	50 mg	SCORPIO	–0.18 (–0.60 to 0.24)	
	50 mg	Study 048	–0.13 (–0.49 to 0.23)	
	50 mg	Study 090	–0.04 (–0.53 to 0.60)	
52 weeks	50 mg	TAURUS	0.01 (–0.30 to 0.32)	



CI = confidence interval; MD = mean difference; MIR = mirabegron; TOL = tolterodine.
[a] SCORPIO and TAURUS data calculated by CADTH.
[b] Negative values indicate the MIR group had a greater reduction in urgency episodes than the TOL group.

FIGURE 9: URGENCY EPISODES PER 24 HOURS — MIRABEGRON VERSUS SOLIFENACIN 5 MG

Duration	Dose	Study	Adjusted MD (95% CI)[a]	
12 weeks	MIR 50 mg	BEYOND	[redacted]	
	MIR 25 mg[b]	SYMPHONY	–0.50 (–1.31 to 0.31)	
	MIR 50 mg[b]	SYMPHONY	–0.71 (–1.52 to 0.10)	
	MIR 25 mg + SOL 5 mg	SYMPHONY	–1.13 (–1.80 to –0.46)	
	MIR 25 mg + SOL 10 mg	SYMPHONY	–0.98 (–1.78 to –0.18)	
	MIR 50 mg + SOL 5 mg	SYMPHONY	–1.37 (–2.03 to –0.72)	
	MIR 50 mg + SOL 10 mg	SYMPHONY	–1.18 (–1.98 to –0.69)	



CI = confidence interval; MD = mean difference; MIR = mirabegron; SOL = solifenacin.
[a] Negative values indicate the MIR group had a greater reduction in urgency episodes than the SOL group.
[b] Calculated by CADTH.

3.6.6 Nocturia

In the subgroup with nocturia at baseline, patients reported at baseline, on average, 1.8 to 2.5 nocturia events per 24 hours in the placebo groups, 1.7 to 2.3 events in the mirabegron groups, 1.7 to 2.4 events in the tolterodine groups, 2.2 to 2.5 events in the solifenacin groups, and 2.3 to 2.7 in the mirabegron plus solifenacin groups. The mean number of nocturia episodes per 24 hours decreased from baseline in all treatment groups, ranging from 0.3 to 0.7 fewer events in the placebo groups, 0.5 to 1.0, for mirabegron, 0.4 to 0.6, for tolterodine, 0.7 to 1.0, for solifenacin, and 0.8 to 1.0, for mirabegron plus solifenacin.

Comparisons between mirabegron and placebo were statistically significantly in favour of mirabegron in the SCORPIO, DRAGON, and ARIES trials, but not in the other four placebo-controlled trials (study 048, study 090, CAPRICORN, and SYMPHONY; –0.01 to –0.30 fewer nocturia events in active versus placebo

groups). The differences between mirabegron and tolterodine groups ranged from –0.18 to 0.07, and none was statistically significant (Table 19 in Appendix 3).

The differences between mirabegron monotherapy or combination therapy and solifenacin 5 mg groups ranged from –0.35 to 0, with only one treatment comparison reaching statistical significance (mirabegron 50 mg plus solifenacin 5 mg: MD –0.35; 95% CI, –0.63 to –0.06; P = 0.017) (Table 16 and Table 17 in Appendix 3).

3.6.7 Health-Related Quality of Life

The SCORPIO, TAURUS, ARIES, CAPRICORN, SYMPHONY, and BEYOND studies measured HRQoL using the OAB-q, a validated instrument that includes a symptom bother scale and an overall HRQoL score. All domains are scored from 0 to 100 with an MCID of 10. In the trials, both the symptom bother and overall HRQoL scores improved for all treatment groups, and the differences exceeded the MCID (mean change from baseline to end of follow-up: placebo 10.7 to 25.5, mirabegron 10.7 to 28.9, tolterodine 11.4 to 18.4, solifenacin 21.6 to 30.8, mirabegron plus solifenacin 22.7 to 33.6). However, the between-group differences were less than 10, including the comparisons between the active treatments and placebo (Table 20, Table 21, and Table 22 in Appendix 3).

The PPBC, a six-point Likert scale, was reported in SCORPIO, TAURUS, ARIES, CAPRICORN, SYMPHONY, and BEYOND; higher scores reflect worse symptoms. At the end of treatment, the mean score decreased 0.5 to 1.8 points across the treatment groups, indicating the symptoms of OAB improved. The difference between mirabegron and placebo ranged from –0.4 to 0.1 points (statistically significant in SCORPIO and ARIES), and between mirabegron and other active therapies from –0.2 to 0.14 (statistically significant in SCORPIO and BEYOND). Three of the four combination-therapy regimens were associated with statistically significant differences compared with solifenacin 5 mg (MD ranged from –0.5 to –0.2). However, the MCID for the PPBC scale is unknown (Table 21, Table 22 and Table 23, Appendix 3).

The KHQ, a validated OAB-specific HRQoL instrument, was used in studies 048 and 090. Each domain on the KHQ is scored from 0 (best) to 100 (worst), with a MCID of 5 reported for domains.[40,41] Data for the general health perception and incontinence impact domains were abstracted from the trials as being the most relevant (Table 24 in Appendix 3). In study 090, neither domain showed a statistically significant difference between mirabegron and placebo or tolterodine. In study 048, the incontinence impact domain was statistically significantly improved for mirabegron compared with placebo, but not with tolterodine, and there were no statistically significant differences observed for the general health perception domain. There were no statistically significant differences between mirabegron and tolterodine for the other domains (data not included in Table 17; i.e., role limitations, physical limitations, social limitations, personal relationships, emotions, sleep/energy, and incontinence severity measures in study 090 and study 048).

The DRAGON study evaluated OAB symptom impact and HRQoL using the International Consultation on Incontinence Questionnaire–OAB (ICIQ-OAB) and ICIQ-OAB-quality of life (ICIQ-OAB-qol) instruments. There were no statistically significant differences for mirabegron versus placebo on the ICIQ-OAB-qol. The symptom impact scale showed statistically significant differences favouring mirabegron 25 mg and 50 mg versus placebo. No statistically significant differences were detected between mirabegron and tolterodine (Table 25 in Appendix 3).

3.7 Harms

Only those harms identified in the review protocol are reported (2.2.1, Protocol). See APPENDIX 3: DETAILED OUTCOME DATA for detailed harms data.

3.7.1 Adverse Events

The incidence of adverse events was similar within trials but varied between studies (Table 9). In the SCORPIO, DRAGON, 090, ARIES, CAPRICORN, SYMPHONY, and BEYOND studies, the incidence of adverse events was 50% or less, but in study 048, the incidence ranged from 74% to 81% across treatment groups. Based on the 12-week trials, the pooled relative risk (RR) of experiencing an adverse event for mirabegron 50 mg was 0.98; 95% CI, 0.92 to 1.03 (I^2 = 0%, seven trials) versus placebo; 0.90; 95% CI, 0.84 to 0.96 (I^2 = 0 %, four trials) versus tolterodine; and 1.00; 95% CI, 0.88 to 1.13 (I^2 = 33%, two trials) versus solifenacin 5 mg. The RR of experiencing an adverse event for mirabegron 25 mg was 1.01; 95% CI 0.90 to 1.13 (I^2 = 0%, three trials) versus placebo; 0.91; 95% CI, 0.69 to 1.20 (one trial) versus tolterodine; and 1.10; 95% CI, 0.83 to 1.46 (one trial) versus solifenacin 5 mg. In the 52-week TAURUS study, the incidence of adverse events was 60% and 63% in the mirabegron 50 mg and tolterodine groups, respectively; RR 0.95; 95% CI, 0.88 to 1.03 (Table 2).

As outlined in the protocol, cardiovascular and anticholinergic adverse events were of interest for this review. Hypertension, arrhythmia, and tachycardia were reported in the trials; however, the incidence was generally similar between groups (Table 9). Dry mouth was reported less frequently among those who received mirabegron (from less than 1% to 5%) or placebo (2% to 5%) compared with tolterodine (8% to 14%), solifenacin (6% to 30%) or mirabegron plus solifenacin combination therapy (9% to 20%). Based on pooled data from the 12-week trials, the RR of experiencing dry mouth for mirabegron 50 mg was 0.32; 95% CI 0.23 to 0.45 (I^2 = 62 %, 4 trials), versus tolterodine; and 0.52; 95% CI 0.35 to 0.78 (I^2 = 0%, 2 trials), versus solifenacin 5 mg (Table 2). The incidence of other anticholinergic adverse events was similar between groups (Table 9).

In the 52 week TAURUS study the incidence of dry mouth was 3% and 9% in the mirabegron 50 mg and tolterodine groups respectively; RR 0.33; 95% CI, 0.21 to 0.52. The incidence of other anticholinergic and cardiovascular adverse events was similar between treatments (Table 9).

3.7.2 Serious Adverse Events

The incidence of serious adverse events (SAEs) ranged from 0% to 3% across all treatment groups in the 12-week studies (Table 9); the pooled RR of SAE for mirabegron 50 mg was 0.98; 95% CI, 0.64 to 1.51 (I^2 = 0%, seven trials) versus placebo; 1.02; 95% CI, 0.57 to 1.82 (I^2 = 0%, four trials) versus tolterodine; and 1.30; 95% CI, 0.65 to 2.60 (I^2 = 50%, two trials) versus solifenacin 5 mg. The RR of SAE for mirabegron 25 mg was 0.62; 95% CI, 0.26 to 1.48 (I^2 = 0%, two trials) versus placebo; 0.50; 95% CI, 0.03 to 7.94 (one trial) versus tolterodine; and was not estimable versus solifenacin 5 mg. The percentage of patients experiencing an SAE in the 52-week TAURUS study was 5% in both the mirabegron 50 mg and tolterodine treatment groups; RR 0.95; 95% CI, 0.63 to 1.44 (Table 2). Few SAEs were reported in two or more patients per treatment group, and those reported are described in Table 27 in Appendix 3.

3.7.3 Withdrawals Due to Adverse Events

Among the 12-week trials, 0% to 4% of patients in the placebo group, 1% to 5% in the mirabegron groups, 1% to 4 % in the tolterodine groups, 0% to 3% in the solifenacin groups, and less than 1% to 3% in the mirabegron plus solifenacin groups experienced an adverse event that led to permanent discontinuation of the study drug (Table 9). The pooled RR of withdrawal due to adverse events (WDAEs) was 1.28; 95% CI, 0.91 to 1.78 (I^2 = 0%, seven trials) for mirabegron 50 mg versus placebo; 1.03; 95% CI,

0.69 to 1.53 (I^2 = 0%, four trials) versus tolterodine; 0.89; 95% CI, 0.45 to 1.76 (I^2 = 41%, two trials) versus solifenacin 5 mg. The RR of WDAE for mirabegron 25 mg was 1.60; 95% CI, 0.82 to 3.13 (I^2 = 0%, three trials) versus placebo; 4.53; 95% CI, 0.58 to 35.14 (1 trial) versus tolterodine, and 2.03; 95% CI, 0.13 to 31.96 (one trial) versus solifenacin 5 mg (Table 2). WDAE in the 52-week TAURUS study was 6% in both the mirabegron 50 mg and tolterodine treatment groups; RR 1.04; 95% CI, 0.70 to 1.55. The specific adverse events that led to withdrawal in two or more patients per treatment group are described in Table 27 in Appendix 3.

3.7.4 Mortality

A total of eight deaths were reported in all the studies: 2 of 2,375 patients who received placebo, 3 of 4,743 who received mirabegron, and 3 of 2,138 who received tolterodine (Table 27 in Appendix 3). No deaths were reported among the 1,247 patients who received solifenacin or the 757 patients who received mirabegron plus solifenacin.

TABLE 9A: HARMS[a]

Study, Follow-up	SCORPIO 12 Weeks			Study 048 12 Weeks			Study 090 12 Weeks			DRAGON 12 Weeks			TAURUS 52 Weeks		
AEs	**PL**	**MIR 50 mg**	**TOL 4 mg**	**PL**	**MIR 50 mg**	**TOL 4 mg**	**PL**	**MIR 50 mg**	**TOL 4 mg**	**PL**	**MIR 25 mg**	**MIR 50 mg**	**TOL 4 mg**	**MIR 50 mg**	**TOL 4 mg**
N	**494**	**493**	**495**	**379**	**379**	**375**	**366**	**366**	**371**	**169**	**169**	**169**	**85**	**812**	**812**
Subjects with ≥ 1 AEs, N (%)	214 (43)	211 (43)	231 (47)	292 (77)	281 (74)	305 (81)	124 (34)	105 (29)	128 (35)	73 (43)	74 (44)	74 (44)	41 (48)	485 (60)	508 (63)
SAEs															
Subjects with ≥ 1 SAE, N (%)	8 (2)	14 (3)	11 (2)	4 (1)	3 (< 1)	4 (1)	7 (2)	5 (1)	6 (2)	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)	42 (5)	44 (5)
WDAEs[b]															
WDAEs, N (%)	13 (3)	24 (5)	22 (4)	8 (2)	12 (3)	12 (3)	8 (2)	9 (3)	11 (3)	5 (3)	9 (5)	4 (2)	1 (1)	48 (6)	46 (6)
Deaths															
Number of deaths, N (%)	0	0	1 (< 1)	0	0	0	1 (< 1)	0	0	0	0	0	0	3 (< 1)	2 (< 1)
Notable Harms — CV AE															
MACE	0	0	1 (< 1)											6 (0.7)	4 (0.5)
Hypertension	38 (8)	29 (6)	40 (8)	1 (< 1)	3 (< 1)	3 (< 1)	1 (< 1)	2 (< 1)	4 (1)	0	3 (2)	3 (2)	0	75 (9)	78 (10)
Arrhythmia	5 (1)	11 (2)	16 (3)	8 (2)	5 (1)	10 (3)	20 (6)	11 (3)	8 (2)					32 (4)	49 (6)
QTc prolongation	0	0	2 (< 1)				4 (1)	2 (< 1)	4 (1)					3 (< 1)	3 (< 1)
Tachycardia	16 (3)	15 (3)	16 (3)	0	1 (< 1)	0				0	3 (2)	4 (2)	1 (1)	8 (1)	25 (3)
Anticholinergic AE															
Dry mouth	13 (3)	14 (3)	50 (10)	11 (3)	10 (3)	53 (14)	18 (5)	18 (5)	30 (8)	3 (2)	5 (3)	3 (2)	3 (4)	23 (3)	70 (9)
Constipation	7 (1)	8 (2)	10 (2)	12 (3)	13 (3)	14 (4)	8 (2)	8 (2)	9 (2)	2 (1)	2 (1)	6 (4)	1 (1)	23 (3)	22 (3)
Urinary retention	3 (< 1)	1 (< 1)	3 (< 1)	6 (2)	7 (2)	4 (1)	2 (< 1)	1 (< 1)	0	0	0	0	0	1 (< 1)	3 (< 1)
Acute urinary retention	1 (< 1)	1 (< 1)	3 (< 1)											0	1 (< 1)
Dizziness	5 (1)	6 (1)	8 (2)	1 (< 1)	3 (1)	2 (1)	5 (1)	5 (1)	8 (2)	1 (< 1)	1 (< 1)	6 (4)	0	22 (3)	21 (3)
Blurred vision	2 (< 1)	1 (< 1)	0	1 (< 1)	0	4 (1)	2 (< 1)	0	3 (< 1)	1 (< 1)	2 (1)	1 (< 1)	1 (1)	4 (< 1)	6 (< 1)

AE = adverse event; CV = cardiovascular; MACE = major adverse cardiovascular event; MIR = mirabegron; PL = placebo; SAE = serious adverse event; TOL = tolterodine; WDAE = withdrawal due to adverse event.

[a] Outcomes identified as important to the review (review protocol is given in Section 2.2); cells left blank indicate that data were not reported.

[b] WDAE in this table indicated the treatment-emergent AEs leading to permanent discontinuation of study drug. There may be a small difference between the values of the total number of patients and the number of events reported in this table and those reported in the patient disposition table.

Source: Clinical Study Report,[27–30,35] Chapple et al. 2013.[18]

TABLE 9B: HARMS[a] (CONTINUED)

Study, Follow-up	ARIES 12 Weeks				CAPRICORN 12 Weeks				SYMPHONY 12 Weeks				BEYOND 12 Weeks			
AEs	**PL**	**MIR 50 mg**	**PL**	**MIR 25 mg**	**MIR 50 mg**	**PL**	**MIR 25 mg**	**MIR 50 mg**	**SOL 5 mg**	**SOL 10 mg**	**MIR 25 mg + SOL 5 mg**	**MIR 25 mg + SOL 10 mg**	**MIR 50 mg + SOL 5 mg**	**MIR 50 mg + SOL 10 mg**	**MIR 50 mg**	**SOL 5 mg**
N	**453**	**442**	**433**	**432**	**440**	**81**	**77**	**78**	**156**	**78**	**144**	**81**	**153**	**81**	[redacted]	[redacted]
Subjects with ≥ 1 AEs, N (%)	227 (50)	228 (52)	217 (50)	210 (49)	208 (47)	32 (40)	38 (49)	41 (53)	70 (45)	47 (60)	71 (49)	47 (58)	67 (44)	48 (59)	274 (29)	282 (30)
SAEs																
Subjects with ≥ 1 SAE, N(%)	9 (2)	11 (3)	12 (3)	7 (2)	4 (1)	0	0	2 (3)	0	1 (1)	2 (1)	1 (1)	2 (1)	1 (1)	14 (2)	13 (1)
WDAEs[b]																
WDAEs, N (%)	17 (4)	18 (4)	16 (4)	17 (4)	12 (3)	0	1 (1)	2 (3)	1 (1)	2 (3)	4 (3)	1 (1)	1 (< 1)	3 (4)	13 (1)	17 (2)
Deaths																
Number of deaths, N (%)	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Notable Harms — CV AE																
MACE	2 (< 1)	0	2 (< 1)	0	0											
Hypertension	32 (7)	33 (8)	37 (9)	52 (12)	49 (11)	7 (9)	9 (12)	11 (14)	18 (12)	5 (6)	11 (8)	7 (9)	9 (6)	11 (14)	[redacted]	[redacted]
Arrhythmia	4 (1)	9 (2)	11 (3)	13 (3)	13 (3)	0	0	1 (1)	0	0	2 (1)	0	0	0	[redacted]	[redacted]
QTc prolongation	0	0	0	0	0	1 (1)	0	0	0	2 (3)	1 (< 1)	0	1 (< 1)	4 (5)	[redacted]	[redacted]
Tachycardia	2 (< 1)	6 (1)	4 (1)	7 (2)	7 (2)	1 (1)	3 (4)	2 (3)	6 (4)	2 (3)	5 (4)	4 (5)	3 (2)	3 (4)	[redacted]	[redacted]
Anticholinergic AE																
Dry mouth	7 (2)	2 (< 1)	9 (2)	8 (2)	7 (2)	3 (4)	2 (3)	4 (5)	18 (12)	23 (30)	21 (15)	16 (20)	20 (13)	14 (17)	29 (3)	54 (6)
Constipation	8 (2)	6 (1)				0	0	3 (4)	3 (2)	4 (5)	4 (3)	6 (7)	2 (1)	8 (10)	21 (2)	23 (3)
Urinary retention	3 (1)	0	1 (< 1)	0	0	0	0	0	0	0	0	0	0	0	[redacted]	[redacted]
Acute urinary retention	2 (< 1)	0	0	0	0										[redacted]	[redacted]

Study, Follow-up	ARIES 12 Weeks				CAPRICORN 12 Weeks				SYMPHONY 12 Weeks				BEYOND 12 Weeks			
AEs	**PL**	**MIR 50 mg**	**PL**	**MIR 25 mg**	**MIR 50 mg**	**PL**	**MIR 25 mg**	**MIR 50 mg**	**SOL 5 mg**	**SOL 10 mg**	**MIR 25 mg + SOL 5 mg**	**MIR 25 mg + SOL 10 mg**	**MIR 50 mg + SOL 5 mg**	**MIR 50 mg + SOL 10 mg**	**MIR 50 mg**	**SOL 5 mg**
Dizziness	5 (1)	3 (< 1)	2 (< 1)	10 (2)	4 (1)	0	1 (1)	0	1 (1)	3 (4)	1 (< 1)	0	0	0	[redacted]	[redacted]
Blurred vision	1 (< 1)	0	0	0	1 (< 1)	0	0	1 (1)	0	1 (1)	2 (1)	2 (3)	2 (1)	1 (1)	[redacted]	[redacted]

AE = adverse event; CV = cardiovascular; MACE = major adverse cardiovascular event; MIR = mirabegron; PL = placebo; SAE = serious adverse event; SOL = solifenacin; TOL = tolterodine; WDAE = withdrawal due to adverse event.

[a] Outcomes identified as important to the review (review protocol is given in Section 2.2); cells left blank indicate that data were not reported.

[b] WDAE in this table indicated the treatment-emergent AEs leading to permanent discontinuation of study drug. There may be a small difference between the values of the total number of patients and the number of events reported in this table and those reported in the patient disposition table.

Source: Clinical Study Report,[32–34] Nitti et al. 2012,[20] Herschorn et al. 2013,[21] Abrams et al. 2014.[22]

4. DISCUSSION

4.1 Summary of Available Evidence

Nine manufacturer-sponsored double-blind RCTs were included in the review. Six trials (SCORPIO, 048, 090, DRAGON, ARIES, and CAPRICORN) were of short duration (12 weeks) and were designed to assess efficacy of mirabegron versus placebo, despite the inclusion of an active comparator (tolterodine) group in four trials. Two additional 12-week trials included solifenacin and were designed to assess the non-inferiority of mirabegron versus solifenacin (BEYOND) or efficacy of mirabegron plus solifenacin compared with solifenacin or placebo. All trials included a mirabegron 50 mg treatment group; three trials (DRAGON, CAPRICORN, and SYMPHONY) included a mirabegron 25 mg group. The primary outcome in seven studies was the change from baseline in number of micturitions per 24 hours at week 12; SCORPIO, ARIES, and CAPRICORN included a co-primary end point: change from baseline in number of incontinence episodes per 24 hours at week 12. The primary outcome in SYMPHONY was the change from baseline in the volume voided per micturition. Secondary outcomes of the 12-week trials included changes in episodes of urgency incontinence, urgency, and nocturia, in addition to HRQoL and harms. One trial (TAURUS) was 52 weeks in duration and was designed to assess the safety of mirabegron compared with tolterodine; however, no formal statistical analyses of between-treatment differences were planned.

It should be noted that, although placebo-controlled trials were included in this review, comparisons of mirabegron with other active comparators are of most interest.

The available efficacy trials were limited by their short duration (12 weeks). In addition, the internal validity of study 090 and TAURUS are limited by premature study withdrawal of approximately 18% and 23%, respectively, in combination with use of last observation carried forward, which may obscure important treatment differences.

4.2 Interpretation of Results

4.2.1 Efficacy

All included studies reported reductions in the frequency of OAB symptoms (incontinence, urgency incontinence, micturition frequency, urgency, and nocturia) from baseline to the end of treatment (12 weeks or 52 weeks) for the placebo, mirabegron, tolterodine, solifenacin, or mirabegron plus solifenacin groups. Interpretation of within- and between-group differences is challenging because there is no known change value that has been judged to be clinically important. Furthermore, a strong placebo effect is common among studies for OAB,[42] which further makes interpretation of the importance of findings difficult. In addition, analysis of secondary outcomes had a possible inflated type I error due to multiplicity, leading to an overstatement of the treatment effect if the inference is based on a statistical significance level of $P < 0.05$.

The mean change from baseline in OAB symptom outcomes for mirabegron versus tolterodine or solifenacin monotherapy was not statistically significantly different, except for the primary outcome of micturition frequency in study 090 and SCORPIO, which favoured mirabegron, and incontinence episodes in TAURUS, which favoured tolterodine. For mirabegron versus tolterodine (study 090 and SCORPIO), the between-treatment difference in micturitions was less than one micturition per 24 hours in patients with a baseline micturition frequency of approximately 11 or 12 per 24 hours. The clinical expert consulted for this CDR review did not consider the magnitude of between-treatment differences to be clinically important. Patient-group input indicated that improvements in urinary incontinence and

urgency are of primary importance to persons with OAB. The reduction in urgency episodes appeared similar between mirabegron and tolterodine or solifenacin monotherapy groups. One trial (TAURUS) resulted in a statistically significant difference in incontinence episodes that favoured tolterodine compared with mirabegron. However, the between-treatment difference was small (0.25 incontinence episode per 24 hours in patients with a baseline incontinency frequency of approximately 2.5 per 24 hours), and the clinical expert consulted on this review did not consider this difference to be clinically important.

There is some evidence to suggest that combination therapy (mirabegron plus solifenacin) may have improved efficacy compared with solifenacin monotherapy; however, data were limited to one trial with small sample size and lack of control for multiple testing. In the SYMPHONY trial, combination therapy showed statistically significant differences in micturition frequency and urgency episodes versus solifenacin 5 mg. The between-treatment difference for combination therapy (mirabegron 25 mg or 50 mg plus solifenacin 5 mg or 10 mg) versus solifenacin 5 mg was less than one micturition per 24 hours (baseline 11 micturitions per 24 hours). Between-treatment differences in urgency were 1.0 to 1.4 fewer urgency episodes per 24 hours for patients with a baseline frequency of six to seven episodes per day. The clinical importance of these differences is unclear.

Patient input further indicated that patients wish to stop using incontinence pads (APPENDIX 2: PATIENT INPUT SUMMARY). The proportion of patients achieving continence did not differ between mirabegron and tolterodine or between mirabegron and solifenacin groups; mirabegron plus solifenacin combinations did not consistently show superiority compared with solifenacin monotherapy. However, it should be noted that this outcome, as with all incontinence-related outcomes, was based on the incontinent subgroups (ranging from approximately 22% to 70% of trial participants). Incontinent subgroups were defined based on short-term diary entries. Patients not included in the incontinent subgroups may well have experienced incontinence before or during the trial; however, incontinence outcomes for these patients are not captured in the trials.

HRQoL was measured using validated OAB-specific instruments. Similar to the findings for OAB symptom outcomes, all treatments resulted in increases in OAB-related HRQoL or reductions in OAB symptom scores from baseline to end of treatment. However, the differences between groups were small, and the clinical importance was unclear. For the OAB-q the difference between mirabegron and placebo, tolterodine, or solifenacin did not exceed the MCID, and for the KHQ differences between mirabegron and tolterodine were either not statistically significant or did not exceed the MCID.

The manufacturer is requesting a listing for mirabegron “in a manner similar to other currently listed second-line OAB treatments.” However, there are a number of considerations in assessing the extent to which the available evidence supports such a request. Only one study (BEYOND) was designed to test the non-inferiority of mirabegron to another second-line OAB treatment. The BEYOND study, which enrolled patients who were non-responders to anticholinergic OAB drugs, failed to demonstrate the non-inferiority of mirabegron versus solifenacin for the primary outcome of micturition frequency at the preset margin of 0.2 micturitions per 24 hours. In addition, the lack of a placebo group in BEYOND means that the efficacy of either mirabegron or solifenacin in this patient population cannot be determined. Thus, there is no evidence to support the use of mirabegron as an efficacious alternative to anticholinergic therapy in patients with an inadequate response to anticholinergic drugs.

The five trials that included a tolterodine comparator group enrolled a mixture of treatment-experienced and treatment-naive patients; however, it is unclear whether treatment-experienced patients were non-responders to anticholinergic OAB drugs. The five trials were not designed as non-inferiority studies and, thus, despite the lack of statistically significant between-treatment differences for many outcomes, a conclusion of non-inferiority cannot be made. However, the magnitude of the between-treatment differences for OAB symptoms (even at the most extreme ends of the 95% CIs) are of uncertain clinical importance.

In the indirect network meta-analysis, no significant differences were observed between mirabegron 50 mg and the other OAB treatments except for solifenacin 10 mg daily. In fact, solifenacin 10 mg was more effective than mirabegron 50 mg daily in reducing the number of micturitions and urgency incontinence episodes per 24 hours (APPENDIX 7: CRITICAL APPRAISAL OF INDIRECT TREATMENT COMPARISON). The findings from the network meta-analysis support CDR's findings that, in a general OAB population, mirabegron appears relatively similar to tolterodine but may be inferior to solifenacin.

Finally, data on the efficacy of the 25 mg mirabegron dose were limited to three trials. Although two of these studies included an active control group, neither was powered to detect differences between active treatments.

4.2.2 Harms

Overall, the incidence of AE, SAE, and WDAE were similar between placebo, mirabegron, tolterodine and solifenacin groups in the 12-week trials, and between mirabegron and tolterodine in the 52-week trial. Mirabegron plus solifenacin was not associated with substantially higher incidence of AE, SAE, or WDAE compared with solifenacin alone. These trials, however, were not powered to detect rare adverse events (AEs), and additional long-term safety data are needed to identify potential risks associated with this new therapeutic class of medications.

Of the notable harms specified in the protocol, the incidence of dry mouth was higher in the tolterodine and solifenacin groups than in the mirabegron or placebo groups, but the incidence of other anticholinergic AEs were similar between treatments. Mirabegron plus solifenacin combination therapy was not associated with statistically significantly increased risk of dry mouth compared with solifenacin alone. The clinical expert consulted for this CDR review considered dry mouth to be of considerable clinical importance, as this AE is often related to treatment adherence. Of note, the network meta-analysis also showed that the incidence of dry mouth was statistically significantly higher for all anticholinergic OAB drugs compared with mirabegron 50 mg daily (Appendix VIII). In addition, darifenacin 15 mg, fesoterodine 8 mg, solifenacin 5 mg and 10 mg, and trospium chloride 60 mg were associated with a statistically significantly higher incidence of constipation versus mirabegron 50 mg. Thus, mirabegron may offer an alternative to patients who cannot tolerate anticholinergic medications due to dry mouth or who have contraindications to anticholinergic medications. No increased risk of cardiovascular AEs was observed for mirabegron versus comparators in the trials.

5. CONCLUSIONS

Nine double-blind RCTs met the inclusion criteria for the systematic review. Non-inferiority was not met for mirabegron versus solifenacin in the trial that enrolled patients who had not responded to previous anticholinergic drug treatment. None of the tolterodine-containing trials, which enrolled a mixture of treatment-naive and treatment-experienced patients, were designed to test the non-inferiority of mirabegron versus tolterodine; however, estimates of treatment effect with regard to reductions in urgency, incontinence, or micturition appeared relatively similar between mirabegron and tolterodine.

The incidence of SAEs and premature discontinuation was similar between treatment groups. Dry mouth was reported more frequently by patients who received solifenacin or tolterodine than by those who received mirabegron. However, there were no notable differences in the frequency of other anticholinergic AEs.

APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 23, 2014
Alerts:	Weekly search updates until October 15, 2014
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY		
1	(mirabegron* or Myrbetriq* or Betanis* or Betmiga* or YM178 or YM–178 or SC211912 or SC–21192).ti,ot,ab,sh,rn,hw,nm.	409
2	(223673-61-8 or 9238324–05-4).rn,nm.	196
3	or/1–2	409
4	3 use pmez	100
5	*mirabegron/	124
6	(mirabegron* or Myrbetriq* or Betanis* or Betmiga* or YM178 or YM–178 or SC–211912 or SC211912).ti,ab.	277
7	or/5-6	283
8	7 use oemezd	193
9	conference abstract.pt.	1452799
10	8 not 9	118
11	4 or 10	218
12	remove duplicates from 11	132

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	May 29 – 30, 2014
Keywords:	Myrbetriq, mirabegron, overactive bladder, OAB
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 2: PATIENT INPUT SUMMARY

This section was summarized by CDR staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.

1. Brief Description of Patient Group(s) Supplying Input

The Canadian Continence Foundation (TCCF) is the only national non-profit organization serving the interest of people experiencing urinary incontinence (UI). TCCF is led by people with UI and by health professionals and is supported by public donations, health care professionals, and private industry. TCCF's mission is to enhance the quality of life for people experiencing UI by helping them or their caregivers to confidently access cures and treatment options. TCCF implements and encourages public and professional education, support, advocacy, and research to advance UI treatment and management.

TCCF is supported by individual and corporate donations and has received both restricted and unrestricted educational grants from Allergan, Astellas, LABORIE, Medtronic, Pfizer, and TENA, but declares no conflict with the preparation of this submission.

2. Condition and Current Therapy-Related Information

Information in this submission was obtained through an online survey available in both English and French, which received 169 responses, as well as through one-on-one telephone conversations with 17 patients. The survey and interviews were conducted in two separate periods: February to March, 2013, and May 26 to June 6, 2014.

Overactive bladder (OAB) affects approximately 15% of the adult population. Symptoms include urgency, usually with frequency, and nocturia, with or without urgency incontinence. Eighty-two per cent of survey respondents and all interviewees said they experienced urinary urgency and urgency incontinence. Unfortunately, very few people talk to their doctor about their symptoms. According to a 2008 Ontario Health Technology Advisory Committee report, UI is one of four major predictors for long-term care admissions, along with falls and fall-related injuries, dementia, and social isolation.

All patients surveyed and interviewed experienced symptoms and problems related to OAB, most of which required limiting or modifying daily activities; for example, limitations include not leaving the house as often as preferred; modifying diet and limiting beverages; planning trips to the bathroom; getting up in the night; avoiding outdoor activities, travelling, and socializing; and wearing incontinence pads. Many of these modifications lead to a sense of isolation and depression. More than 58% of patients described urinary frequency and nocturia as problems affecting them every day; 56% said their sleep was interrupted; 52% worried about smelling of urine; and 35% stated that buying UI supplies such as pads or underwear is quite costly. More than 20% of patients described activities they limit, such as going on trips, socializing, going to movies, and participating in outdoor activities such as skiing, hiking, and biking, for fear of not getting to the toilet in time. More than 20% of individuals felt that the symptoms of OAB were compromising their work productivity or affecting their ability to work. Further, 34% of patients had a decrease in sexual activity due to the fear of leakage. A number of patients described needing to plan what they drink every day around what they need to get done at home or work. Interviewed patients commented that they suffered constipation as a result of limiting fluid intake during the day. One patient described their experience as a "loss of self-esteem and sense of control over my life. My bladder controls every aspect of my day."

All surveyed patients have had some kind of therapy for OAB including medications (Detrol, Enablex, and Vesicare were most frequently mentioned as well as oxybutynin and Botox), behavioural treatment, bladder training, Kegel exercises, and surgery; however, these treatments have had no sustained benefit. Sixty-three per cent of patients surveyed had been prescribed medication for OAB, yet more than half stopped taking their medications because they were not effective at controlling their symptoms and because the side effects such as dry mouth, constipation, and blurred vision were often difficult to tolerate. Many patients noted their physicians did not prescribe new medications when available because they were not covered by public drug plans. Many patients had undergone surgery but found symptoms returned after a period of time.

Twenty-five caregivers completed the survey, and two were contacted in telephone interviews. Over half “often” or “always” need to help eliminate odours and clean up after accidents, get up often or always during the night with their family member, help their family member to the bathroom on time, and do laundry and change bedding frequently. Patients report being embarrassed that family members must adjust to their frequent and urgent need to visit the bathroom.

3. Related Information About the Drug Being Reviewed

Among the patients without experience taking mirabegron, 80.3% hope it will better control their symptoms, particularly urinary urgency and urgency incontinence, and close to 50% are hopeful there will be fewer side effects than with their current medications, especially dry mouth, constipation, and dry eyes. Several patients noted they wished to be able to sleep through the night and not wake up their spouse/partner. Another individual noted that he/she would like to stop wearing incontinence pads and having such frequent urgency incontinence.

All patients interviewed who had experience with mirabegron found that their symptoms were controlled far better than with any previous therapy. Several patients commented that they no longer had to use pads while on mirabegron, while one described having to return to using pads and suffering constipation after returning to her previous therapy. One patient mentioned that it was the first time in years that she was sleeping though the night and was disappointed that she was unable to remain on the drug after the trial ended. All patients are hoping mirabegron will be made available soon and would gladly take the medication again to experience symptom relief. Patients without drug plan coverage noted the high cost of the drug but felt they had no choice but to cover the cost, since mirabegron was providing them with symptom relief. Several patients with drug plans still had to pay a portion of the cost but said it was worth it to avoid spending money on pads.

In the words of one patient, it was “life-changing to be on this drug and have it work so well.” Another patient commented that it was the first time he/she felt symptom-free.

APPENDIX 3: DETAILED OUTCOME DATA

TABLE 10: INCONTINENCE — PLACEBO- AND TOLTERODINE-CONTROLLED TRIALS

Study	Treatment			
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**TOL 4 mg**
Mean Incontinence Episodes/24 Hours				
SCORPIO[a]	**N = 291**		**N = 293**	**N = 300**
Baseline (SE)	2.67 (0.14)		2.83 (0.17)	2.63 (0.15)
Adjusted mean change from baseline (SE)	–1.17 (0.11)		–1.57 (0.11)	–1.27 (0.11)
MD (95% CI), *P* value versus placebo	ref		–0.41 (–0.72 to –0.09), *P* = 0.003	–0.10 (–0.42 to 0.21), *P* = 0.11
MD (95% CI), *P* value versus TOL[b]	–		–0.30 (–0.61 to 0.01), *P* = NS	ref
Study 048	**N = 264**		**N = 266**	**N = 240**
Baseline (SD)	1.91 (1.76)		1.99 (2.05)	1.89 (1.83)
Adjusted mean change from baseline (SE)	−0.67 (NR)		−1.09 (NR)	−0.99 (NR)
MD (95% CI), *P* value versus placebo	ref		−0.42 (−0.67 to −0.17), *P* = NR	−0.32 (−0.57 to−0.06), *P* = NR
MD (95% CI), *P* value versus TOL	–		−0.10 (−0.36 to 0.15), *P* = NS	ref
Study 090	**N = 127**		**N = 135**	**N = 137**
Baseline (SD)	2.35 (2.70)		2.37 (2.54)	2.25 (2.78)
Adjusted mean change from baseline (SE)	–1.10 (0.18)		–1.21 (0.17)	–1.17 (0.17)
MD (95% CI), *P* value versus placebo	ref		–0.11 (–0.59 to 0.37), *P* = 0.36	–0.07 (–0.54 to 0.41), *P* = 0.51
MD (95% CI), *P* value versus TOL	–		–0.04 (–0.51 to 0.43), *P* = 0.81	ref
DRAGON	**N = 106**	**N = 99**	**N = 108**	**N = 53**
Baseline (SD)	2.45 (2.35)	2.92 (3.23)	2.41 (2.30)	2.85 (2.76)
Adjusted mean change from baseline (SE)	–0.53	–1.36	–1.15	–0.81
MD (95% CI), *P* value versus placebo	ref	–0.84 (–1.45 to –0.23), *P* = 0.007	–0.62 (–1.22 to –0.02), *P* = 0.04	–0.28 (–1.01 to 0.45) *P* = NS
MD (95% CI), *P* value versus TOL	–	–0.56 (–1.29 to 0.18), *P* = 0.14	–0.34 (–1.06 to 0.39), *P* = 0.36	ref
TAURUS			**N = 479**	**N = 488**
Baseline (SE)			2.66 (0.12)	2.42 (0.11)
Adjusted mean change from baseline (SE)			–1.01 (0.087)	–1.26 (0.086)
MD (95% CI), *P* value versus TOL[b]			0.25 (0.01 to 0.49), *P* = 0.04	ref
ARIES	**N = 325**		**N = 312**	

Study	Treatment			
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**TOL 4 mg**
Baseline (SD)	3.0 (3.1)		2.8 (2.7)	
Adjusted mean change from baseline (SE)	–1.13 (0.11)		–1.47 (0.11)	
MD (95% CI), *P* value versus placebo	ref		–0.34 (–0.66 to –0.03), *P* = 0.026	
CAPRICORN	**N = 262**	**N = 254**	**N = 257**	
Baseline (SE)	2.43 (0.15)	2.65 (0.16)	2.51 (0.15)	
Adjusted mean change from baseline (SE)	–0.96 (0.12)	–1.36 (0.12)	–1.38 (0.12)	
MD (95% CI), *P* value versus placebo	ref	–0.40 (–0.74 to –0.06), *P* = 0.005	–0.42 (–0.76 to –0.08), *P* = 0.001	

CI = confidence interval; MD = mean difference; MIR = mirabegron; NR = not reported; ref = reference group; SD = standard deviation; SE = standard error; TOL = tolterodine.
[a] SCORPIO reported data for the intention to treat population (any patient who received study drug and had a baseline outcome measure), and the results were similar to the full analysis set population.
[b] Calculated by CADTH using Review Manager; negative values indicate patients in the MIR group had fewer episodes than TOL.
Source: Clinical Study Report,[27–30,35] Chapple et al. 2013,[18] Nitti et al. 2012,[20] Herschorn et al. 2013,[21] FDA.[25]

TABLE 11: INCONTINENCE-RELATED OUTCOMES FOR BEYOND TRIAL

Outcome	BEYOND	
	MIR 50 mg	**SOL 5 mg**
Mean Incontinence Episodes/24 Hours		
Baseline (SE)		
Adjusted mean change from baseline (SE)		
MD (95% CI), *P* value, MIR versus SOL		
Mean Urgency incontinence Episodes/24 Hours		
Baseline (SE)		
Adjusted mean change from baseline (SE)		
MD (95% CI), *P* value, MIR versus SOL		
Achievement of Continence		
Final visit, n (%)	(67)	(69)
ARD (95% CI), MIR versus SOL	–1.2%	ref

ARD = absolute risk difference; CI = confidence interval; MD = mean difference; MIR = mirabegron; SE = standard error; SOL = solifenacin.
Source: Clinical Study Report.[31]

TABLE 12: INCONTINENCE-RELATED OUTCOMES FOR SYMPHONY TRIAL

Study	SYMPHONY								
Outcome	Placebo	MIR 25 mg	MIR 50 mg	SOL 5 mg	SOL 10 mg	MIR 25 mg + SOL 5 mg	MIR 25 mg + SOL 10 mg	MIR 50 mg + SOL 5 mg	MIR 50 mg + SOL 10 mg
Mean Incontinence Episodes/24 Hours									
	N = 17	**N = 13**	**N = 18**	**N = 35**	**N = 15**	**N = 32**	**N = 24**	**N = 24**	**N = 20**
Baseline (SD)	0.9 (0.8)	1.9 (1.6)	1.3 (1.0)	1.3 (1.2)	1.4 (1.3)	1.2 (1.1)	1.5 (1.2)	1.2 (1.2)	1.3 (0.9)
Adjusted mean change from baseline (SE)	–0.95 (0.365)	–0.74 (0.415)	–0.90 (0.353)	–0.88 (0.252)	–0.97 (0.386)	–1.22 (0.266)	–0.27 (0.304)	–1.14 (0.306)	–0.97 (0.333)
MD (95% CI), *P* value, versus placebo	ref	0.21 (–0.88 to 1.30), *P* = 0.44	0.05 (–0.95 to 1.04), *P* = 0.85	0.07 (–0.80 to 0.95), *P* = 0.56	–0.02 (–1.07 to 1.03), *P* = 0.48	–0.27 (–1.16 to 0.63), *P* = 0.34	0.68 (–0.26 to 1.61), *P* = 0.88	–0.19 (–1.12 to 0.74), *P* = 0.24	–0.02 (–0.99 to 0.95), *P* = 0.83
MD (95% CI), *P* value, versus SOL 5 mg	–	0.14 (–0.81 to 1.09), *P* = 0.77[a]	–0.02 (–0.87 to 0.83), *P* = 0.96[a]	ref	–	–0.34(–1.06 to 0.38), *P* = 0.001[b]	0.60 (–0.17 to 1.38), *P* = 0.15	–0.26 (–1.04 to 0.52), *P* = 0.058	–0.09 (–0.91 to 0.73), *P* = 0.41
Mean Urgency incontinence Episodes/24 Hours[c]									
	N = 14	**N = 13**	**N = 17**	**N = 35**	**N = 13**	**N = 31**	**N = 24**	**N = 23**	**N = 19**
Baseline (SE)	0.95 (0.212)	1.54 (0.371)	1.25 (0.250)	1.32 (0.207)	1.36 (0.365)	1.27 (0.200)	1.51 (0.254)	1.13 (0.249)	1.26 (0.202)
Adjusted mean change from baseline (SE)	–0.86 (0.411)	–0.80 (0.424)	–0.88 (0.372)	–0.86 (0.258)	–1.13 (0.424)	–1.20 (0.277)	–0.28 (0.312)	–1.08 (0.321)	–0.94 (0.351)
MD (95% CI), *P* value, versus placebo	ref	0.06 (–1.10 to 1.22), *P* = 0.95	–0.02 (–1.11 to 1.07), *P* = 0.74	–0.00 (–0.96 to 0.96), *P* = 0.82	–0.27 (–1.44 to 0.90), *P* = 0.58	–0.34 (–1.32 to 0.65), *P* = 0.18	0.58 (–0.43 to 1.60), *P* = 0.72	–0.22 (–1.24 to 0.80), *P* = 0.21	–0.08 (–1.15 to 0.98), *P* = 0.92
MD (95% CI), *P* value, versus SOL 5 mg	–	0.06 (–0.91 to 1.03), *P* = 0.90[a]	–0.02 (–0.91 to 087), *P* = 0.96[a]	ref	–	–0.34 (–1.08 to 0.41), *P* = 0.003[b]	0.58 (–0.21 to 1.38), *P* = 0.24	–0.22 (–1.04 to 0.59), *P* = 0.12	–0.08 (–0.94 to 0.78), *P* = 0.54

Study	SYMPHONY								
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**SOL 5 mg**	**SOL 10 mg**	**MIR 25 mg + SOL 5 mg**	**MIR 25 mg + SOL 10 mg**	**MIR 50 mg + SOL 5 mg**	**MIR 50 mg + SOL 10 mg**
Achievement of Continence									
	N = 17	**N = 13**	**N = 18**	**N = 35**	**N = 15**	**N = 32**	**N = 24**	**N = 24**	**N = 20**
Final visit, n (%)	14 (82)	6 (46)	11 (61)	21 (60)	8 (53)	28 (88)	19 (79)	21 (88)	15 (75)
ARD (95% CI) versus placebo	ref	–36% (–69 to –4)	–21% (–50 to 8)	–22% (–47 to 2)	–29% (–60 to 2)	5% (–16 to 27)	–3% (–28 to 21)	5% (–17 to 28)	–7% (–34 to 19)
ARD (95% CI), versus SOL 5 mg	–	–14% (–45 to 18)[a]	1% (–27 to 29)[a]	ref	–	28% (8 to 47)	19% (–4 to 42)	28% (7 to 48)	15% (–10 to 40)

ARD = absolute risk difference; CI = confidence interval; MD = mean difference; MIR = mirabegron; ref = reference group; SOL = solifenacin.
[a] Calculated by CADTH using Review Manager.
[b] MD versus solifenacin 5 mg was reported as statistically significantly different with *P* value < 0.05. However, the 95% CI included the null value.
[c] Analyses include patients with one event of interest at baseline (i.e., one or more urgency incontinence, grade 3 or 4 urgency or nocturia episode at baseline).
Source: Clinical Study Report,[32] Abrams et al. 2014.[22]

TABLE 13: URGENCY INCONTINENCE — PLACEBO- AND TOLTERODINE-CONTROLLED TRIALS

Study	Treatment			
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**TOL 4 mg**
Mean Urgency incontinence Episodes/24 Hours				
SCORPIO[a]	**N = 283**		**N = 286**	**N = 289**
Baseline (SE)	2.43 (0.13)		2.52 (0.15)	2.37 (0.13)
Adjusted mean change from baseline (SE)	–1.11 (0.11)		–1.46 (0.11)	–1.18 (0.11)
MD (95% CI), *P* value versus placebo	ref		–0.35 (–0.65 to –0.05), *P* = 0.003	–0.07 (–0.38 to 0.23), *P* = 0.26
MD (95% CI), *P* value versus TOL[b]	–		–0.28 (–0.58 to 0.02), *P* = NS	ref
Study 048	**N = 258**		**N = 254**	**N = 230**
Baseline (SD)	1.67 (1.37)		1.78 (1.75)	1.71 (1.57)
Adjusted mean change from baseline (SE)	−0.63 (NR)		−0.98 (NR)	−0.95 (NR)
MD (95% CI), *P* value versus placebo	ref		−0.36 (−0.59 to −0.12), *P* = NR	−0.32 (−0.56 to −0.08), *P* = NR
MD (95% CI), *P* value versus TOL	–		–0.04 (–0.28 to 0.21), *P* = NS	ref
Study 090[a]	**N = 98**		**N = 108**	**N = 108**
Baseline (SD)	2.13 (2.72)		1.70 (1.60)	1.93 (2.34)
Adjusted mean change from baseline (SE)	–1.05 (0.16)		–1.22 (0.15)	–1.21 (0.15)
MD (95% CI), *P* value versus placebo	ref		–0.17 (–0.60 to 0.26), *P* = 0.56	–0.16 (–0.59 to 0.27), *P* = 0.42
MD (95% CI), *P* value versus TOL	–		–0.01 (–0.43 to 0.40), *P* = 0.48	ref
DRAGON[a]	**N = 106**	**N = 93**	**N = 106**	**N = 52**
Baseline (SD)	2.21 (2.00)	2.88 (3.09)	2.21 (2.17)	2.63 (2.53)
Adjusted mean change from baseline (SE)	–0.44 (NR)	–1.31 (NR)	–1.13 (NR)	–0.76 (NR)
MD (95% CI), *P* value versus placebo	ref	–0.86 (–1.38 to –0.35), *P* < 0.01	–0.69 (–1.18 to –0.19), *P* < 0.01	–0.31 (–0.92 to 0.30), *P* = NS
MD (95% CI), *P* value versus TOL	–	–0.55 (–1.18 to 0.07), *P* = 0.08	–0.37 (–0.99 to 0.24), *P* = 0.23	ref
TAURUS[a]			**N = 472**	**N = 474**
Baseline (SE)			2.46 (0.11)	2.26 (0.10)
Adjusted mean change from baseline (SE)			–1.01 (0.082)	–1.21 (0.081)
MD (95% CI), *P* value versus TOL[b]			0.20 (–0.03 to 0.43), *P* = NS	ref

Study	Treatment			
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**TOL 4 mg**
ARIES[a]	**N = 319**		**N = 297**	
Baseline (SD)	2.5 (2.5)		2.3 (2.4)	
Adjusted mean change from baseline (SE)	–0.89 (0.10)		–1.32 (0.10)	
MD (95% CI), *P* value versus placebo	ref		–0.43 (–0.72 to –0.15), *P* = 0.005	
CAPRICORN[a]	**N = 256**	**N = 247**	**N = 251**	
Baseline (SE)	2.24 (0.14)	2.45 (0.14)	2.33 (0.14)	
Adjusted mean change from baseline (SE)	–0.95 (0.11)	–1.31 (0.11)	–1.33 (0.11)	
MD (95% CI), *P* value versus placebo	ref	–0.36 (–0.67 to –0.05), *P* = 0.004	–0.39 (–0.69 to –0.08), *P* = 0.002	

CI = confidence interval; MD = mean difference; MIR = mirabegron; NR = not reported; NS = not statistically significant; ref = reference group; SD = standard deviation; SE = standard error; TOL = tolterodine.
[a] Includes patients with at least one urgency incontinence episode at baseline.
[b] Calculated by CADTH using Review Manager; negative values indicate patients in the MIR group had fewer episodes than those in the TOL group.
Source: Clinical Study Report,[27–30,33,35] Chapple et al. 2013,[18] Nitti et al. 2012,[20] Herschorn et al. 2013,[21] FDA.[26]

TABLE 14: ACHIEVEMENT OF CONTINENCE — PLACEBO- AND TOLTERODINE-CONTROLLED TRIALS

Study	Treatment			
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**TOL 4 mg**
Proportion of Patients Who Were Continent at End of Treatment				
SCORPIO	**N = 291**		**N = 293**	**N = 300**
Continent, n (%)	118 (41)		132 (45)	142 (47)
ARD (95% CI), *P* value versus TOL[a]	–		2% (–10% to 6%), *P* = NS	ref
Study 048	**N = 264**		**N = 266**	**N = 240**
Continent, n (%)	104 (39)		135 (51)	117 (49)
ARD (95% CI), *P* value versus TOL[a]	–		2% (–7% to 11%), *P* = NS	ref
Study 090	**N = 127**		**N = 135**	**N = 137**
Continent, n (%)	75 (59)		69 (51)	74 (54)
ARD (95% CI), *P* value versus TOL[a]	–		–3% (–15% to 9%), *P* = NS	ref
DRAGON	**N = 106**	**N = 99**	**N = 108**	**N = 53**
Continent, n (%)	39 (37)	42 (42)	45 (42)	19 (36)
ARD (95% CI), *P* value versus TOL[a]	–	7% (–10% to 23%), *P* = NS	6% (–10% to 22%), *P* = NS	ref
TAURUS			**N = 479**	**N = 488**
Continent, n (%)			208 (43)	220 (45)
ARD (95% CI), *P* value versus TOL[a]			–2% (–8% to 5%), *P* = NS	ref
ARIES	**N = 325**		**N = 312**	
Continent, n (%)	110 (34)		127 (41)	
ARD (95% CI), *P* value versus placebo	ref		6.9% (–0.6% to 14.4%), *P* = NS	

Study	Treatment			
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**TOL 4 mg**
CAPRICORN	**N = 262**	**N = 254**	**N = 257**	
Continent, n (%)	104 (40)	116 (46)	121 (47)	
ARD (95% CI), *P* value versus placebo	ref	6% (–3% to 15%), *P* = 0.081	7% (–1% to 16%), *P* = 0.057	

ARD = absolute risk difference; CI = confidence interval; MIR = mirabegron; NS = not statistically significant; ref = reference group; TOL = tolterodine.
[a] Calculated by CADTH using Review Manager. Positive numbers indicate that a higher proportion of patients in the MIR group achieved continence than in the TOL or placebo group.
Source: Clinical Study Report,[27–30,34,35] Chapple et al. 2013,[18] Nitti et al. 2012,[20] Herschorn et al. 2013,[21] FDA.[25]

TABLE 15: MICTURITIONS — PLACEBO- AND TOLTERODINE-CONTROLLED TRIALS

Study	Treatment			
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**TOL 4 mg**
Mean Number of Micturitions/24 Hours				
SCORPIO[a]	**N = 480**		**N = 473**	**N = 475**
Baseline (SE)	11.7 (0.14)		11.7 (0.14)	11.6 (0.13)
Adjusted mean change from baseline (SE)	–1.34 (0.11)		–1.93 (0.11)	–1.59 (0.11)
MD (95% CI), *P* value versus placebo	ref		–0.60 (–0.90 to –0.29), *P* < 0.001	–0.25 (–0.55 to 0.06), *P* = 0.11
MD (95% CI), *P* value versus TOL[b]	–		–0.34 (–0.64 to –0.04), *P* = 0.03	ref
Study 048	**N = 368**		**N = 369**	**N = 368**
Baseline (SD)	11.3 (2.7)		11.2 (2.7)	11.1 (2.6)
Adjusted mean change from baseline (SD)	−0.82 (NR)		−1.68 (NR)	−1.43 (NR)
MD (95% CI), *P* value versus placebo	ref		−0.86 (−1.16 to −0.57), *P* = NR	−0.61 (−0.90 to −0.32), *P* = NR
MD (95% CI), *P* value versus TOL	–		−0.25 (−0.55 to 0.04), *P* = NS	ref
Study 090	**N = 323**		**N = 338**	**N = 333**
Baseline (SD)	12.6 (4.9)		12.1 (4.1)	12.1 (3.7)
Adjusted mean change from baseline (SE)	–1.48 (0.18)		–2.04 (0.17)	–1.45 (0.18)
MD (95% CI), *P* value versus placebo	ref		–0.57 (–1.04,-0.09), *P* = 0.019	0.03 (–0.44 to 0.51), *P* = 0.90
MD (95% CI), *P* value versus TOL			–0.60 (–1.07 to –0.13), *P* = 0.012	ref
DRAGON	**N = 166**	**N = 167**	**N = 167**	**N = 85**
Baseline (SD)	11.7 (3.4)	11.9 (2.9)	11.9 (3.3)	12.3 (3.7)
Adjusted mean change from baseline (SE)	–1.44	–1.88	–2.08	–1.99
MD (95% CI), *P* value versus placebo	ref	–0.45 (–0.99 to 0.10), *P* = 0.11	–0.64 (–1.19 to –0.10), *P* = 0.02	–0.52 (–1.18 to 0.15), *P* = NS

Study	Treatment			
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**TOL 4 mg**
MD (95% CI), *P* value versus TOL	–	0.06 (–0.60 to 0.72), *P* = 0.87	–0.14 (–0.80 to 0.53), *P* = 0.68	ref
TAURUS			**N = 789**	**N = 791**
Baseline (SE)			11.1 (0.10)	10.9 (0.09)
Adjusted mean change from baseline (SE)			–1.27 (0.083)	–1.39 (0.083)
MD (95% CI), *P* value versus TOL[b]			0.12 (–0.11 to 0.35), *P* = NS	ref
ARIES	**N = 433**		**N = 425**	
Baseline (SD)	11.5 (3.3)		11.8 (3.5)	
Adjusted mean change from baseline (SE)	–1.05 (0.13)		–1.66 (0.13)	
MD (95% CI), *P* value versus placebo	ref		–0.61 (–0.98 to –0.24), *P* = 0.001	
CAPRICORN	**N = 415**	**N = 410**	**N = 426**	
Baseline (SE)	11.5 (0.14)	11.7 (0.15)	11.7 (0.16)	
Adjusted mean change from baseline (SE)	–1.18 (0.12)	–1.65 (0.13)	–1.60 (0.12)	
MD (95% CI), *P* value versus placebo	ref	–0.47 (–0.82 to –0.13), *P* = 0.007	–0.42 (–0.76 to –0.08), *P* = 0.015	

CI = confidence interval; MD = mean difference; MIR = mirabegron; NS = not statistically significant; ref = reference group; SD = standard deviation; SE = standard error; TOL = tolterodine.

[a] SCORPIO reported data for the intention to treat population (any patient who received study drug and had a baseline outcome measure), and the results were similar to the full analysis set population.

[b] Calculated by CADTH using Review Manager; negative values indicate patients in the MIR group had fewer episodes than TOL.

Source: Clinical Study Report,[27–30,35] Chapple et al. 2013,[18] Nitti et al. 2012,[20] Herschorn et al. 2013,[21] FDA.[25]

TABLE 16: MICTURITION, URGENCY, AND NOCTURIA OUTCOMES FOR BEYOND TRIAL

Outcome	BEYOND	
	MIR 50 mg	SOL 5 mg
Mean Micturitions/24 Hours		
PPS		
Baseline (SE)		
Adjusted mean change from baseline (SE)	–2.95	–3.13
MD (95% CI), *P* value, MIR versus SOL	0.18 (–0.06,0.42), non-inferiority not met	ref
FAS		
Baseline (SE)		
Adjusted mean change from baseline (SE)		
MD (95% CI), *P* value, MIR versus SOL	0.20 (–0.05 to 0.44), non-inferiority not met	ref
Mean Urgency Episodes/24 Hours (Grade 3 or 4)[ab]		
Baseline (SE)		
Adjusted mean change from baseline (SE)		
MD (95% CI), *P* value, MIR versus SOL		
Nocturia Episodes/24 Hours[c]		
Baseline (SE)		
Adjusted mean change from baseline (SE)		
MD (95% CI), *P* value, MIR versus SOL		

CI = confidence interval; FAS = full analysis set; MD = mean difference; MIR = mirabegron; PPS = per-protocol set; ref = reference group; SOL = solifenacin.

[a] Severe urgency or urgency incontinence as per the Patient Perception of Intensity of Urgency Scale (0 = no urgency; 1 = mild; 2 = moderate; 3 = severe urgency; 4 = urgency incontinence).

[b] Analysis included patients with > 0 urgency episodes at baseline.

[c] Analysis included patients with > 0 nocturia episodes at baseline.

Source: Clinical Study Report.[31]

TABLE 17: MICTURITION, URGENCY, AND NOCTURIA OUTCOMES FOR SYMPHONY TRIAL

	SYMPHONY								
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**SOL 5 mg**	**SOL 10 mg**	**MIR 25 mg + SOL 5 mg**	**MIR 25 mg + SOL 10 mg**	**MIR 50 mg + SOL 5 mg**	**MIR 50 mg + SOL 10 mg**
Mean Micturitions/24 Hours									
	N = 80	**N = 76**	**N = 77**	**N = 150**	**N = 76**	**N = 141**	**N = 78**	**N = 150**	**N = 80**
Baseline (SD)	10.4 (2.0)	11.3 (2.6)	10.8 (2.3)	11.4 (3.2)	11.3 (2.9)	10.9 (2.3)	11.1 (2.2)	11.3 (3.1)	11.2 (2.4)
Adjusted mean change from baseline (SE)	–2.43 (0.291)	–2.48 (0.298)	–2.56 (0.296)	–2.54 (0.212)	–3.22 (0.298)	–2.56 (0.219)	–3.42 (0.294)	–3.34 (0.212)	–3.52 (0.291)
MD (95% CI), *P* value, versus placebo	ref	–0.05 (–0.87 to 0.77), *P* = 0.91	–0.13 (–0.94 to 0.69), *P* = 0.76	–0.11 (–0.82 to 0.60), *P* = 0.77	–0.79 (–1.61 to 0.03), *P* = 0.058	–0.12 (–0.84 to 0.59), *P* = 0.73	–0.98 (–1.80 to –0.17), *P* = 0.018	–0.91 (–1.62 to –0.20), *P* = 0.012	–1.08 (–1.89 to –0.28), *P* = 0.009
MD (95% CI), *P* value, versus SOL 5 mg	–	0.06 (–0.66 to 0.78), *P* = 0.87[a]	–0.02 (–0.73 to 0.69), *P* = 0.96[a]	ref	–	–0.02 (–0.62 to 0.58), *P* = 0.96	–0.88 (–1.59 to –0.16), *P* = 0.016	–0.80 (–1.39 to –0.22), *P* = 0.007	–0.98 (–1.68 to –0.27), *P* = 0.007
Mean Urgency Episodes/24 Hours (Grade 3 or 4)[bc]									
	N = 80	**N = 76**	**N = 77**	**N = 150**	**N = 76**	**N = 141**	**N = 78**	**N = 150**	**N = 80**
Baseline (SD)	5.3 (3.1)	6.3 (3.3)	6.6 (4.0)	6.4 (4.2)	6.4 (4.6)	6.2 (3.9)	6.9 (4.3)	6.5 (4.2)	6.9 (4.3)
Adjusted mean change from baseline (SE)	–3.53 (0.328)	–3.23 (0.336)	–3.44 (0.334)	–2.73 (0.239)	–3.98 (0.336)	–3.86 (0.247)	–3.71 (0.332)	–4.10 (0.239)	–3.91 (0.327)
MD (95% CI), *P* value, versus placebo	ref	0.29 (–0.63 to 1.22), *P* = 0.53	0.09 (–0.83 to 1.01), *P* = 0.85	0.08 (–0.00 to 1.59), *P* = 0.05	–0.46 to – 1.38 to 0.46), *P* = 0.33	–0.33 (–1.14 to 0.47), *P* = 0.42	–0.18 (–1.10 to 0.73), *P* = 0.70	–0.57 (–1.37 to 0.23), *P* = 0.16	–0.39 (–1.30 to 0.52), *P* = 0.40
MD (95% CI), *P* value, versus SOL 5 mg	–	–0.50 (–1.31 to 0.31), *P* = 0.23[c]	–0.71 (–1.52 to 0.10), *P* = 0.08[c]	ref	–	–1.13 (–1.80 to –0.46), *P* = 0.001	–0.98 (–1.78 to –0.18), *P* = 0.017	–1.37 (–2.03 to –0.72), *P* < 0.001	–1.18 (–1.98 to –0.69), *P* = 0.004

Outcome	SYMPHONY								
	Placebo	MIR 25 mg	MIR 50 mg	SOL 5 mg	SOL 10 mg	MIR 25 mg + SOL 5 mg	MIR 25 mg + SOL 10 mg	MIR 50 mg + SOL 5 mg	MIR 50 mg + SOL 10 mg
Nocturia Episodes/24 Hours[b]									
	N = 78	**N = 73**	**N = 76**	**N = 146**	**N = 74**	**N = 137**	**N = 75**	**N = 147**	**N = 76**
Baseline (SD)	2.2 (1.6)	2.2 (1.4)	2.3 (1.5)	2.2 (1.4)	2.5 (1.9)	2.3 (1.4)	2.7 (2.6)	2.3 (1.3)	2.4 (2.0)
Adjusted mean change from baseline (SE)	–0.74 (0.140)	–0.69 (0.145)	–0.82 (0.142)	–0.69 (0.102)	–0.95 (0.144)	–0.77 (0.106)	–0.94 (0.143)	–1.04 (0.102)	–0.96 (0.142)
MD (95% CI), *P* value, versus placebo	ref	0.05 (–0.35 to 0.44), *P* = 0.81	–0.08 (–0.48 to 0.31), *P* = 0.67	0.04 (–0.30 to 0.38), *P* = 0.81	–0.21 (–0.60 to 0.18), *P* = 0.30	–0.04 (–0.38 to 0.31), *P* = 0.84	–0.21 (–0.60 to 0.18), *P* = 0.30	–0.30 (–0.64 to 0.04), *P* = 0.08	–0.22 (–0.62 to 0.17), *P* = 0.26
MD (95% CI), *P* value, versus SOL 5 mg	–	0.0 (–0.35 to 0.35), *P* = 1.0 [a]	–0.13 (–0.47 to 0.21), *P* = 0.46 [a]	ref	–	–0.08 (–0.37 to 0.21), *P* = 0.60	–0.25 (–0.60 to 0.10), *P* = 0.16	–0.35 (–0.63 to –0.06), *P* = 0.017	–0.27 (–0.61 to 0.08), *P* = 0.13

CI = confidence interval; MD = mean difference; MIR = mirabegron; ref = reference group; SOL = solifenacin.
[a] Calculated by CADTH using Review Manager.
[b] Analyses include patients with one event of interest at baseline (i.e., one or more urgency incontinence, grade 3 or 4 urgency or nocturia episode at baseline).
[c] Severe urgency or urgency incontinence as per the Patient Perception of Intensity of Urgency Scale (0 = no urgency; 1 = mild; 2 = moderate; 3 = severe urgency; 4 = urgency incontinence).
Source: Clinical Study Report,[32] Abrams et al. 2014.[22]

TABLE 18: URGENCY EPISODES — PLACEBO- AND TOLTERODINE-CONTROLLED TRIALS

Study	Treatment			
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**TOL 4 mg**
Mean Number of Urgency Episodes/24 Hours				
SCORPIO[a] **Grade 3 or 4[b]**	**N = 479**		**N = 470**	**N = 472**
Baseline (SE)	5.78 (0.18)		5.72 (0.17)	5.79 (0.16)
Adjusted mean change from baseline (SE)	–1.65 (0.15)		–2.25 (–0.15)	–2.07 (0.15)
MD (95% CI), *P* value versus placebo[c]	ref		–0.60 (–1.02 to –0.18), *P* = 0.005	–0.42 (–0.84 to –0.00), *P* = 0.05
MD (95% CI), *P* value versus TOL[c]	–		–0.18 (–0.60 to 0.24), *P* = NS	ref
Study 048 **Urgency Severity Undefined**	**N = 368**		**N = 369**	**N = 368**
Baseline (SD)	4.42 (2.99)		4.27 (2.85)	4.13 (2.81)
Adjusted mean change from baseline (SE)	−1.31 (NR)		−1.85 (NR)	−1.71 (NR)
MD (95% CI), *P* value versus placebo	ref		−0.54 (−0.90 to −0.18), *P* = NR	−0.41 (−0.77 to −0.05), *P* = NR
MD (95% CI), *P* value versus TOL	–		−0.13 (−0.49, 0.23), *P* = NS	ref
Study 090[a] **Urgency Severity Undefined**	**N = 323**		**N = 337**	**N = 333**
Baseline (SD)	5.58 (5.34)		5.18 (4.58)	5.39 (4.30)
Adjusted mean change from baseline (SE)	–2.22 (0.22)		–2.36 (0.21)	–2.40 (0.21)
MD (95% CI), *P* value versus placebo	ref		–0.15 (–0.72 to 0.43), *P* = 0.61	–0.18 (–0.76 to 0.39), *P* = 0.53
MD (95% CI), *P* value versus TOL	–		–0.04 (–0.53 to 0.60), *P* = 0.90	ref
DRAGON[a] **Grade 3 or 4[b]**	**N = 165**	**N = 167**	**N = 166**	**N = 85**
Baseline (SD)	5.75 (3.95)	5.77 (4.12)	5.94 (3.87)	5.83 (3.72)
Adjusted mean change from baseline (SE)	–1.07 (NR)	–1.77 (NR)	–1.67 (NR)	–1.46 (NR)
MD (95% CI), *P* value versus placebo	ref	–0.70 (–1.38 to –0.01), *P* < 0.05	–0.60 (–1.29, 0.08), *P* = NS	–0.37 (–1.21 to 0.47), *P* = NS
MD (95% CI), *P* value versus TOL	–	–0.31 (–1.14 to 0.52), *P* = 0.46	–0.22 (–1.06 to 0.62), *P* = 0.61	ref
TAURUS **Grade 3 or 4[b]**			**N = 788**	**N = 788**
Baseline (SE)			5.67 (0.13)	5.45 (0.12)
Adjusted mean change from baseline (SE)			–1.62 (0.11)	–1.63 (0.11)
MD (95% CI), *P* value versus TOL[b]			0.01 (–0.30 to 0.32), *P* = NS	ref

Study	Treatment			
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**TOL 4 mg**
ARIES[a] **Grade 3 or 4[b]**	**N = 432**		**N = 424**	
Baseline (SD)	5.6 (3.2)		5.9 (3.8)	
Adjusted mean change from baseline (SE)	–0.82 (0.16)		–1.57 (0.16)	
MD (95% CI), *P* value versus placebo	ref		–0.75 (–1.20 to –0.30), *P* = 0.001	
CAPRICORN[a] **Grade 3 or 4[b]**	**N = 413**	**N = 410**	**N = 426**	
Baseline (SE)	5.42 (0.16)	5.57 (0.18)	5.80 (0.17)	
Adjusted mean change from baseline (SE)	–1.35 (0.15)	–1.68 (0.16)	–1.94 (0.15)	
MD (95% CI), *P* value versus placebo	ref	–0.33 (–0.76 to 0.10), *P* = 0.13	–0.59 (–1.01 to –0.16), *P* = 0.007	

CI = confidence interval; MD = mean difference; MIR = mirabegron; NR = not reported; NS = not statistically significant; ref = reference group; SD = standard deviation; SE = standard error; TOL = tolterodine.
[a] Excludes patients with no severe urgency episodes at baseline.
[b] Severe urgency or urgency incontinence as per the Patient Perception of Intensity of Urgency Scale (0 = no urgency; 1 = mild; 2 = moderate; 3 = severe urgency; 4 = urgency incontinence).
[c] Calculated by CADTH using Review Manager; negative values indicate patients in the MIR group had fewer episodes than those in the TOL group.
Source: Clinical Study Report,[27–30,33,35] Chapple et al. 2013,[18] Nitti et al. 2012,[20] Herschorn et al. 2013,[21] FDA[26].

TABLE 19: NOCTURIA — PLACEBO- AND TOLTERODINE-CONTROLLED TRIALS

Study	Treatment			
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**TOL 4 mg**
Mean Nocturia Episodes/24 Hours				
SCORPIO[a]	**N = 428**		**N = 423**	**N = 433**
Baseline (SE)	2.22 (0.063)		2.09 (0.058)	2.14 (0.064)
Adjusted mean change from baseline (SE)	–0.41 (0.047)		–0.56 (0.047)	–0.45 (0.047)
MD (95% CI), *P* value versus placebo	ref		–0.15 (–0.28 to –0.02), *P* = 0.022	–0.04 (–0.017 to 0.09), *P* = 0.52
MD (95% CI), *P* value versus TOL[b]	–		–0.11 (–0.24 to 0.02), *P* = NS	ref
Study 048	**N = 322**		**N = 323**	**N = 332**
Baseline (SD)	1.81 (1.20)		1.72 (1.00)	1.71 (1.08)
Adjusted mean change from baseline (SE)	−0.33 (NR)		−0.45 (NR)	−0.43 (NR)
MD (95% CI), *P* value versus placebo	ref		−0.12 (−0.25 to 0.01), *P* = NS	−0.10 (−0.23 to 0.03), *P* = NS
MD (95% CI), *P* value versus TOL	–		−0.02 (−0.15 to 0.11), *P* = NS	ref

Study	Treatment			
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**TOL 4 mg**
Study 090[a]	**N = 293**		**N = 318**	**N = 309**
Baseline (SD)	2.51 (1.75)		2.32 (1.47)	2.39 (1.72)
Adjusted mean change from baseline (SE)	–0.41 (0.07)		–0.54 (0.07)	–0.40 (0.07)
MD (95% CI), *P* value versus placebo	ref		–0.13 (–0.33 to 0.06), *P* = 0.17	0.01 (–0.18 to 0.21), *P* = 0.90
MD (95% CI), *P* value versus TOL	–		–0.15 (–0.34 to 0.04), *P* = 0.13	ref
DRAGON[a]	**N = 144**	**N = 145**	**N = 142**	**N = 72**
Baseline (SD)	1.77 (1.12)	1.76 (1.17)	1.70 (1.02)	1.78 (0.98)
Adjusted mean change from baseline (SE)	–0.38 (NR)	–0.52 (NR)	–0.60 (NR)	–0.59 (NR)
MD (95% CI), *P* value versus placebo	ref	–0.15 (–0.36 to 0.07), *P* = 0.18	–0.22 (–0.44 to –0.01), *P* = 0.04	–0.21 (–0.47 to 0.05), *P* = NS
MD (95% CI), *P* value versus TOL	–	0.06 (–0.20 to 0.32), *P* = 0.63	–0.01 (–0.27 to 0.25), *P* = 0.94	ref
TAURUS[a]			**N = 693**	**N = 693**
Baseline (SE)			2.08 (0.05)	2.02 (0.05)
Adjusted mean change from baseline (SE)			–0.46 (0.038)	–0.43 (0.038)
MD (95% CI), *P* value versus TOL[b]			–0.03 (–0.14 to 0.08), *P* = NS	ref
ARIES[a]	**N = 366**		**N = 348**	
Baseline (SE)	2.3 (0.08)		2.3 (0.08)	
Adjusted mean change from baseline (SE)	–0.38 (0.06)		–0.57 (0.07)	
MD (95% CI), *P* value versus placebo	ref		–0.18 (–0.36 to –0.01), *P* < 0.05	
CAPRICORN[a]	**N = 362**	**N = 362**	**N = 378**	
Baseline (SE)	2.04 (0.06)	2.22 (0.08)	2.28 (0.07)	
Adjusted mean change from baseline (SE)	–0.48 (0.06)	–0.49 (0.06)	–0.52 (0.06)	
MD (95% CI), *P* value versus placebo	ref	–0.01 (–0.17 to 0.015), *P* = 0.93	–0.04 (–0.20 to 0.12), *P* = 0.63	

CI = confidence interval; MD = mean difference; MIR = mirabegron; NR = not reported; NS = not statistically significant; ref = reference group; SD = standard deviation; SE = standard error; TOL = tolterodine.

[a] Includes patients with at least one nocturia episode at baseline.

[b] Calculated by CADTH using Review Manager; negative values indicate patients in the MIR group had fewer episodes than those in the TOL group.

Source: Clinical Study Report,[27–30,35] Chapple et al. 2013,[18] Nitti et al. 2012,[20] Herschorn et al. 2013.[21]

TABLE 20: OAB QUESTIONNAIRE — PLACEBO- AND TOLTERODINE-CONTROLLED TRIALS

Study	Treatment			
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**TOL 4 mg**
OAB-q Symptom Bother Scale[a]				
SCORPIO	**N = 475**		**N = 465**	**N = 469**
Baseline (SE)	49.6 (0.93)		49.6 (0.93)	50.3 (0.93)
Adjusted mean change from baseline (SE)	–14.9 (0.84)		–19.6 (0.85)	–18.4 (0.85)
MD (95% CI), *P* value versus placebo	ref		–4.7 (–7.1 to –2.4), *P* < 0.001[b]	–3.5 (–5.9 to –1.2), *P* < 0.003[b]
MD (95% CI), *P* value versus TOL[b]	–		–1.2 (–3.6 to 1.2), *P* = NS	ref
TAURUS			**N = 779**	**N = 781**
Baseline (SE)			44.6 (0.8)	44.2 (0.7)
Adjusted mean change from baseline (SE)			–13.1 (0.65)	–14.3 (0.65)
MD (95% CI), *P* value versus TOL[b]			1.2 (–0.6 to 3.0), *P* = NS	ref
ARIES	**N = 356**		**N = 350**	
Baseline (SE)	48.1 (1.06)		49.7 (1.08)	
Adjusted mean change from baseline (SE)	–10.8 (0.97)		–17.0 (0.98)	
MD (95% CI), *P* value versus placebo	ref		–6.2 (–8.9, –3.5), *P* < 0.001	
CAPRICORN	**N = 405**	**N = 407**	**N = 422**	
Baseline (SE)	49.1 (0.95)	48.5 (0.97)	50.6 (0.99)	
Adjusted mean change from baseline (SE)	–16.0 (0.90)	–17.9 (0.90)	–18.8 (0.90)	
MD (95% CI), *P* value versus placebo	ref	–1.8 (–4.3 to 0.7), *P* = 0.15	–2.8 (–5.3 to –0.3), *P* = 0.028	
OAB-q HRQoL Scale[c]				
SCORPIO	**N = 473**		**N = 468**	**N = 470**
Baseline (SE)	60.9 (1.02)		62.0 (0.96)	61.0 (0.97)
Adjusted mean change from baseline (SE)	13.7 (0.76)		16.1 (0.77)	14.8 (0.77)
MD (95% CI), *P* value versus placebo			2.3 (0.2 to 4.5), *P* = 0.031	1.1 (–1.1 to 3.2), *P* = 0.32
MD (95% CI), *P* value versus TOL[b]			1.3 (–0.8 to 3.4), *P* = NS	ref
TAURUS			**N = 779**	**N = 783**
Baseline (SE)			66.6 (0.8)	67.3 (0.8)
Adjusted mean change from baseline (SE)			10.7 (0.58)	11.4 (0.58)
MD (95% CI), *P* value versus TOL[b]			–0.7 (–2.3 to 0.9), *P* = NS	ref

Study	Treatment			
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**TOL 4 mg**
ARIES	**N = 355**		**N = 350**	
Baseline (SE)	63.4 (1.2)		62.2 (1.2)	
Adjusted mean change from Baseline (SE)	10.7 (0.9)		14.8 (0.9)	
MD (95% CI), *P* value versus placebo	ref		4.1 (1.6 to 6.6), *P* = 0.01	
CAPRICORN	**N = 406**	**N = 408**	**N = 419**	
Baseline (SE)	64.5 (1.01)	65.0 (1.04)	63.7 (1.09)	
Adjusted mean change from baseline (SE)	13.0 (0.80)	14.3 (0.79)	14.2 (0.78)	
MD (95% CI), *P* value versus placebo	ref	1.3 (–0.9 to 3.5), *P* = 0.26	1.2 (–1.0 to 3.4), *P* = 0.28	

CI = confidence interval; HRQoL = health-related quality of life; MD = mean difference; MIR = mirabegron; NS = not statistically significant; OAB-q = Overactive Bladder Questionnaire; ref = reference group; SE = standard error; TOL = tolterodine.
[a] Scores on OAB-q symptom bother scale range from 0 to 100 (worst severity) with a negative change indicating improvement.
[b] Calculated by CADTH using Review Manager.
[c] Scores on OAB-q HRQoL scale range from 0 to 100 (best HRQoL) with a positive change indicating improvement.
Source : Clinical Study Report,[27,30,33,34] Chapple et al. 2013,[18] Nitti et al. 2012,[20] Herschorn et al. 2013.[21]

TABLE 21: HRQOL OUTCOMES FOR BEYOND TRIAL

Outcome	BEYOND	
	MIR 50 mg	**SOL 5 mg**
OAB-q Symptom Bother Scale[a]		
Baseline (SE)		
Adjusted mean change from baseline (SE)		
MD (95% CI), *P* value, MIR versus SOL		
OAB-q HRQoL Total Score[b]		
Baseline (SE)		
Adjusted mean change from baseline (SE)		
MD (95% CI), *P* value, MIR versus SOL		
PPBC[c]		
Baseline (SE)		
Adjusted mean change from baseline (SE)		
MD (95% CI), *P* value, MIR versus SOL		

CI = confidence interval; HRQoL = health-related quality of life; MD = mean difference; MIR = mirabegron; OAB-q = Overactive Bladder Questionnaire; PPBC = Patient Perception of Bladder Condition questionnaire; SE = standard error; SOL = solifenacin.
[a] Scores on OAB-q symptom bother scale range from 0 to 100 (worst severity) with a negative change indicating improvement.
[b] Scores on OAB-q HRQoL scale range from 0 to 100 (best HRQoL) with a positive change indicating improvement.
[c] PPBC is a six-point Likert scale from 1 = no problems at all, to 6 = many severe problems. A negative change indicates improvement.
Source: Clinical Study Report.[31]

TABLE 22: HRQOL OUTCOMES FOR SYMPHONY TRIAL

	SYMPHONY								
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**SOL 5 mg**	**SOL 10 mg**	**MIR 25 mg + SOL 5 mg**	**MIR 25 mg + SOL 10 mg**	**MIR 50 mg + SOL 5 mg**	**MIR 50 mg + SOL 10 mg**
OAB-q Symptom Bother Scale[a]									
	N = 79	**N = 75**	**N = 76**	**N = 150**	**N = 75**	**N = 139**	**N = 78**	**N = 146**	**N = 78**
Baseline (SE)	52.6 (2.14)	56.3 (2.12)	55.1 (2.06)	55.3 (1.66)	54.2 (2.23)	56.1 (1.74)	57.1 (1.87)	56.2 (1.47)	58.3 (1.90)
Adjusted mean change from baseline (SE)	–25.5 (1.96)	–27.1 (2.01)	–27.5 (2.00)	–26.8 (1.42)	–29.9 (2.01)	–32.0 (1.48)	–33.6 (1.97)	–33.5 (1.44)	–31.4 (1.97)
MD (95% CI), *P* value, versus placebo	ref	–1.6 (–7.1 to 3.9), *P* = 0.56	–2.0 (–7.5 to 3.5), *P* = 0.48	–1.2 (–6.0 to 3.5), *P* = 0.61	–4.4 (–9.9 to 1.2), *P* = 0.12	–6.5 (–11.3 to –1.7), *P* = 0.008	–8.0 (–13.5 to –2.6), *P* = 0.004	–8.0 (–12.8 to –3.2), *P* = 0.001	–5.9, (–11.4 to –0.4), *P* = 0.035
MD (95% CI), *P* value, versus SOL 5 mg	–	–0.30 (–5.12 to 4.52), *P* = 0.90[b]	–0.70 (–5.51 to 4.11), *P* = 0.78[b]	ref	–	–5.2 (–9.3 to –1.2), *P* = 0.11	–6.8 (–11.6 to –2.0), *P* = 0.005	–6.7 (–10.7. –2.8), *P* < 0.001	–4.7 (–9.4 to 0.1), *P* = 0.056
OAB-q HRQoL Total Score[c]									
	N = 79	**N = 75**	**N = 76**	**N = 150**	**N = 75**	**N = 139**	**N = 78**	**N = 146**	**N = 78**
Baseline (SE)	60.2 (2.28)	56.4 (2.40)	60.0 (2.33)	55.5 (1.75)	53.5 (2.53)	57.1 (1.79)	53.8 (2.34)	55.7 (1.69)	50.4 (2.38)
Adjusted mean change from baseline (SE)	22.0 (1.83)	20.2 (1.88)	23.1 (1.87)	21.6 (1.33)	23.5 (1.88)	26.4 (1.38)	27.4 (1.84)	28.4 (1.34)	27.0 (1.84)
MD (95% CI), *P* value, versus placebo	ref	–1.8 (–6.9, 3.4), *P* = 0.50	1.1 (–4.0 to 6.2), *P* = 0.67	–0.3 (–4.8 to 4.1), *P* = 0.88	1.5 (–3.6 to 6.7), *P* = 0.56	4.4 (–0.1 to 8.9), *P* = 0.055	5.5 (0.4 to 10.6), *P* = 0.036	6.4 (2.0 to 10.9), *P* = 0.005	5.0 (–0.1 to 10.1), *P* = 0.053
MD (95% CI), *P* value, versus SOL 5 mg	–	–1.40 (–5.91 to 3.11), *P* = 0.54[b]	1.50 (–3.00 to 6.00), *P* = 0.51[b]	ref	–	4.8 (1.0 to 8.5), *P* = 0.013	5.8 (1.4 to 10.3), *P* = 0.011	6.8 (3.1 to 10.5), *P* < 0.001	5.4 (0.9, 9.8), *P* = 0.018

	SYMPHONY								
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**SOL 5 mg**	**SOL 10 mg**	**MIR 25 mg + SOL 5 mg**	**MIR 25 mg + SOL 10 mg**	**MIR 50 mg + SOL 5 mg**	**MIR 50 mg + SOL 10 mg**
PPBC[d]									
	N = 78	**N = 73**	**N = 76**	**N = 147**	**N = 73**	**N = 136**	**N = 76**	**N = 144**	**N = 78**
Baseline (SE)	4.5 (0.12)	4.8 (0.11)	4.6 (0.11)	4.7 (0.08)	4.8 (0.12)	4.6 (0.09)	5.0 (0.11)	4.6 (0.08)	4.7 (0.10)
Adjusted mean change from baseline (SE)	–1.4 (0.14)	–1.4 (0.14)	–1.5 (0.14)	- 1.3 (0.10)	–1.5 (0.14)	–1.7 (0.10)	–1.8 (0.14)	–1.8 (0.10)	–1.6 (0.14)
MD (95% CI), *P* value, versus placebo	ref	0.0 (–0.4 to 0.4), *P* = 0.99	–0.1 (–0.5 to 0.3), *P* = 0.67	0.0 (–0.3 to 0.4), *P* = 0.88	–0.1 (–0.5 to 0.3), *P* = 0.53	–0.4 (–0.7 to –0.0), *P* = 0.030	–0.5 (–0.8 to –0.1), *P* = 0.017	–0.4 (–0.7 to –0.1), *P* = 0.020	–0.2 (–0.6 to 0.2), *P* = 0.26
MD (95% CI), *P* value, versus SOL 5 mg	–	–0.10 (–0.44 to 0.24), *P* = 0.56[b]	–0.20 (–0.54 to 0.14), *P* = 0.24[b]	ref	–	–0.4 (–0.7 to –0.1), *P* = 0.005	–0.5 (–0.8 to –0.2), *P* = 0.004	–0.4 (–0.7 to –0.1), *P* = 0.003	–0.2 (–0.6 to 0.1), *P* = 0.26

CI = confidence interval; HRQoL = health-related quality of life; MD = mean difference; MIR = mirabegron; OAB-q = Overactive Bladder Questionnaire; PPBC = Patient Perception of Bladder Condition questionnaire; ref = reference group; SE = standard error; SOL = solifenacin.

[a] Scores on OAB-q symptom bother scale range from 0 to 100 (worst severity) with a negative change indicating improvement.

[b] Calculated by CADTH using Review Manager.

[c] Scores on OAB-q HRQoL scale range from 0 to 100 (best HRQoL) with a positive change indicating improvement.

[d] PPBC is a six-point Likert scale from 1 = no problems at all, to 6 = many severe problems. A negative change indicates improvement.

Source: Clinical Study Report,[32] Abrams et al. 2014.[22]

TABLE 23: PATIENT PERCEPTION OF BLADDER CONDITION — PLACEBO- AND TOLTERODINE-CONTROLLED TRIALS

Study	Treatment			
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**TOL 4 mg**
PPBC[a]				
SCORPIO	**N = 433**		**N = 416**	**N = 426**
Baseline (SE)	4.3 (0.05)		4.1 (0.05)	4.3 (0.05)
Adjusted mean change from baseline (SE)	–0.8 (0.05)		–1.0 (0.06)	–1.0 (0.06)
MD (95% CI), *P* value versus placebo	ref		–0.2 (–0.3 to –0.0), *P* = 0.045	–0.2 (–0.3 to –0.0), *P* = 0.023
MD (95% CI), *P* value versus TOL[b]	–		0 (–0.2 to 0.2), *P* = NS	ref
TAURUS			**N = 655**	**N = 673**
Baseline (SE)			3.9 (0.04)	3.8 (0.04)
Adjusted mean change from baseline (SE)			–0.8 (0.04)	–0.8 (0.04)
MD (95% CI), *P* value versus TOL[b]			0 (–0.1 to 0.1), *P* = NS	ref
ARIES	**N = 392**		**N = 388**	
Baseline (SE)	3.8 (0.05)		3.8 (0.05)	
Adjusted mean change from baseline (SE)	–0.5 (0.06)		–0.7 (0.05)	
MD (95% CI), *P* value versus placebo	ref		–0.2 (–0.3 to –0.0), *P* = 0.032	
CAPRICORN	**N = 376**	**N = 391**	**N = 395**	
Baseline (SE)	4.0 (0.05)	4.0 (0.05)	4.0 (0.05)	
Adjusted mean change from baseline (SE)	–0.7 (0.06)	–0.8 (0.06)	–0.7 (0.06)	
MD (95% CI), *P* value versus placebo	ref	–0.1 (–0.2 to 0.1), *P* = 0.49	–0.0 (–0.2 to 0.1), *P* = 0.64	

CI = confidence interval; MD = mean difference; MIR = mirabegron; NS = not statistically significant; PPBC = Patient Perception of Bladder Condition questionnaire; ref = reference group; SE = standard error; TOL = tolterodine.

[a] PPBC is a six-point Likert scale from 1 = no problems at all, to 6 = many severe problems. A negative change indicates improvement.

[b] Calculated by CADTH using Review Manager.

Source: Clinical Study Report,[27,30,34] Nitti et al. 2012,[20] Herschorn et al. 2013.[21]

TABLE 24: KING'S HEALTH QUESTIONNAIRE — PLACEBO- AND TOLTERODINE-CONTROLLED TRIALS

Study	Treatment			
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**TOL 4 mg**
KHQ — General Health Perception[a]				
Study 048	**N = 368**		**N = 365**	**N = 365**
Baseline (SD)	32.3 (18.5)		31.9 (17.8)	33.8 (17.9)
Mean change from baseline (SD)	–0.1 (20.1)		–2.2 (20.4)	–2.1 (20.4)
MD (95% CI), *P* value versus placebo[b]	ref		–2.1 (–5.0 to 0.8), *P* = NS	–2.0 (–4.9 to 0.9), *P* = NS
MD (95% CI), *P* value versus TOL[b]	–		–0.1 (–3.1 to 2.9), *P* = NS	ref
Study 090	**N = 302**		**N = 313**	**N = 311**
Baseline (SD)	43.1 (18.8)		45.2 (19.6)	45.5 (22.6)
Mean change from baseline (SD)	–3.8 (21.2)		–6.1 (22.6)	–4.8 (22.6)
Adjusted MD (95% CI), *P* value versus placebo	ref		–1.03 (–3.97 to 1.90), *P* = 0.49	0.32 (–2.63 to 3.26), *P* = 0.83
Adjusted MD (95% CI), *P* value versus TOL	–		–1.35 (–4.26 to 1.56), *P* = 0.36	ref
KHQ — Incontinence Impact[a]				
Study 048	**N = 368**		**N = 365**	**N = 365**
Baseline (SD)	49.1 (27.6)		47.8 (26.8)	49.5 (26.3)
Mean change from baseline (SD)	–6.7 (28.8)		–13.9 (28.3)	–11.0 (28.0)
MD (95% CI), *P* value versus placebo[b]	ref		–7.2 (–11.3 to –3.1), *P* < 0.05	–4.3 (–8.4 to –0.2), *P* < 0.05
MD (95% CI), *P* value versus TOL[b]	–		–2.9 (–7.0 to 1.2), *P* = NS	ref
Study 090	**N = 302**		**N = 313**	**N = 311**
Baseline (SD)	67.2 (28.2)		68.5 (28.6)	71.4 (26.6)
Mean change from baseline (SD)	–13.0 (29.1)		–11.5 (27.5)	–16.5 (31.8)
Adjusted MD (95% CI), *P* value versus placebo	ref		1.75 (–2.46 to 5.96), *P* = 0.41	–1.86 (–6.08 to 2.36), *P* = 0.39
Adjusted MD (95% CI), *P* value versus TOL	–		3.61 (–0.57 to 7.79), *P* = 0.09	ref

CI = confidence interval; KHQ = King's Health Questionnaire; MD = mean difference; MIR = mirabegron; NS = not statistically significant; ref = reference group; SD = standard deviation; TOL = tolterodine.

[a] Scores on KHQ scale range from 0 to 100 (worst severity) with a negative change indicating improvement.

[b] Calculated by CADTH using Review Manager.

Source: Clinical Study Report.[28,29]

TABLE 25: OTHER HRQOL OUTCOMES — PLACEBO- AND TOLTERODINE-CONTROLLED TRIALS

Study	Treatment			
Outcome	Placebo	MIR 25 mg	MIR 50 mg	TOL 4 mg
ICIQ-OAB-qol[a]				
DRAGON	**N = 162**	**N = 163**	**N = 165**	**N = 84**
Baseline (SD)	79.6 (23.6)	79.1 (24.4)	79.9 (23.8)	82.8 (26.5)
Adjusted mean change from baseline (SE)	–16.1 (NR)	–17.1 (NR)	–20.3 (NR)	–17.4 (NR)
MD (95% CI), *P* value versus placebo	ref	–0.98 (–5.88 to 3.92), *P* = 0.69	–4.25 (–9.13 to 0.62), *P* = 0.09	–1.32 (–7.32 to 4.69), *P* = 0.67
MD (95% CI), *P* value versus TOL	–	0.32 (–5.64 to 6.29,) *P* = 0.92	–2.91 (–8.88 to 3.07), *P* = 0.34	ref
ICIQ-OAB[b]				
DRAGON	**N = 166**	**N = 167**	**N = 166**	**N = 85**
Baseline (SD)	8.8 (2.3)	8.7 (2.3)	8.9 (2.3)	NR
Adjusted mean change from baseline (SE)	–1.82 (NR)	–2.40 (NR)	–2.51 (NR)	–2.21 (NR)
MD (95% CI), *P* value versus placebo	ref	–0.58 (–1.13 to –0.02), *P* = 0.04	–0.69 (–1.24 to –0.13), *P* = 0.015	–0.37 (–1.05 to 0.31),*P* = 0.29
MD (95% CI), *P* value versus TOL	–	–0.24 (–0.88 to 0.47), *P* = 0.55	–0.32 (–1.00 to 0.36), *P* = 0.35	ref

CI = confidence interval; ICIQ = international Consultation on Incontinence Questionnaire; MD = mean difference; MIR = mirabegron; NR = not reported; OAB = overactive bladder; qol = quality of life; SD = standard deviation; SE = standard error; TOL = tolterodine.

[a] ICIQ-OAB-qol is an OAB-specific quality of life tool scored from 25 to 160 with greater values indicating increased impact on quality of life. Negative change indicates improvement.

[b] ICIQ-OAB is an OAB-specific symptom impact tool scored from 0 to 16 with greater values indicating increased symptom severity. Negative change indicates improvement.

Source: Clinical Study Report,[35] Chapple 2012.[18]

TABLE 26: INCONTINENCE AND MICTURITION FREQUENCY — SUBGROUP DATA BY PRIOR TREATMENT FOR OAB

Study	Treatment			
Outcome	**Placebo**	**MIR 25 mg**	**MIR 50 mg**	**TOL 4 mg**
Mean Incontinence Episodes/24 Hours				
SCORPIO Previous OAB Therapy	**N = 167**		**N = 164**	**N = 160**
Baseline (SE)	2.97 (0.20)		3.31 (0.24)	2.86 (0.21)
Adjusted mean change from baseline (SE)	–1.00 (0.15)		–1.48 (0.15)	–1.10 (0.15)
MD (95% CI), *P* value versus placebo	ref		–0.48 (–0.90 to –0.06), *P* < 0.05	–0.10 (–0.52 to 0.32), *P* = NS
MD (95% CI), *P* value versus TOL[a]	–		–0.38 (–0.80 to 0.04), *P* = 0.08	ref
SCORPIO No Previous OAB Therapy	**N = 124**		**N = 129**	**N = 140**
Baseline (SE)	2.28 (0.19)		2.22 (0.20)	2.38 (0.20)
Adjusted mean change from baseline (SE)	−1.39 (0.17)		−1.69 (0.17)	−1.47 (0.16)
MD (95% CI), *P* value versus placebo	ref		−0.29 (−0.77 to 0.18), *P* = NS	−0.08 (−0.55 to 0.39), *P* = NS
MD (95% CI), *P* value versus TOL[a]	–		–0.22 (–0.68 to 0.24), *P* = 0.35	ref
Treatment by subgroup interaction: all treatments versus placebo *P* = 0.84; mirabegron 50 mg versus tolterodine *P* = 0.62[a]				
Mean Micturitions/24 Hours				
SCORPIO Previous OAB Therapy	**N = 238**		**N = 240**	**N = 231**
Baseline (SE)	11.90 (0.20)		11.85 (0.20)	11.76 (0.20)
Adjusted mean change from baseline (SE)	–1.06 (0.16)		–1.74 (0.16)	–1.26 (0.16)
MD (95% CI), *P* value versus placebo	ref		–0.68 (–1.12 to –0.25), *P* < 0.05	–0.20 (–0.64 to 0.23), *P* = NS
MD (95% CI), *P* value versus TOL[a]	–		–0.48 (–0.91 to –0.05), *P* = 0.03	ref
SCORPIO No Previous OAB Therapy	**N = 242**		**N = 233**	**N = 244**
Baseline (SE)	11.53 (0.21)		11.44 (0.18)	11.35 (0.16)
Adjusted mean change from baseline (SE)	−1.61 (0.16)		−2.13 (0.16)	−1.90 (0.15)
MD (95% CI), *P* value versus placebo	ref		−0.52 (−0.95 to –0.09), *P* < 0.05	−0.29 (−0.71 to 0.14), *P* = NS
MD (95% CI), *P* value versus TOL[a]	–		–0.23 (–0.66 to 0.20), *P* = 0.30	ref
Treatment by subgroup interaction: all treatments versus placebo *P* = 0.84; mirabegron 50 mg versus tolterodine *P* = 0.42[a]				

CI = confidence interval; MD = mean difference; MIR = mirabegron; NS = not statistically significant; ref = reference group; SE = standard error; TOL = tolterodine.

[a] Calculated by CADTH using Review Manager; negative values indicate patients in the MIR group had fewer episodes than TOL.

Source: Kullar et al.,[36] Manufacturer's submission (Module 2.7.3).[23]

TABLE 27: DESCRIPTION OF DEATHS, SERIOUS ADVERSE EVENTS, AND WITHDRAWAL DUE TO ADVERSE EVENTS

Study	AE	Placebo	MIR 25 mg	MIR 50 mg	TOL	SOL	MIR + SOL
SCORPIO[a]	Death				Cerebral aneurysm (1)		
	WDAE	Nausea (2), chest pain (2), viral infection (2)		Tachycardia (2), hypertensive crisis (2)	Fatigue (3), headache (2), urinary retention (3)		
Study 048[a]	WDAE			Rash (2)	Dry mouth (3), malaise (2)		
Study 090[a]	Death	Sudden death (1)					
	WDAE	Abdominal pain (2)		Erectile dysfunction (2)	Dry mouth (2)		
DRAGON[a]	WDAE	Abdominal pain (1), dizziness (1), nausea or vomiting (1)	Abdominal pain (3), nausea or vomiting (1)	Abdominal pain (1), dizziness (1), nausea or vomiting (2)	Nausea or vomiting (1)		
TAURUS	Deaths			Suicide (1), cardiac failure (1), pneumonia/sepsis/ organ failure (1)	Coronary artery disease (1), cerebrovascular accident/aspiration pneumonia (1)		
	SAE			Atrial fibrillation (2), osteoarthritis (2), cerebrovascular accident (3)	Breast cancer (2), atrial fibrillation (3), myocardial infarction (2), angina (2), cholelithiasis (2)		
	WDAE			Constipation (7), nausea (3), dry mouth (3), gastritis (2), headache (5), dizziness (4), pain (2), blurred vision (3), dry eye (3), UTI (3), hypertension (4)	Dry mouth (4), abdominal pain (3), headache (3), MI (2), angina (2), atrial fibrillation (2), hypertension (3)		
ARIES	Death	Cardiac arrest (1)			–		
	SAE			Prostate cancer (2)	–		
	WDAE	Nausea (3), hypertension (1), dyspnea (2)		Diarrhea (3), hypertension (2)			

Study	AE	Placebo	MIR 25 mg	MIR 50 mg	TOL	SOL	MIR + SOL
CAPRICORN	SAE	Cerebrovascular accident (2)					
	WDAE	Constipation (1), nausea (3), vomiting (2), headache (4), vertigo (2)	Constipation (1), nausea (1), hypertension (2)	Constipation (2), nausea (1), vomiting (1), headache (3)			
BEYOND	SAE			[redacted]	[redacted]		
	WDAE			[redacted]	[redacted]		
SYMPHONY[a]	WDAE						QT prolongation (3), fatigue (2)

AE = adverse event; MI = myocardial infarction; MIR = mirabegron; SAE = serious adverse event; SOL = solifenacin; TOL = tolterodine; UTI = urinary tract infection; WDAE = withdrawal due to adverse event.

[a] SAE or WDAE were listed in the table if reported in two or more patients in a treatment group. No SAE occurred in more than one patient per treatment group in study SCORPIO, DRAGON, 048, 090, or SYMPHONY.

Note: No deaths occurred in study 048, 074, DRAGON, CAPRICORN, SYMPHONY, or BEYOND.

Source: Clinical Study Report,[27–30,35] Nitti et al. 2012,[20] Herschorn et al. 2013.[21]

APPENDIX 4: EXCLUDED STUDIES

Reference	Reason for Exclusion
Otsuki H, et al. Int Urol Nephrol. 2013 Feb;45(1):53-60.	Not an RCT
Pavesi M, et al. J Med Econ. 2013 May 6;16(7):866-76.	Not an RCT
Kaplan SA. J Urol. 2014 May;191(5):1344-6.	Not an RCT
Wein AJ. J Urol. 2013 Jun;189(6):2204-5.	Not an RCT

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

The Overactive Bladder Questionnaire (OAB-q), Patient Perception of Bladder Condition (PPBC), and the King's Health Questionnaire (KHQ) are commonly used instruments in clinical trials of patients with OAB.[14] The aim of this document is to summarize the validity and the minimal clinically important difference (MCID) for the OAB-q, PPBC, and KHQ in patients with OAB.

Findings

Instrument	Scale Type	Validation (Yes/No)	MCID	References
OAB-q	0–100 point scale for each domain (Symptom bother and HRQoL)	Yes	10 points	Coyne et al.(2000)[43] Coyne et al. (2002)[44] Coyne et al.(2006)[39] Coyne et al.(2008)[45]
PPBC	6-point Likert scale	Yes	Unknown	Coyne et al. (2006)[38] Coyne et al.(2008)[45]
KHQ	0–100 point scale	Yes	5 points	Kelleher et al.(1997)[46] Margolis el al.(2011)[47] Reese et al. (2003)[48] Van Kerrebroeck et al. (2009)[49]

HRQoL = health-related quality of life; KHQ = King's Health Questionnaire; OAB-q = Overactive Bladder Questionnaire; PPBC = Patient Perception of Bladder Condition.

1. OAB-q

The OAB-q is a 33-item, self-administered questionnaire contains a symptom bother subscale (7-item scale) and a Health-Related Quality of Life (HRQoL) subscale (25-item scale).[43,44] The symptom bother scale includes the frequency of urgency, nocturia, and incontinence symptoms. The HRQoL scale has four domains that address coping, concern, sleep, and social interaction. Symptom and HRQoL items are scored using six-point Likert scales ranging from 1 = "not at all" to 6 = "a very great deal" for the symptom bother items and 1 = "none of the time" to 6 = "all of the time" for the HRQoL items. The score for each of OAB-q domain are summed and transformed to a score ranging from zero to 100.[45] Higher scores indicate more severe symptoms or better quality of life.[44,45]

OAB-q was developed from focus groups in 2000[43] and validated by Coyne et al. in 2002.[44] In the validation study, both the OAB-q and the Short Form (36) Health Survey (SF-36) were completed by two groups of participants: normal participants and patients with OAB. The author concluded that the OAB-q is a reliable and valid instrument that discriminates between normal and clinically diagnosed continent and incontinent OAB patients. The OAB-q demonstrated that both continent and incontinent OAB symptoms caused significant symptom bother and had a negative impact on HRQoL. In another post hoc analysis, Coyne et al.[45] found that tolterodine-related improvements in all bladder diary variables were significantly correlated with improvements in OAB-q symptom bother ($r = 0.30$ to 0.51, $P < 0.001$) and all OAB-q HRQoL domains ($r = 0.24$ to 0.42; $P < 0.001$).[45]

The minimal clinically important difference (MCID) of the OAB-q was evaluated by Coyne et al.[39] in a post hoc analysis using data from two clinical trials. The author used anchor and distribution-based methods to determine the MCID and from these analyses recommended a 10-point MCID for all OAB-q subscales. The results in two OAB patient samples were consistent. However, the author pointed out

that the generalizability of the MCID findings may be limited as a result of its post hoc nature and limited patient population, which included some participants without an OAB diagnosis.[39]

2. PPBC

The PPBC is a single item that assesses the patients' subjective impression of their current urinary problems.[38] Patients are asked to rate their perceived bladder condition on a six-point scale ranging from 1 = "no problems at all'' to 6 = "many severe problems." In trials of OAB drugs, the change from baseline score typically ranges from –2 to 2, with negative values indicating patient improvement. The PPBC has demonstrated test-retest reliability among a small sample of patients with OAB.[50] Coyne et al.[38] studied the validity of PPBC based on a post hoc analysis of two 12-week clinical studies in patients with OAB. They observed that patients with major improvements according to PPBC had significantly greater reductions in frequency, urgency episodes, incontinence episodes, and symptom bother as well as significantly greater improvements in HRQoL than patients with only minor improvements. The authors concluded that the PPBC, a global patient-reported measure of bladder condition, demonstrated good construct validity and responsiveness to change.[38] Moderate in magnitude but statistically significant correlations between PPBC and patient-reported OAB symptoms such as urgency incontinence episodes were also observed in patients after 12 weeks of treatment with tolterodine (r = 0.26 to 0.36, $P < 0.001$).[45] No MCID for PPBC was identified.

3. KHQ

The standard version of KHQ is a 21-item disease-specific questionnaire that has been developed and validated for participants with urinary incontinence.[46] The KHQ consists of nine domains: general health perceptions, impact on life, role limitations, physical limitations, social limitations, personal relationships, emotions, sleep/energy, and incontinence severity measures. Item scores are converted to a standardized scale. Scores for the KHQ range from 0 to 100, where 0 indicates the best outcome or response and 100 indicates the worst outcome or response.[46]

KHQ was validated in a study of 24 patients with OAB[47] in the United States, and Reese et al.[48] evaluated the psychometric properties of the KHQ in 1,284 patients with OAB. Reese et al. concluded that psychometric testing supports the reliability and validity of the KHQ as an OAB-specific measure of HRQoL.[48] Statistically significant correlations between KHQ and patient-reported OAB symptoms such as urgency incontinence episodes (median percentage change) were also observed in patients after 12 weeks of treatment with tolterodine ($r = 0.16–0.32$, $P \leq 0.0011$).[49] An MCID of five points has been reported for each domain of the KHQ in patients with overactive bladder.[40,41]

Summary

The OAB-q, PPBC, and KHQ are validated and widely used instruments in the study of OAB. However, the evidence of their validity showed a weak to moderate correlation between these instruments and patient-reported symptoms (r = 0.16 to 0.42) in clinical trials. The reported MCID for OAB-q (symptom bother or HRQoL subscale) was 10 points. Nevertheless, it is unclear to what extent this MCID is generalizable to all patients with OAB. No MCID was identified for PPBC or KHQ.

APPENDIX 6: SUMMARY OF COMPARATORS

Aims

The available antimuscarinic (or anticholinergic) drugs for the treatment of overactive bladder (OAB) in Canada include oxybutynin, tolterodine, trospium chloride, darifenacin, solifenacin, and fesoterodine.[9] Among them, oxybutynin and tolterodine are the most widely prescribed.[14] This summary provides a comparative overview of efficacy and safety of antimuscarinic drugs for patients with OAB.

Findings

A supplemental search was completed using the PubMed database. The search conducted compared the drug mirabegron with other drug names including tolterodine, trospium chloride, darifenacin, solifenacin, oxybutynin, and fesoterodine. Methodological filters were applied to limit the retrieval to systematic reviews only and searched the time period 2008–2013. After screening the literature search result, three systematic reviews[14,51,52] comparing the efficacy and safety of different antimuscarinic drugs in the treatment of patients with OAB were identified. Of the three, the systematic review by Madhuvrata et al.[14] was considered the most comprehensive one in terms of drugs studied and outcomes reported, with the highest methodological quality based on the quality assessment by AMSTAR,[53] and was the most recently published (in 2012). Therefore, this document mainly summarized the findings reported by Madhuvrata et al.[14] on the comparative efficacy and safety of antimuscarinic drugs for patients with OAB.

In 2012, Madhuvrata et al.[14] published a systematic review comparing the efficacy and safety of antimuscarinics (including oxybutynin, tolterodine, trospium chloride, darifenacin, solifenacin, and fesoterodine) for OAB from head-to-head RCTs or quasi-RCTs. Other antimuscarinic drugs, such as propantheline bromide, propiverine, and imidafenacin were also included in the systematic review; however, those data are not reported in this document because these drugs are not marketed in Canada. The primary outcome of the systematic review was quality of life (QoL). Secondary outcomes included the number of incontinence episodes, urgency episodes, micturitions per 24 hours, adverse events, and withdrawals due to adverse events (WDAEs). Study-level QoL data measured by OAB-specific QoL instruments (such as the KHQ, OAB-q, and PPBC) were pooled together as condition-specific QoL outcome. Key results for oxybutynin, tolterodine, trospium chloride, darifenacin, solifenacin, and fesoterodine are presented in Table 28 and Table 29. No statistically significant differences were reported between tolterodine and oxybutynin in terms of QoL, incontinence frequency, or micturitions. Compared with tolterodine, solifenacin or fesoterodine showed a statistically significant greater improvement in terms of QoL, frequency of incontinence, and urgency episodes (Table 28).

TABLE 28: COMPARATIVE EFFICACY BETWEEN ANTIMUSCARINIC DRUGS[A]

Comparisons	Outcome	Number of Studies	Number of Patients	MD (95%CI)[b]
TOL versus OXY	QoL[c]	2	480	SMD: 0.00 (–0.18 to 0.18)
	Incontinence/24 hours	7	1,374	0.08 (–0.16 to 0.31)
	Micturitions/24 hours	7	1,749	–0.12 (–0.40 to 0.15)
TRO versus OXY	Incontinence/24 hours	1	1,572	–0.10 (–0.32 to 0.12)
	micturitions/24 hours	1	1,488	0.10 (–0.14 to 0.34)
SOL versus TOL	QoL[c]	3	1,293	SMD: –0.12 (–0.23 to –0.01)
	Incontinence/24 hours	4	1,300	–0.30 (–0.53 to –0.08)
	Micturitions/24 hours	4	1,858	–0.23 (–0.49, 0.02)
	Urgency episodes/24 hours	4	1,979	–0.43 (–0.74 to –0.13)
FES versus TOL	QoL[c]	3	3,492	SMD: –0.20 (–0.27 to –0.14)
	Incontinence/24 hours	3	3,525	–0.19 (–0.30 to –0.09)
	Micturitions/24 hours	3	3,672	–0.27 (–0.47 to –0.06)
	Urgency episodes/24 hours	3	3,666	–0.44 (–0.72 to –0.16)

CI = conference interval; FES = fesoterodine; MD = mean difference; OXY = oxybutynin; QoL = quality of life; SMD = standard mean difference; SOL = solifenacin; TOL = tolterodine; TRO = trospium chloride.
[a] Other antimuscarinic drugs, such as propantheline bromide, propiverine, and imidafenacin were also included in the systematic review; however, those data are not presented in this document because they are not marketed in Canada.
[b] Data were pooled from the between-group difference of changes from baseline or between-group difference at the end of the treatment.
[c] Reported as condition-specific QoL.

Regarding adverse events, those who received tolterodine reported a lower incidence of dry mouth and fewer WDAEs compared with those who received oxybutynin. Patients taking fesoterodine experienced a higher rate of WDAEs and dry mouth compared with those taking tolterodine. No statistically significant difference was observed between solifenacin and tolterodine in terms of WDAEs and dry mouth (Table 29).

TABLE 29: RELATIVE RISK OF AES AND WDAES BETWEEN ANTIMUSCARINIC DRUGS

Comparisons	Outcome	Number of Studies	Number of Patients	RR (95%CI)
TOL versus OXY	WDAE	8	2,686	0.52 (0.40 to 0.66)
	Dry mouth	10	3,140	0.65 (0.60 to 0.71)
TRO versus OXY	WDAE	3	2,110	0.66 (0.48 to 0.91)
SOL versus OXY	WDAE	1	132	0.45 (0.22 to 0.91)
	Dry mouth	1	132	0.43 (0.30 to 0.60)
SOL versus TOL	WDAE	5	2,127	1.37 (0.84 to 2.23)
	Dry mouth	5	2,127	1.04 (0.89 to 1.22)
FES versus TOL	WDAE	3	3,876	1.45 (1.07 to 1.98)
	Dry mouth	3	3,858	1.80 (1.58 to 2.05)

AE = adverse event; CI = conference interval; FES = fesoterodine; OXY = oxybutynin; RR = relative risk; SOL = solifenacin; TOL = tolterodine; TRO = trospium chloride; WDAE = withdrawal due to adverse event.

The systematic review by Madhuvrata et al.[14] was well conducted methodologically. However, when interpreting the effectiveness and safety of one drug compared with another, several limitations should be considered:

- None of the included trials reported subgroup analysis for patients with or without urgency urinary incontinence.
- Various methods of drug delivery (that is, oral, transdermal, immediate-release, and extended-release preparations) and different drug doses were used in different included studies.
- Allocation concealment was rarely described.
- Between-group differences in the changes from baseline were combined with the between-group differences at the end of treatment.
- The trial duration of the majority of included studies was 12 weeks or less.
- Different OAB-specific QoL scales were used in the included studies.

No subgroup QoL data were analyzed based on different OAB-specific QoL scales (e.g., OAB-q).

In addition to the systematic review by Madhuvrata et al.,[14] Novara et al.[51] evaluated the efficacy and safety of different doses, formulations, and routes of administration of the available anticholinergic drugs, including oxybutynin, tolterodine, solifenacin, and darifenacin in 2008. The authors concluded that more clinical studies are needed to indicate which of the drugs should be used as first, second, or third-line treatment.[51] In a systematic review, Chapple et al.[52] reported that antimuscarinic drugs (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium chloride) are more effective than placebo. They suggested that profiles of each drug and dosage differ and should be considered in making treatment choices.[52]

Summary

The available evidence suggests that there is no statistically significant difference in terms of QoL, frequency of incontinence, and micturition between tolterodine and oxybutynin. Compared with tolterodine, both solifenacin and fesoterodine showed statistically greater improvements in QoL and decreased frequency of incontinence and urgency episodes. Tolterodine therapy was associated with statistically significant fewer AEs and WDAEs than oxybutynin treatment. However, these findings need to be interpreted with caution because of various potential heterogeneities in the body of evidence. The clinical importance of the differences observed between drugs is unclear.

APPENDIX 7: CRITICAL APPRAISAL OF INDIRECT TREATMENT COMPARISON

This supplemental issue provides a summary and appraisal of a systematic review and network meta-analysis (NMA) of pharmacologic treatments for overactive bladder (OAB) by Maman et al.[1]

Rationale

There is a need to assess the comparative efficacy and safety of mirabegron versus existing treatments for OAB. Limited head-to-head evidence is available; thus, the authors conducted an NMA that incorporated existing evidence for the most widely used drugs for OAB.

Methods

Eligibility Criteria

The systematic review included full text of randomized controlled trials (RCTs) of pharmacologic treatments for OAB, detrusor overactivity, or urinary urgency that were published in 2000 or later. No language restrictions were applied. Studies of patients with neurogenic detrusor overactivity or men with lower urinary tract symptoms associated with benign prostatic hyperplasia were excluded.

Interventions and Comparators

The following oral drugs were included in the systematic review: placebo, mirabegron (50 mg daily), darifenacin (7.5 mg, 15 mg), fesoterodine (4 mg, 8 mg), oxybutynin (extended-release [ER] 5 mg, 10 mg or 15 mg; immediate-release [IR] 10 mg, 15 mg), solifenacin (5 mg, 10 mg), tolterodine (ER 4 mg, IR 4 mg), or trospium chloride (40 mg, 60 mg). Although no justification was provided for the dosages included in the review, they appear to be consistent with Health Canada–approved doses. The mirabegron 25 mg dose was excluded.

The intervention group could have received an anticholinergic drug or mirabegron 50 mg, and the control group could have received an anticholinergic drug (different drug, formulation, or dose) or placebo.

Outcomes

The outcomes of interest included the change over 8 to 16 weeks in number of micturitions, incontinence or urgency incontinence episodes per 24 hours. Safety outcomes included dry mouth, constipation, or blurred vision assessed over 4 to 16 weeks.

Analysis

Fixed and random effects Bayesian hierarchical models were used to combine direct and indirect evidence (WinBUGS v1.4):

- Separate analyses were conducted for the general OAB population and incontinent subgroup.
- There were vague priors.
- Data on change from baseline were assumed to follow a normal distribution and reported as mean values plus 95% credible intervals (CrIs): adverse events followed a binomial distribution with outcomes reported as odds ratios (95% CrI).
- Model fit was assessed by the deviance information criterion.
- The probability of each treatment being more effective than mirabegron was calculated for different superiority margins (0, 0.5, and 1 episode per day).

Results

Study and Patient Characteristics

A total of 44 RCTs that enrolled 27,309 patients met the inclusion criteria. Most trials were placebo-controlled (77%). The active drugs evaluated included tolterodine 4 mg ER (16 trials), tolterodine 4 mg IR (7), solifenacin 5 mg (6), solifenacin 10 mg (5), mirabegron 50 mg (6), fesoterodine 4 mg (4), fesoterodine 8 mg (4), and oxybutynin 10 mg ER (4). Other drugs included were darifenacin (4 trials), oxybutynin IR (6), and trospium chloride (3).

None of the RCTs were rated as high risk of bias, and all were included in the NMA.

Results of the Network Meta-analysis

All analyses were conducted using fixed effects models except for dry mouth, which used a random effects model because of heterogeneity between studies.

Mirabegron 50 mg daily was more effective than placebo in reducing the number of micturitions and of incontinence and urgency incontinence episodes per 24 hours (Table 30). Patients who received mirabegron 50 mg had on average 0.7, 0.5, and 0.4 fewer micturitions, incontinence, or urgency incontinence episodes per day, respectively, compared with placebo. No significant differences were observed between mirabegron 50 mg and the other OAB treatments except for solifenacin 10 mg daily. Solifenacin 10 mg was more effective than mirabegron 50 mg daily in reducing the number of micturitions (mean difference [MD] –0.58 episodes per 24 hours; 95% CrI, –0.84 to –0.33) and urgency incontinence episodes per 24 hours (MD –0.42; 95% CrI, –0.79 to –0.06).

TABLE 30: ESTIMATE OF THE EFFECT OF COMPARATOR TREATMENTS ON MICTURITION, INCONTINENCE, AND URGENCY INCONTINENCE FREQUENCY VERSUS MIRABEGRON 50 MG

Comparator (Daily Dose)	Mean Difference (95% CrI) Versus Mirabegron 50 mg		
	Micturitions / 24 Hours[a]	Incontinence Episodes/ 24 Hours[a]	Urgency Incontinence Episodes/24 Hours[a]
Included studies	26 RCTs, N = 22,040	17 RCTs, N = 13,101	18 RCTs, N = 16,044
Tolterodine 4 mg	0.16 (–0.00 to 0.32)	0.09 (–0.06 to 0.23)	0.09 (–0.12 to 0.31)
Darifenacin 7.5 mg	0.07 (–0.41 to 0.55)	0.29 (–0.20 to 0.79)	NA
Darifenacin 15 mg	0.07 (–0.26 to 0.39)	0.13 (–0.27 to 0.54)	0.04 (–0.49 to 0.57)
Fesoterodine 4 mg	0.14 (–0.16 to 0.44)	0.10 (–0.38 to 0.59)	–0.04 (–0.38 to 0.30)
Fesoterodine 8 mg	–0.05 (–0.25 to 0.15)	0.22 (–0.28 to 0.73)	–0.22 (–0.53 to 0.05)
Oxybutynin 10 mg	0.14 (–0.53 to 0.81)	0.14 (–0.40 to 0.68)	–0.28 (–0.95 to 0.39)
Placebo	**0.70 (0.55 to 0.84)**	**0.49 (0.37 to 0.62)**	**0.44 (0.26 to 0.62)**
Solifenacin 5 mg	–0.24 (–0.50 to 0.01)	–0.23 (–0.48 to 0.01)	–0.29 (–0.64 to 0.06)
Solifenacin 10 mg	**–0.58 (–0.84 to –0.33)**	–0.24 (–0.49, 0.01)	**–0.42 (–0.79, –0.06)**
Trospium chloride 60 mg	–0.13 (–0.58 to 0.33)	NA	–0.11 (–0.71 to 0.49)

CrI = credible interval; NA = not available; RCT = randomized controlled trial.
[a] Fixed effects model; results in which the 95% CrI does not include the null value are in bold.

No statistically significant differences were detected between mirabegron 50 mg and placebo for the frequency of dry mouth, constipation, or blurred vision (Table 31). The incidence of dry mouth was statistically significantly higher for all anticholinergic OAB drugs compared with mirabegron 50 mg daily. In addition, darifenacin 15 mg, fesoterodine 8 mg, solifenacin 5 mg and 10 mg, and trospium 60 mg

were associated with a statistically significantly higher incidence of constipation versus mirabegron 50 mg. No statistically significant differences were found between anticholinergic OAB medications and mirabegron 50 mg with regard to blurred vision.

TABLE 31: ESTIMATE OF THE EFFECT OF COMPARATOR TREATMENTS ON THE INCIDENCE OF DRY MOUTH, CONSTIPATION OR BLURRED VISION VERSUS MIRABEGRON 50 MG

Comparator (Daily Dose)	OR (95% CrI) Versus Mirabegron 50 mg		
	Dry Mouth[a]	Constipation[b]	Blurred Vision[b]
Included studies	44 RCTs, N = 27,309	41 RCTs, N = 25,257	25 RCTs, N = 14,348
Tolterodine ER 4 mg	**4.26 (2.74 to 6.39)**	1.11 (0.71 to 1.65)	1.44 (0.56 to 3.10)
Tolterodine IR 4 mg	**7.29 (4.37 to 11.64)**	1.02 (0.59, 1.65)	1.15 (0.38 to 2.70)
Darifenacin 7.5 mg	**5.20 (2.45 to 9.84)**	1.72 (0.80 to 3.23)	1.32 (0.23 to 4.36)
Darifenacin 15 mg	**8.38 (4.30 to 14.94)**	**3.15 (1.67 to 5.48)**	NA
Fesoterodine 4 mg	**4.57 (2.70 to 7.35)**	1.06 (0.58 to 1.80)	0.80 (0.04 to 3.72)
Fesoterodine 8 mg	**9.98 (6.13 to 15.44)**	**1.91 (1.14 to 3.03)**	0.73 (0.04 to 3.40)
Oxybutynin ER 5 mg	**4.22 (1.52 to 9.51)**	2.45 (0.42 to 8.65)	4.97 (0.05 to 28.12)
Oxybutynin ER 10 mg	**7.05 (3.89 to 11.96)**	1.01 (0.52 to 1.78)	2.60 (0.20 to 11.97)
Oxybutynin ER 15 mg	**8.16 (2.83 to 18.71)**	2.16 (0.27 to 8.28)	7.16 (0.02 to 41.81)
Oxybutynin IR 9 mg	**11.17 (5.62 to 20.21)**	0.99 (0.41 to 1.99)	0.42 (0.00 to 2.61)
Oxybutynin IR 10 mg	**14.63 (6.50 to 28.05)**	NA	NA
Oxybutynin IR 15 mg	**40.70 (15.21 to 91.59)**	1.55 (0.40 to 4.15)	2.47 (0.07 to 14.02)
Placebo	1.34 (0.86 to 2.00)	0.73 (0.48 to 1.07)	5.27 (0.91 to 18.36)
Solifenacin 5 mg	**4.21 (2.43 to 6.90)**	**2.38 (1.35 to 3.91)**	1.94 (0.67 to 4.48)
Solifenacin 10 mg	**10.30 (6.01 to 16.64)**	**4.24 (2.47 to 6.86)**	0.79 (0.30 to 1.71)
Trospium chloride 40 mg	**5.97 (3.00 to 10.79)**	1.69 (0.88 to 2.98)	0.75 (0.24 to 1.82)
Trospium chloride 60 mg	**4.85 (1.66 to 11.59)**	**7.60 (2.08 to 22.66)**	2.42 (0.15 to 11.79)

CrI = credible interval; ER = extended-release; IR = immediate-release; NA = not available; OR = odds ratio; RCT = randomized controlled trial.
[a] Random effects model.
[b] Fixed effects model; results in which the 95% CrI does not include the null value are in bold.

Critical Appraisal of Network Meta-analysis

The quality of the NMA was assessed according to the recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[54,55] Details and commentary for each of the relevant items identified by ISPOR are provided in Table 32.

The study was funded by Astellas.

Strengths

The methods used to identify, select, and appraise the individual studies included in the report appear to be robust. The authors used Bayesian NMA methods for this mixed-treatment comparison.

TABLE 32: APPRAISAL OF NETWORK META-ANALYSIS USING ISPOR CRITERIA

ISPOR Checklist Item[54,55]	Details and Comments
1. Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting an NMA and the study objectives were clearly stated.
2. Does the methods section include the following? • eligibility criteria • information sources • search strategy • study selection process • data extraction • validity/quality assessment of individual studies	• Eligibility criteria of RCTs were clear and focused. • Literature search included multiple databases, reference lists, and information from manufacturers. • Detailed search strategy was provided. • Study selection and validity assessment were done independently by two researchers. No description of data extraction methods. • Outcomes extracted from the included studies are clearly described. • Validity/quality assessment of the included studies was completed as per National Institute for Health and Care Excellence (NICE) recommendations.
3. Are the outcome measures described?	• The outcomes of interest are described and included efficacy and harms; however, harms were limited to specific anticholinergic side effects (dry mouth, constipation, and blurred vision). No examination of adverse events associated with mirabegron or the incidence of SAEs was undertaken.
4. Is there a description of methods for analysis/synthesis of evidence? • description of analyses methods/models • handling of potential bias/inconsistency • analysis framework	• A description of the Bayesian NMA statistical methods was provided for continuous and dichotomous outcomes. Rationale for methods used was listed. WinBUGS code was reported. ○ No attempts were made to examine possible effect modifiers or to assess consistency. ○ Not all placebo-controlled studies were included in the NMA (except for RCTs that included mirabegron); thus, comparisons with placebo may be biased.
5. Are sensitivity analyses presented?	• No sensitivity analyses were presented. • Subgroup analysis for patients with incontinence at baseline was reported for the micturition frequency outcome only. In the mirabegron RCTs, incontinence and urgency incontinence outcomes are reported for the incontinence subgroup only (in the published report and US Food and Drug Administration documents); yet in the NMA, these data appear to be analyzed for the overall OAB population. Since the raw data from the included RCTs are not reported, it is not possible to verify which population data were included in the NMA for incontinence outcomes and whether the populations were comparable across studies.
6. Do the results include a summary of the studies included in the network of evidence? • individual study data? • network of studies?	• A table with study-level characteristics was provided; however, the table provided limited details on study and patient characteristics. Figures showing the network of studies for each outcome were provided. • No individual study outcome data were provided.
7. Does the study describe an assessment of model fit?	• Model fit was assessed by the DIC; however, DIC values were not reported.

ISPOR Checklist Item[54,55]	Details and Comments
8. Are the results of the evidence synthesis presented clearly?	• The NMA results are presented numerically and in figures for comparator treatments versus mirabegron 50 mg and include point estimates and 95% credible intervals. Results for all treatment comparisons are not reported. • Probability that treatment is better than mirabegron 50 mg is reported in the appendix.
9. Sensitivity/scenario analyses	• No sensitivity analyses or meta-regression models were conducted.
10. Does the discussion include the following? • description/summary of main findings • internal validity of analysis • external validity • implications of results for target audience	• The discussion included a summary of findings and internal validity, but was limited in terms of external validity and implications of findings.

DIC = deviance information criterion; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NMA = network meta-analysis; NICE = National Institute for Health and Care Excellence; RCT = randomized controlled trial; SAE = serious adverse event.

Limitations

This NMA has a number of limitations related to the study inclusion criteria and the reporting and conduct of the NMA. The review did not include all placebo-controlled trials for OAB drugs other than mirabegron; thus, comparisons versus placebo may be biased. It is unclear whether exclusion of some placebo-controlled trials may have impacted the strength of the network or the NMA results for the other treatment comparisons. The review also excluded studies published prior to 2000, which meant there were limited data for some of the older treatments (e.g., oxybutynin IR). Exclusion of older trials may, however, have reduced some heterogeneity as, according to Maman et al., the definition of OAB was not established until 2001, and in studies published prior to 2000, most patients would be treatment-naive. The mirabegron 25 mg dose was excluded; the analysis included only mirabegron 50 mg, which is the Health Canada–approved maximum daily dose. This restriction of dosage compromised the generalizability of the findings to real-world practice.

The authors reported insufficient information on patient characteristics and outcomes from individual trials to allow the reader to assess heterogeneity across studies. The authors state that there were differences across studies in patients' OAB symptom severity and in the proportion that had been treated previously, but the authors did not provide these data from the trials. In addition, the study durations varied, ranging from 8 to 16 weeks for efficacy outcomes and from 4 to 16 weeks for harms. No sensitivity analyses or meta-regression analyses were conducted to assess potential heterogeneity across the studies. The authors indicated that it was not feasible to conduct a meta-regression as the measures of heterogeneity were not reported in a consistent way across the trials.

The report was also limited by incomplete reporting of the NMA results. The authors reported the results for placebo or anticholinergic drugs compared with mirabegron 50 mg only; comparisons between anticholinergic drugs were not reported. Furthermore, there was no assessment of consistency between direct and indirect evidence. Deviance information criterion values for fixed and random effects models were not reported.

Summary

Maman et al. conducted a systematic review and NMA of pharmacologic treatments for OAB. The review included 44 RCTs that enrolled 27,309 patients. Mirabegron 50 mg daily was reported to be more effective than placebo but less effective than solifenacin 10 mg daily in reducing the frequency of micturition or urgency incontinence episodes. On the other hand, mirabegron 50 mg daily was reportedly associated with less dry mouth than other anticholinergic drugs used to treat OAB symptoms. Given the limitations of the NMA, and the limited evidence for mirabegron from direct head-to-head active-controlled trials, the comparative efficacy and safety of mirabegron versus other OAB treatments is still subject to some uncertainty.

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