NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Mirabegron
for the treatment of
overactive bladder

Submitted by Astellas

Single technology appraisal (STA)

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Abbreviations

ß3-AR	beta-3 adrenoreceptor
ATC	Anatomical Therapeutic Chemical
AE	Adverse event
AESI	Adverse event of special interest
AFS	Autologous fascial slings
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BD	Twice daily
BMI	Body mass index
BNF	British National Formulary
BPH	Benign prostatic hyperplasia
bpm	Beats per minute
CCA	Cost-consequence analyses
CEA	Cost-effectiveness analyses
CEAC	Cost-effectiveness acceptability curve
CFB	Change from baseline
CG	Clinical guideline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
cm	Centimetre
CR	Controlled-release
CrI	Credible interval
CUA	Cost-utility analyses
DBP	Diastolic blood pressure
DIC	Deviance information criterion
DSA	Deterministic sensitivity analysis
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EQ-5D	European quality of life-5 dimensions

EMA	European Medicines Agency
EPAR	European public assessment report
EPIC	European Prospective Investigation into Cancer and Nutrition
EpiLUTS	Epidemiology of lower urinary tract symptoms
ER	Extended-release
EU	European Union
FAS	Full analysis set
FAS-I	Full analysis set – incontinence set
FDA	US Food and Drug Administration
FE	Fixed effects
GGT	Gamma glutamyl transferase
GP	General practitioner
hr	Hour
HRQoL	Health-related quality of life
HS	Health state
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost-utility ratio
ICS	International Continence Society
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
ITT-I	Intent-to-treat – incontinence set
IVRS	Interactive voice response system
Kg	Kilogram
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LS	Least squares
LUTS	Lower urinary tract symptoms
LY	Life year
LYG	Life year gained
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MID	Minimal important difference

m-ITT	Modified-intent-to-treat
mL	Millilitre
mm Hg	Millimetres of mercury
MMRM	Mixed model repeated measures
Mo	Month
MR	Modified-release
MTC	Mixed treatment comparison
N/A	Not applicable
NHS	National Health Service
NR	Not reported
OAB	Overactive bladder
OABq	Overactive bladder questionnaire
OAB-5D	Overactive bladder – five dimensions
OD	Once daily
ONS	Office for National Statistics
OR	Odds ratio
PbR	Payment by results
PPBC	Patient perception of bladder condition scale
PPIUS	Patient perception of intensity of urgency scale
PPS	Per protocol set
PPS-I	Per protocol set – incontinence set
PSA	Probabilistic sensitivity analysis
PSS	Personal and social services
PVR	Post-void residual volume
QALY(s)	Quality adjusted life year(s)
QoL	Quality of life
QTc	Corrected QT interval
RAS	Randomised analysis set
RCT	Randomised controlled trial
RE	Random effects
RPAS	Run-in period analysis set
SA	Sensitivity analysis
SAE	Serious adverse event

SAS	Safety analysis set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SF-12	Short form-12
SG	Subgroup
SMC	Scottish Medicines Consortium
SOC	System organ class
SR	Slow-release
SUI	Stress urinary incontinence
TD	Transdermal
TDS	Three times daily
TEAE	Treatment-emergent adverse event
TS VAS	Treatment satisfaction visual analogue scale
TUI	Total urinary incontinence
UI	Urinary incontinence
ULN	Upper limit of normal
US	United States
UTI	Urinary tract infection
UUI	Urge incontinence
VAS	Visual analogue scale
vs	versus
Wk	Week
WPAI:SHP	Work productivity and activity impairment: specific health problem
XL	Extended-release

Executive summary

Background

Mirabegron (brand name: Betmiga®) is a first-in-class beta-3 adrenoreceptor (ß3-AR) agonist for the treatment of overactive bladder (OAB). This submission demonstrates the clinical and cost-effectiveness of mirabegron versus all relevant comparators in all OAB patients. The addition of mirabegron to the prescribing schedule will provide clinicians and patients with a new option for the effective treatment of OAB within a disease area currently limited by the poor tolerability of existing pharmacological options.

Overactive bladder (OAB) syndrome has been described by the International Continence Society (ICS) as urgency, with or without urge incontinence, usually with frequency and nocturia. The prevalence of OAB in the UK has been estimated at approximately 5 million people aged 40 years and older, with prevalence increasing with advancing age.

Approximately, two thirds of patients with OAB indicate that their symptoms have an effect on their daily lives. The impact of OAB can be less work productivity, increased rates of erectile dysfunction and lower sexual satisfaction, disrupted sleep patterns due to nocturia resulting in lower levels of overall health and decreased health-related quality of life (HRQoL). OAB is also associated with a variety of co-morbidities such as increased risk of falls and fractures, depression, urinary tract infections (UTIs) and skin infections.

The treatment pathway for OAB starts with conservative management (e.g. bladder training), followed by pharmacotherapy and finally surgical intervention. Current NICE guidelines recommend bladder training and lifestyle advice upon diagnosis of OAB in both men and women, followed by pharmacotherapy using an antimuscarinic (oxybutynin in CG40 and a non-specified antimuscarinic in CG97) as first-line therapy. Antimuscarinics block the muscarinic receptors but are not selective for the bladder therefore also affect the salivary gland, intestine and eye, resulting in unwanted side-effects such as dry mouth, constipation and blurred vision. Mirabegron has a different and novel mechanism of action, activating ß-adrenoreceptors (ß-ARs) in the detrusor muscle and trigone area of the bladder, facilitating urine storage through the relaxation of the detrusor, and eliciting a tolerability profile similar and comparable to placebo.

European Medicines Agency (EMA) filing occurred on 24th August 2011. Positive opinion from the Committee for Medicinal Products for Human Use (CHMP) was published on 19th October 2012 and EMA marketing authorisation is expected in late January 2013.

Mirabegron will be supplied as 25 mg and 50 mg (recommended dose) prolonged-release tablets, both at a list price of £29.00 per pack of 30 tablets. Treatment is not curative and therefore patients should continue mirabegron long-term.

Mirabegron will be indicated for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in patients with overactive bladder (OAB) syndrome.

Clinical evidence for mirabegron

Key clinical evidence for mirabegron comes from head-to-head RCTs versus placebo and tolterodine 4 mg extended-release (ER) and from a mixed treatment comparison (MTC) versus placebo, tolterodine, oxybutynin, solifenacin, fesoterodine and trospium.

Clinical trial evidence for mirabegron is based on three primary Phase III randomised controlled trials (RCTs); SCORPIO, ARIES and CAPRICORN. Significant improvements were observed in the two primary endpoints of change from baseline to endpoint for mirabegron and placebo in:

1. Mean number of micturitions per 24 hours
    - SCORPIO, placebo = -1.34, mirabegron = -1.93; (p<0.001)
    - ARIES, placebo = -1.05, mirabegron = -1.66; (p=0.001)
    - CAPRICORN, placebo = -1.18, mirabegron = -1.60; (p=0.015)
2. Mean number of incontinence episodes per 24 hours
    - SCORPIO, placebo = -1.17, mirabegron = -1.57; (p=0.003)
    - ARIES, placebo = -1.13, mirabegron = -1.47; (p=0.026)
    - CAPRICORN, placebo = -0.96, mirabegron = -1.38; (p=0.001)

Statistically significant improvements in placebo subtracted change from baseline to final visit were observed for mirabegron 50 mg groups in the secondary efficacy endpoints of:

1. Mean volume voided per micturition
    - SCORPIO, 11.9 mL; (p<0.001)
    - ARIES, 11.1 mL; (p=0.001)
    - CAPRICORN, 12.4 mL; (p<0.001)
2. Mean number of urgency episodes (Grade 3 or 4) per 24 hours:
    - SCORPIO, -0.60; (p=0.005)
    - ARIES, -0.75; (p=0.001)
3. Mean level of urgency:
    - SCORPIO, -0.09; (p=0.018)
    - ARIES, -0.01; (p=0.004)
4. Mean number of urge incontinence episodes per 24 hours:
    - SCORPIO, -0.35; (p=0.003)
    - ARIES, -0.43; (p=0.005)
5. Mean number of nocturia episodes per 24 hours:
    - SCORPIO, -0.15; (p=0.022)
    - ARIES, -0.18; (p=0.043)

Health related quality of life was recorded using both the EuroQOL 5-Dimension (EQ-5D) questionnaire and the disease specific Overactive Bladder Questionnaire (OAB-q). EQ-5D responses were pooled from the three primary studies, SCORPIO, ARIES and CAPRICORN, and after adjusting for baseline confounding factors, mirabegron 50 mg

was found to be superior to tolterodine 4mg in terms of change from baseline utility score after 12 weeks (mean change of 0.045 vs 0.026, respectively; p≤ 0.05). Analyses of OAB-q responses showed statistically significant improvements in symptom bother score at 12 weeks for the 50 mg mirabegron groups compared with placebo.

The long-term safety study, TAURUS, demonstrated that the incidence of treatment-related treatment-emergent adverse events (TEAEs) was similar between the mirabegron 50 mg (26.2%) and tolterodine groups (27.6%), the incidence of treatment-related serious adverse events (SAEs) was 1.2% in the mirabegron 50 mg group and 0.6% in the tolterodine group and the incidence of treatment-related TEAEs leading to study drug discontinuation was 4.3% in the mirabegron 50 mg group and 3.8% in the tolterodine group.

Dry mouth is the most commonly cited reason for discontinuation of antimuscarinic therapy for OAB. Mirabegron shows favourable rates of dry mouth. In SCORPIO, rates of dry mouth for mirabegron 50 mg were the same as placebo (1.8%) and much lower than tolterodine (9.5%). In the long-term safety study, TAURUS, rates of treatment-related dry mouth were 2.5% on mirabegron and 8.3% on tolterodine.

The primary Phase III studies, SCORPIO, ARIES and CAPRICORN have shown that 50 mg doses of mirabegron once daily for 12 weeks are efficacious. Long-term evidence from the safety study, TAURUS, shows that the treatment effect trends continued up to 52 weeks. The long-term safety study, TAURUS, has also shown that 50 mg doses of mirabegron are generally safe and well tolerated for up to 1 year.

Economic evidence for mirabegron

A *de novo* Markov model was developed to analyse the cost-effectiveness of mirabegron 50 mg vs appropriate antimuscarinics for the treatment of OAB. The model simulated the therapeutic management, the course of disease, and complications in hypothetical cohorts of patients with OAB and was used to predict costs and QALYs over 5 years.

Base case analysis of the general OAB population compared mirabegron 50 mg with tolterodine ER 4 mg, based on results from SCORPIO. Subgroup analyses for male vs female and previously treated vs treatment-naïve populations were also conducted in line with the final scope. Secondary analyses compared mirabegron 50 mg with alternative comparators (solifenacin 5 mg and 10 mg, fesoterodine 4 mg, trospium chloride 60 mg MR and oxybutynin 10 mg IR and ER), based on MTC results.

In the base case analyses of the general OAB population, the ICER for mirabegron vs tolterodine was £4,386 per QALY gained using EQ-5D responses (Table 1) and £3,008 when using OAB-5D responses.

Table 1: Base-case cost-effectiveness results

Treatment	Total			Incremental			ICER (£) versus tolterodine
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Tolterodine 4 mg	£1,607.75	4.666	3.755	-	-	-	-
Mirabegron 50 mg	£1,645.62	4.666	3.764	£37.88	0	0.00864	£4,386

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; mg, milligram; QALY, quality adjusted life year.

When analysis using the MTC results was performed, mirabegron is cost-effective in all cases (Table 2).

Table 2: Base case results, general OAB population, mirabegron vs antimuscarinics, based on MTC results

Treatment	Total			Incremental			ICER (£) versus mirabegron
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Solifenacin 10 mg	£1,647.60	4.666	3.762	£3.53	0	0.0104	£340
Fesoterodine 4 mg	£1,601.40	4.666	3.758	£38.09	0	0.0106	£3,607
Tolterodine 4 mg	£1,601.64	4.666	3.759	£37.85	0	0.0102	£3,715
Oxybutynin 10mg ER	£1,587.06	4.666	3.755	£42.12	0	0.0109	£3,878
Trospium chloride 60 mg MR	£1,551.86	4.666	3.759	£83.89	0	0.0094	£8,881
Solifenacin 5 mg	£1,592.94	4.666	3.768	£58.19	0	0.0047	£12,493
Oxybutynin 10 mg IR	£1,392.42	4.666	3.755	£236.76	0	0.0109	£21,796

Abbreviations: ER, extended-release; ICER, incremental cost-effectiveness ratio; IR, immediate-release; LYG, life year gained; mg, milligram; MR, modified-release; QALY, quality adjusted life year.

In the subgroup analysis of previously treated vs treatment-naïve, and males and females, the mirabegron strategy was found to be cost-effective vs tolterodine ER 4mg in all subgroups, except for male patients (Table 3).

Table 3: Cost-effectiveness results in subgroups

Subgroup	Inc. costs	Inc. QALYs (EQ-5D)	ICER (EQ-5D)	Inc. QALYs (OAB-5D)	ICER (OAB-5D)
General OAB population	£37.88	0.0086	£4,386	0.0126	£3,008
Previously treated	£38.07	0.0099	£3,836	0.0148	£2,577
Treatment-naïve	£40.27	0.0076	£5,315	0.011	£3,652
Women	£37.73	0.0122	£3,091	0.0167	£2,266
Men	£43.96	0.0011	£38,708	0.0007	£65,968

Abbreviations: EQ-5D, European quality of life – five dimensions questionnaire; ICER, incremental cost-effectiveness ratio; Inc., incremental; OAB-5D, overactive bladder – five dimensions questionnaire; QALY, quality adjusted life year.

Conclusion

Mirabegron is a first-in-class pharmacotherapy with a new mechanism of action resulting in a differing side-effect profile to the currently available antimuscarinics, particularly low rates of dry mouth, similar to placebo. Mirabegron is both clinically and cost-effective versus all relevant comparators and in all OAB patients, which provides clinicians and patients with a new option for the effective treatment of OAB.

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: Betmiga®.

Approved name: Mirabegron.

Therapeutic class: Mirabegron is a first-in-class beta-3 adrenoreceptor (ß3-AR) agonist. The Anatomical Therapeutic Chemical (ATC) Classification System code is G04BD12.

1.2 What is the principal mechanism of action of the technology?

Mirabegron is a potent and selective ß3-AR agonist developed for the treatment of overactive bladder (OAB). It has a distinct mechanism of action compared with the antimuscarinic agents currently prescribed as pharmacotherapy for OAB.

Mirabegron's mechanism of action is activation of ß-adrenoreceptors (ß-ARs) in the detrusor muscle and trigone area of the bladder facilitating urine storage through the flattening and lengthening of the bladder base (1). In human bladder tissue, the adrenergic receptor promoting urine storage was identified as the ß3-AR (2). This indicates that human ß3-AR specific agonists may be an effective treatment for OAB (3, 4). Mirabegron has high selectivity for the human ß3-AR and has been shown to relax precontracted human detrusor muscle strips (5).

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

European Medicines Agency (EMA) filing occurred on 24th August 2011. Positive Committee for Medicinal Products for Human Use (CHMP) opinion is anticipated in October 2012 and EMA marketing authorisation late January 2013.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

As the European public assessment report (EPAR) has not yet been published it is not possible to answer this question at this time. However, Astellas is not expecting any special conditions attached to the marketing authorisation.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Mirabegron is anticipated to be indicated for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in patients with overactive bladder (OAB) syndrome.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

There are three ongoing studies in the mirabegron clinical development programme that are estimated to report within the next 12 months:

- **BEYOND, NCT01638000** is a Phase IIIb, double-blind, randomised, parallel group, multi-centre study to evaluate the efficacy and safety of mirabegron compared with solifenacin in patients with OAB previously treated with antimuscarinics and dissatisfied due to lack of efficacy. Results are expected to be reported in November 2013.
- **SYMPHONY, NCT01340027** is a Phase II, randomised, double-blind, factorial, parallel-group, active and placebo-controlled, multi-centre, dose-ranging study to evaluate the efficacy, safety and tolerability of solifenacin and mirabegron in combination, compared with mirabegron and solifenacin monotherapies in the treatment of OAB. Results are expected to be reported in November 2013.
- **NCT01489696** is a Phase I, randomised, open-label study to evaluate cardiovascular interactions between mirabegron and tamsulosin in healthy male volunteers. Results are expected to be reported in November 2012.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Astellas intends to launch mirabegron shortly after UK marketing authorisation is granted. We anticipate mirabegron will be available in the UK from mid February 2013.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

- Approval was obtained in Japan in July 2011 and mirabegron was launched in September 2011 under the trade name Betanis®.
- FDA approval was obtained in the USA in June 2012 and mirabegron was launched in October 2012 under the trade name Myrbetriq®.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Astellas plans to submit mirabegron for appraisal by the Scottish Medicines Consortium (SMC) in December 2012, with a decision expected in April 2013.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 4: Unit costs of technology being appraised

Pharmaceutical formulation	Mirabegron is supplied as 25 mg and 50 mg prolonged-release tablets
Acquisition cost (excluding VAT)	25 mg and 50 mg list price of £29.00 per pack of 30 tablets
Method of administration	Oral, with or without food
Doses	The recommended dose of mirabegron is 50 mg per day
Dosing frequency	Once daily
Average length of a course of treatment	Treatment is not curative and therefore patients should continue mirabegron long-term
Average cost of a course of treatment	As mirabegron is to be taken continuously, a price per month has been calculated: For both 25 mg and 50 mg doses, the price is £29.40 per month (adjusted to a monthly cost by assuming (365/12) days per month)
Anticipated average interval between courses of treatments	None – mirabegron should be taken daily without interruption
Anticipated number of repeat courses of treatments	Treatment is taken continuously
Dose adjustments	25 mg once daily is the recommended mirabegron dose in patients with: • severe renal impairment (eGFR 15-29 ml/min/1.73 m^2) • moderate hepatic impairment (Child-Pugh Class B)

Abbreviations: eGFR, estimated glomerular filtration rate; mg, milligram; VAT, value added tax.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

There are no additional tests or investigations required as long as a clinical diagnosis of idiopathic OAB is established.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

There is no general need for monitoring of patients on mirabegron above and beyond what is done in routine clinical practice.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

No other concomitant therapy is needed for OAB for patients started on mirabegron, although some patients may persist with bladder training.

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Overactive bladder (OAB) syndrome (or urge syndrome or urgency-frequency syndrome) has been described by the International Continence Society (ICS) as urgency, with or without urge incontinence, usually with frequency and nocturia (6).

The exact aetiology of OAB is unknown, but may have a neurological (7) or myogenic (8) basis. Damage to central inhibitory pathways, leads to sensitisation of afferent nerves and increased afferent activity. Furthermore, decreased inhibitory control and increased sensitivity of the detrusor muscle can occur with trigger involuntary overactive detrusor contractions. Alterations in the functional properties of detrusor myocytes, including hypersensitivity can result in excessive spontaneous excitation and propagation.

The prevalence of OAB in the UK has been estimated at approximately 5 million people aged 40 years and older (9), with prevalence increasing with advancing age (10, 11). The prevalence of OAB is similar between men and women (9-11). A community-based survey of 2,063 adult men and women aged 40 years or older in the UK (as part of a larger European study) revealed that 19% had symptoms of OAB (9). Within the full European dataset, frequency was the most commonly reported symptom (85% of patients), followed by urgency (54%) and urgency incontinence (36%). Overall, 65% of men and 67% of women with OAB indicated that their symptoms had an effect on their daily lives and 60% had consulted a medical practitioner about their symptoms, although only 27% of patients were currently receiving treatment.

In a European case-control study, participants (19.3% from the UK) with OAB with or without additional lower urinary tract symptoms (LUTS) reported significantly less work productivity and sexual satisfaction, higher rates of depressive symptoms and erectile dysfunction, and lower levels of overall health (12). In the US, patients with OAB and nocturia have reported significantly higher symptom bother and decreased health-related quality of life (HRQoL) due to disrupted sleep patterns (13). The negative impact on HRQoL increases with the number of night-time voids.

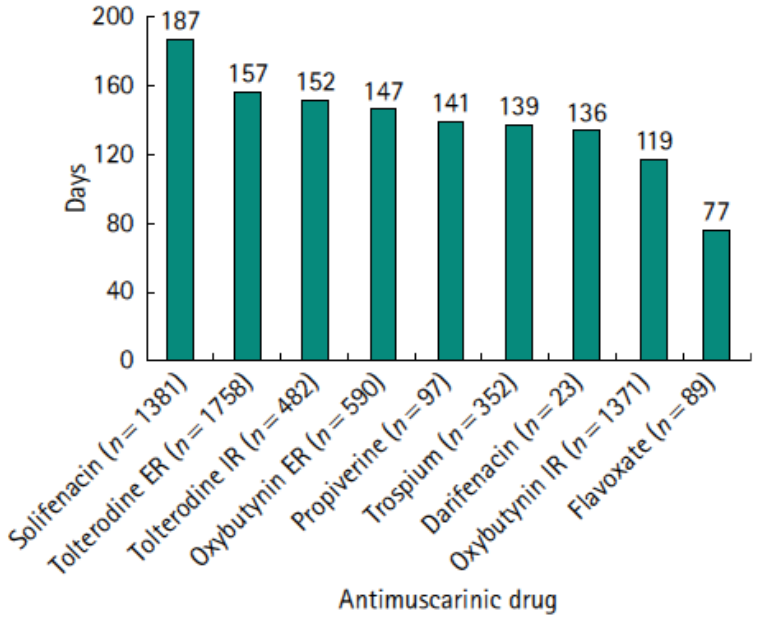
OAB is associated with a variety of co-morbidities. In a US retrospective claims database analysis, the prevalence of falls and fractures (25.3% vs 16.1%), depression (10.5% vs 4.9%), urinary tract infections (UTIs) (28.0% vs 8.4%) and skin infections (3.9% vs 2.3%) was significantly higher ($p<0.0001$) for patients with OAB than for controls (14).

Treatment options for OAB include conservative management (e.g. bladder training and electrical stimulation), pharmacotherapy and surgical intervention. In the UK, bladder training and lifestyle advice is recommended for OAB in both men and women, followed by pharmacotherapy (15, 16). The primary pharmacotherapy option is currently muscarinic receptor treatments (antimuscarinics), although the market share of the drugs prescribed has changed over recent years. In the year to March 2009 tolterodine, oxybutynin and solifenacin were the most commonly prescribed and dispensed antimuscarinics in England, accounting for 39%, 34%, 20% of the market, respectively (17). More recent data from July 2012 has shown that whilst these drugs are still the most commonly prescribed, the share has changed with solifenacin being the most

common followed by oxybutynin and tolterodine with shares of 36%, 29% and 22%, respectively, of prescriptions issued in the UK (18). Antimuscarinics block the muscarinic receptors in the bladder wall and therefore inhibit abnormal detrusor contractions in the bladder. The effects of these agents are not selective for the bladder but also affect the salivary gland, intestine and eye, resulting in unwanted side-effects such as dry mouth, blurred vision and constipation (19, 20).

When compared with other chronic conditions, persistence with OAB medication is low at 28% (21). A retrospective database analysis of UK prescription data by number of patients assessed persistence with antimuscarinics over a 12 month period (22). Solifenacin 10 mg had the highest mean duration of therapy per patient (216 days), followed by solifenacin 5 mg (158.7) (Figure 1). Overall, persistence at 12 months was generally low: the therapy with the highest persistence was solifenacin at 35% of patients.

Figure 1: Mean time on therapy, by antimuscarinic



Abbreviations: ER, extended-release; IR, immediate-release.
Source: Wagg et al, 2012 (22). Data are for combined doses for each antimuscarinic. Numbers are for patients starting treatment.

In a US study of 1,322 respondents who reported discontinuing antimuscarinic therapy in the previous 12 months, the top four reasons cited for discontinuation were: ‘didn’t work as expected’, 46.2%; ‘switched to a new medication’, 25.2%; ‘learned to get by without medication’, 23.3% and ‘I had side-effects’, 21.1% (23). In a more recent European study of physician’s reasons for switching their patient’s antimuscarinic therapy, the strongest independent driver for switching patients from their first-line therapy was lack of efficacy (36% of 1,067 patients) (24). When side-effects were examined as a reason for switching, dry mouth was cited most frequently, followed by constipation, dizziness, drowsiness and nausea.

Current treatment regimens for OAB are limited because of a lack of well-tolerated non-surgical treatment options. Mirabegron is a first-in-class pharmacotherapy with a new mechanism of action resulting in a differing side-effect profile to the currently available

antimuscarinics, particularly low rates of dry mouth, similar to placebo. The addition of mirabegron to the prescribing schedule in England and Wales will provide patients with an alternative treatment for OAB with an approved efficacy and tolerability balance. Mirabegron has the potential to greatly improve patient compliance and outcomes, and may avoid the need for more invasive surgical treatments.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

The marketing authorisation is anticipated to cover the general OAB population; approximately 5 million people aged 40 years and older in England and Wales (9).

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

The life expectancy of people with OAB is not thought to differ from the life expectancy of the general population within England and Wales. The only available published information on life expectancy from the Office for National Statistics (ONS) is at birth or at age 65 years. Men have a life expectancy of 18.17 years and women of 20.78 years at age 65 years (25).

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

NICE has issued separate guidelines including the management of OAB for men and women:

NICE Clinical Guideline Number 40, October 2006 'Urinary incontinence: The management of urinary incontinence in women' (15). The guidelines (currently under review) state that 'Immediate-release non-proprietary oxybutynin should be offered to women with OAB or mixed urinary incontinence as first-line drug treatment if bladder training has been ineffective. If immediate-release oxybutynin is not well tolerated, darifenacin, solifenacin, tolterodine, trospium or an extended-release or transdermal formulation of oxybutynin should be considered as alternatives.'

NICE Clinical Guideline Number 97, May 2010 'The management of lower urinary tract symptoms in men' (16). Anticholinergics should be offered as first-line pharmacotherapy to men with storage LUTS suggestive of OAB if bladder training, lifestyle and behavioural advice and containment devices have failed.

In addition, two further interventional procedure guidance documents exist:

NICE Interventional Procedure Guidance Number 362, October 2010 'Percutaneous posterior tibial nerve stimulation for overactive bladder syndrome' (26).

NICE Interventional Procedure Guidance Number 64, June 2004 'Sacral nerve stimulation for urge incontinence and urgency-frequency' (27).

However, these two interventions are not included as comparators in the NICE scope as they come later in the treatment pathway and do not have comparable costs, efficacy or treatment settings. Furthermore, such treatments are not available in all centres.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

Current NICE guidelines for urinary incontinence in women and LUTS in men cover the management of OAB (15, 16). These guidelines date from 2006 (CG40 – women) and 2010 (CG97 – men) and recommend an antimuscarinic (oxybutynin in CG40 and non-specified antimuscarinic in CG97) as first-line therapy. Currently available antimuscarinics have been shown to fail to achieve a balance between efficacy and tolerability in many patients and this is reflected by the general low persistence with treatment (22). It is anticipated that mirabegron would offer an alternative pharmacotherapy to antimuscarinics within the existing pathway for both treatment naive patients and previously treated patients – for example, for patients in whom the desired efficacy has not been achieved with antimuscarinic treatment, or for those patients who have been unable to tolerate antimuscarinic treatment. Currently these patients may progress to surgery or symptom management using incontinence pads.

Recent advice from clinicians at an Astellas advisory board suggested that treatment for OAB tended to be on a patient-by-patient basis. Market share data shows that solifenacin is currently the most widely prescribed antimuscarinic (18), rather than oxybutynin, possibly due to its better tolerability profile.

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Current NICE guidelines recommend that women with OAB should be prescribed non-proprietary oxybutynin as first-line pharmacotherapy (15). However, the poor tolerability profile of oxybutynin and low persistence rates with treatment (22) means that oxybutynin is not the treatment of choice for healthcare professionals. Alternative once daily antimuscarinics with a better tolerability profile are more commonly prescribed in the UK (18).

2.7 Please identify the main comparator(s) and justify their selection.

The comparators, as defined in the scope, are the five most commonly used antimuscarinics in the UK (18):

- solifenacin
- oxybutynin (including modified-release preparations)
- tolterodine
- fesoterodine
- trospium.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

In the European 12-week Phase III registration study, the four most commonly reported adverse events (AEs) in patients taking mirabegron 50mg were hypertension, headache, dry mouth and nasopharyngitis. The incidence of these AEs was similar to that

experienced in the placebo group. Therefore it is not anticipated that medication would be required to manage any such AEs.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Mirabegron will be prescribed in both primary and secondary care as an alternative to solifenacin, oxybutynin, tolterodine, fesoterodine and trospium. No additional costs are anticipated to arise based on location of care, staff usage, administration costs, monitoring or tests. A reduction in the side-effects experienced by mirabegron-treated patients is expected to result in a reduction in the number of physician visits required.

2.10 Does the technology require additional infrastructure to be put in place?

No.

3 Equality

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- ***could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;***
- ***could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology***
- ***could lead to recommendations that have any adverse impact on people with a particular disability or disabilities***

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

There are no equality issues surrounding the use of mirabegron for OAB.

3.1.2 How has the analysis addressed these issues?

Not applicable.

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

The management of OAB is based on finding a treatment option for patients which provides the right balance of efficacy and tolerability. Astellas believe that this new class of ß3-ARs provides a valuable treatment option to achieve such a balance. Antimuscarinics have been shown to fail to achieve such a balance in many patients, reflected by the general low persistence with treatment (22). For patients in whom the desired efficacy is not achieved with antimuscarinic treatment, or for those who are unable to tolerate their medication there are currently no further pharmacological treatment options, leaving surgery or symptom management via incontinence pads as the most likely options. Mirabegron has significant efficacy and tolerability advantages to support its use in patients for whom previous antimuscarinic therapy has failed.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

OAB adversely affects many aspects of patients' quality of life. OAB has been shown to have significant social, psychological, occupational, domestic, and physical stigmas (28), as well as a strong association with depression (12). OAB patients become anxious in unfamiliar environments: they focus on and may be preoccupied with such concerns as locating the closest bathroom, looking for aisle seating, and estimating the amount of time until their next work break. Embarrassment, frustration, anxiety, annoyance, depression, and fear of odour can have a negative impact on daily activities, such as travel, physical activity, relationships, and sexual function, resulting in social isolation. While the EQ-5D instrument may capture some reduction in quality of life from depression and anxiety, it may not adequately reflect the impact of OAB. Such activity may be associated with costly management of absenteeism, presenteeism[a], and depression (29).

OAB symptoms such as increased micturition frequency, urgency and incontinence may have substantial consequences for the quality of life (QoL) of partners/family of OAB patients and these are unlikely to be captured in the quality adjusted life year (QALY) approach.

[a] Presenteeism is defined as productivity loss while at work.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Through the mirabegron clinical development programme, Astellas have collected patient reported outcome data using both the European quality of life – 5 dimensions (EQ-5D) and the overactive bladder – questionnaire (OABq) instruments. OAB-q is a disease specific instrument validated in a large cohort of OAB patients, with an established minimal important difference (MID) (30). EQ-5D offers a broader assessment of quality of life, but has been shown to be less sensitive to symptoms of OAB, especially at the mild end of the spectrum. Recent research has shown that OAB-q may be more sensitive to changes in OAB symptom severity, notably urgency, than EQ-5D (31).

Additional generic instruments such as the treatment satisfaction visual analogue scale (TS VAS), and disease specific instruments such as the patient perception of bladder scale (PPBC) and work productivity and activity impairment: specific health problem scale (WPAI:SHP) have also been utilised.

Further clinical details are reported in Section 6.5.4 and economic details in Section 7.4.

This data has been used to inform the health economic model where appropriate, and health benefits which are not captured by the QALY calculation are reported. Depression has been reported to occur in 60% of patients with incontinence (32). UTIs are observed in 22.5% of patients with OAB, and skin infections in 8% of OAB patients (34). Patients with frequent urge incontinence have a 26% increased risk of falls, and a 34% increased risk of fractures (34).

5 Statement of the decision problem

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with symptoms of OAB	As per NICE scope	N/A
Intervention	Mirabegron	As per NICE scope	N/A
Comparator(s)	Antimuscarinic drugs including: • oxybutynin (including modified-release preparations) • tolterodine • fesoterodine • solifenacin • trospium	As per NICE scope	N/A
Outcomes	• urinary frequency • frequency of urge urinary incontinence • symptoms of urgency • nocturia • adverse effects of treatments • HRQoL	As per NICE scope, and additionally: • number of incontinence episodes	N/A
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being	As per NICE scope	N/A

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	compared. Costs will be considered from an NHS and Personal Social Services perspective.		
Subgroups to be considered	If the evidence allows: • men and women • previously untreated and previously treated OAB	As per NICE scope	N/A
Special considerations, including issues related to equity or equality	None	N/A	N/A

Abbreviations: HRQoL, health-related quality of life; N/A, not applicable; NHS, National Health Service; OAB, overactive bladder; QALY, quality adjusted life year.

Section B – Clinical and cost effectiveness

6 Clinical evidence

Summary of clinical evidence

RCT evidence for mirabegron is based on three primary Phase III studies; 178-CL-046 (SCORPIO), 178-CL-047 (ARIES) and 178-CL-074 (CAPRICORN).

- Significant improvements were observed in the co-primary endpoints of change from baseline to endpoint for mirabegron and placebo in mean number of micturitions (SCORPIO, placebo = -1.34, mirabegron = -1.93; ARIES, placebo = -1.05, mirabegron = -1.66; CAPRICORN, placebo = -1.18, mirabegron = -1.60) and mean number of incontinence episodes per 24 hours (SCORPIO, placebo = -1.17, mirabegron = -1.57; ARIES, placebo = -1.13, mirabegron = -1.47; CAPRICORN, placebo = -0.96, mirabegron = -1.38)
  - The change in mean number of micturitions was significant versus placebo in SCORPIO ($p<0.001$), ARIES ($p=0.001$) and CAPRICORN ($p=0.015$)
  - The change in mean number of incontinence episodes per 24 hours was significant versus placebo in SCORPIO ($p=0.003$), ARIES ($p=0.026$) and CAPRICORN ($p=0.001$).
- Statistically significant improvements in placebo subtracted change from baseline to final visit were observed for mirabegron 50 mg groups in the secondary efficacy endpoints of:
  - mean volume voided per micturition (SCORPIO, 11.9 mL, $p<0.001$; ARIES, 11.1 mL, $p=0.001$; CAPRICORN, 12.4 mL, $p<0.001$)
  - mean number of urgency episodes (Grade 3 or 4)[b] per 24 hours (SCORPIO, -0.60, $p=0.005$; ARIES, -0.75, $p=0.001$)
  - mean level of urgency (SCORPIO, -0.09, $p=0.018$; ARIES, -0.01, $p=0.004$)
  - mean number of urge incontinence episodes per 24 hours (SCORPIO, -0.35, $p=0.003$; ARIES, -0.43, $p=0.005$)
  - mean number of nocturia episodes per 24 hours (SCORPIO, -0.15, $p=0.022$; ARIES, -0.18, $p=0.043$).
- Using the disease specific instrument, OAB-q, statistically significant improvements in quality of life at 12 weeks for the 50 mg mirabegron groups compared with placebo were observed in:

[b] Grade 3 urgency is defined as severe urgency (I could not postpone voiding, but had to rush to the toilet in order not to wet myself) and Grade 4 urgency as urge incontinence (I leaked before arriving to the toilet).

- symptom bother score (SCORPIO, placebo = -14.9, mirabegron = -19.6, p<0.001; ARIES, placebo = -11, mirabegron = -17, p<0.001; CAPRICORN, placebo = -16.0, mirabegron = -18.8, p=0.028)
- HRQoL score (SCORPIO, placebo = 13.7, mirabegron = 16.1, p=0.031) and ARIES, placebo = 10.7, mirabegron = 14.8, p=0.001).

Long-term evidence from safety study 178-CL-049 (TAURUS) shows that the treatment effect trends continued up to 52 weeks, although no statistical comparisons of efficacy between treatment groups were performed.

A pre-specified pooled analysis of SCORPIO, ARIES and CAPRICORN was conducted.

- In the general OAB population (all patients), 50 mg mirabegron produced statistically significant improvements at final visit compared with placebo in the mean number of incontinence episodes per 24 hours, mean number of micturitions per 24 hours, mean volume voided per micturition, mean level of urgency, mean number of urgency incontinence episodes per 24 hours, mean number of urgency episodes (Grade 3/4) per 24 hours and mean number of nocturia episodes per 24 hours.
- In a male/female subgroup analysis, statistically significant improvements at final visit were noted in females for the mean number of incontinence episodes per 24 hours and the mean number of micturitions per 24 hours. In males, a statistically significant improvement was noted for the mean number of micturitions and a numerical improvement was noted for the mean number of incontinence episodes.
- In a previously treated/treatment-naïve subgroup analysis, statistically significant improvements at final visit were noted in the previously treated population for the mean number of incontinence episodes per 24 hours and the mean number of micturitions per 24 hours. Numerical improvements were noted in the treatment-naïve population.

A mixed treatment comparison of 40 studies (6 mirabegron studies and 34 comparator studies) was conducted.

- The effect of mirabegron 50 mg did not differ significantly from other treatments in the **number of micturitions**, except solifenacin 10 mg which is more effective (mean difference vs mirabegron 50 mg of -0.583) and tolterodine 4 mg, which is less effective (mean difference vs mirabegron 50 mg of +0.157).
- Mean changes in daily **number of incontinence episodes** were greater with mirabegron 50 mg compared with tolterodine 4 mg, oxybutynin 10 mg, fesoterodine 4, and 8 mg, but differences were not statistically significant. Solifenacin 10 mg and 5 mg were associated with a statistically significantly higher improvement than mirabegron 50 mg.
- The effect of mirabegron 50 mg on **urge incontinence** did not differ significantly from antimuscarinics, except solifenacin 10 mg, which was statistically significantly greater (mean difference vs mirabegron 50 mg of -0.420).

- Mirabegron 50 mg had a probability of **dry mouth** similar to placebo (with OR 1.303 [95% CrI: 0.859 to 1.916] in favour of mirabegron 50 mg). Moreover, all antimuscarinics were associated with a significantly higher risk of dry mouth compared with mirabegron 50 mg.
- The probability of **constipation** associated with mirabegron 50 mg is similar to tolterodine ER 4 mg, with an OR estimated at 1.109 [95% CrI 0.716 to 1.647]. Solifenacin 5 mg and 10, fesoterodine 8mg, and trospium 60 mg were associated with greater risks of constipation compared with mirabegron 50 mg.
- **Blurred vision** is relatively rare and no clear difference in risk was found between treatments.

The primary Phase III studies, 178-CL-046 (SCORPIO), 178-CL-047 (ARIES) and 178-CL-074 (CAPRICORN) have shown that 50 mg doses of mirabegron once daily for 12 weeks are efficacious, and generally safe and well tolerated.

The long-term safety study, 178-CL-049 (TAURUS) has shown that 50 mg doses of mirabegron are generally safe and well tolerated for up to 1 year.

- The incidence of treatment-related TEAEs was similar between the mirabegron 50 mg (26.2%) and tolterodine groups (27.6%).
- The incidence of treatment-related SAEs was 1.2% in the mirabegron 50 mg group and 0.6% in the tolterodine group.
- The incidence of treatment-related TEAEs leading to study drug discontinuation was 4.3% in the mirabegron 50 mg group and 3.8% in the tolterodine group.

Dry mouth is a common reason for discontinuation of antimuscarinic therapy for OAB. Mirabegron shows favourable rates of dry mouth:

- In SCORPIO, rates of dry mouth on mirabegron 50 mg were the same as placebo (1.8%) and much lower than tolterodine (9.5%)
- In the long-term safety study, TAURUS, rates of treatment-related dry mouth were 2.5% on mirabegron and 8.3% on tolterodine.

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in Section 10.2, appendix 2.

Two systematic reviews were conducted to retrieve relevant clinical data from the published literature regarding the efficacy and safety of mirabegron and relevant

comparators as outlined in the scope. The systematic reviews were also conducted to inform a mixed treatment comparison (MTC).

1) Randomised controlled trial (RCT) evidence on the efficacy and safety of mirabegron and relevant comparators for OAB in adults with symptoms of OAB.
2) Non-RCT evidence on the efficacy and safety of mirabegron for OAB in adults with symptoms of OAB.

This was supplemented by hand searching the bibliographies of relevant review articles, conference proceedings and trial databases and with unpublished data from the manufacturer.

Using Boolean operators, the searches combined terms (including MeSH headings as appropriate) for overactive bladder, pharmacological intervention(s) of interest, and clinical trial design.

The search strategy is provided in Section 10.2.

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent.

Studies identified were initially assessed based on title and abstract (i1). Papers not meeting the inclusion criteria were excluded, and allocated a “reason code” to document the rationale for exclusion (e1). Papers included after this stage were then assessed based on the full text (i2). Further papers were excluded (e2), and studies from Astellas’s clinical study programme were included, yielding the final data set for interrogation (i3). The final included data set consisted of clinical studies for mirabegron (i4).

The full text of the final data set was also screened for studies suitable for the MTC (i5).

Inclusion and exclusion selection criteria are detailed in Section 10.2.6. Prospective RCTs of mirabegron in adults with OAB were included. Outcomes of interest included urgency, number of micturitions, urge incontinence episodes, nocturia and adverse events (AEs).

Transdermal oxybutynin was not included as a comparator due to the differences in placebo administration (placebo patch) in the clinical trials assessing the therapy. In addition, patch-specific AEs such as rash (33), would have complicated the economic model. The OAB-medication market share for patches is also very low at 1.4% of the antimuscarinic market (34). For these reasons, the focus of this submission has been on oral medications for OAB.

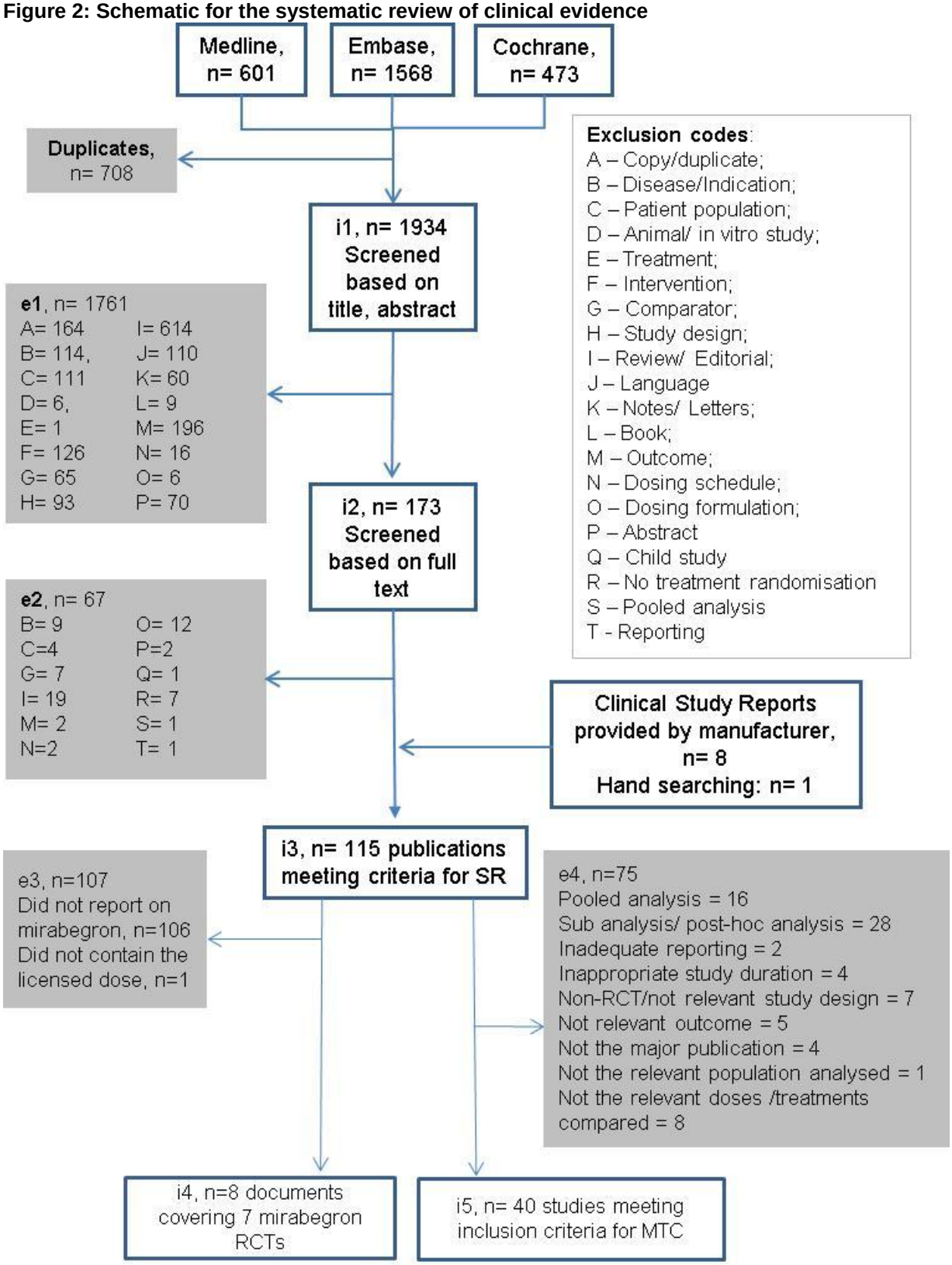
6.2.2 A flow diagram of included and excluded studies at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses. Such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in Section 6.2.4.

Following assessment and exclusion of studies based on title, abstract and full text, seven RCTs examined mirabegron at the licenced dose:

- 178-CL-044 (DRAGON)
- 178-CL-045
- 178-CL-046 (SCORPIO)
- 178-CL-047 (ARIES)
- 178-CL-048
- 178-CL-049 (TAURUS)
- 178-CL-074 (CAPRICORN).

A total of 40 studies were identified for inclusion in the MTC, further details of which are reported in Section 6.7. The SR schematic is shown in Figure 2.

Figure 2: Schematic for the systematic review of clinical evidence



Abbreviations: MTC, mixed treatment comparison; SR, systematic review.

6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials

are linked (for example, an open-label extension to an RCT), this should be made clear.

In total, the systematic review identified seven RCTs in the population of interest (Table 5). Data for mirabegron within this submission are reported from the following sources:

Table 5: List of data sources for mirabegron

Trial name	Trial number	Data source
DRAGON	178–CL-044	• CSR (35)
	178-CL-045	• CSR (36)
SCORPIO	178-CL-046	• CSR (37) • Publication – Nitti, 2011 (38)
ARIES	178-CL-047	• CSR (39)
	178-CL-048	• CSR (40)
TAURUS	178-CL-049	• CSR (41)
CAPRICORN	178-CL-074	• CSR (42)

Abbreviations: CSR, clinical study report.

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form.

The systematic review of clinical evidence identified seven RCTs of mirabegron in the population of interest to this submission (Table 6). Placebo was the comparator in three studies, with active controls used in one study. A further three studies used both placebo and active control. These studies which include an active control arm are not head-to-head studies as they were not powered to detect superiority or non-inferiority. The active control arm has been included only as a non-statistical comparison.

Table 6: List of relevant RCTs

Study no. (acronym)	Intervention	Active control/ comparator	Population	Trial duration	Primary study ref.
Primary Phase III RCTs					
178-CL-046 (SCORPIO)	• 50 mg mirabegron • 100 mg mirabegron	• 4 mg tolterodine SR • placebo	Adults with symptomatic OAB	12 weeks	(37)
178-CL-047 (ARIES)	• 50 mg mirabegron • 100 mg mirabegron	• placebo	Adults with symptomatic OAB	12 weeks	(39)
178-CL-074 (CAPRICORN)	• 25 mg mirabegron • 50 mg mirabegron	• placebo	Adults with symptomatic OAB	12 weeks	(42)
Long-term Phase III RCT					

Study no. (acronym)	Intervention	Active control/ comparator	Population	Trial duration	Primary study ref.
178-CL-049 (TAURUS)	• 50 mg mirabegron • 100 mg mirabegron	• 4 mg tolterodine ER	Adults with symptomatic OAB	52 weeks	(41)
Phase II RCT					
178-CL-044 (DRAGON)	• 25 mg mirabegron • 50 mg mirabegron • 100 mg mirabegron • 200 mg mirabegron	• 4 mg tolterodine SR • placebo	Adults with symptomatic OAB	12 weeks	(35)
Supporting Japanese RCTs					
178-CL-045	• 25 mg mirabegron • 50 mg mirabegron • 100 mg mirabegron	• placebo	Adults with symptomatic OAB	12 weeks	(36)
178-CL-048	• 50 mg mirabegron	• 4 mg tolterodine ER • placebo	Adults with symptomatic OAB	12 weeks	(40)

Abbreviations: ER, extended-release; mg, milligram; OAB, overactive bladder; SR, slow-release.

The Phase III 12-week studies, 178-CL-046 (SCORPIO), 178-CL-047 (ARIES) and 178-CL-074 (CAPRICORN) and the long-term Phase III safety study 178-CL-049 (TAURUS) are reported in full in this submission. The methodology and results of the Phase III 12-week studies are reported in Sections 6.3 to 6.5. As TAURUS was designed to primarily assess safety, this study is reported in full in Section 6.9, however the secondary efficacy results from this study are reported in Section 6.5.

The Phase II study 178-CL-044 (DRAGON) and two studies in Japanese populations Phase II 178-CL-045 and Phase III 178-CL-048, are summarised in Section 10.14, as supporting evidence.

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

Two primary Phase III studies compare the intervention with appropriate comparators:

- 178-CL-046 (SCORPIO) compares mirabegron and placebo with tolterodine SR as an active control
- 178-CL-049 (TAURUS) compares mirabegron with tolterodine ER as an active control.

Tolterodine has been included as an active control; these are not head-to-head studies.

In addition, two supporting studies compare the intervention with an appropriate comparator:

- 178-CL-044 (DRAGON) compares mirabegron and placebo with tolterodine SR as an active control

- 178-CL-048 compares mirabegron and placebo with tolterodine ER as an active control.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

No identified studies were excluded from further discussion.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in Section 6.8 and key details should be presented in a table.

The non-RCT relevant to this submission is summarised in Table 7.

Table 7: List of relevant non-RCTs

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
178-CL-051	50 mg mirabegron increased to 100 mg mirabegron (optional at week 8)	Adults with symptomatic OAB	Safety and efficacy of long-term (52 weeks) treatment with mirabegron 50 mg, with optional dose increase to 100 mg	(43)	Provides evidence for the long-term use of mirabegron

Abbreviations: mg, milligram; OAB, overactive bladder.

6.3 Summary of methodology of relevant RCTs

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments.

The methodology of the primary RCTs is summarised in Table 8.

Table 8: Comparative summary of methodology of the primary RCTs

Study no. (acronym)	178-CL-046 (SCORPIO)	178-CL-047 (ARIES)	178-CL-074 (CAPRICORN)
Study objective	Efficacy and safety of mirabegron in patients with symptoms of OAB		
Location	189 sites in 27 EU and non-EU countries (Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Netherlands, Poland, Romania, Slovakia, Spain, Sweden, UK[†], Australia, Belarus, Norway, Russian Federation, Switzerland)	132 sites in US and Canada	151 sites in Europe and North America (Czech Republic, Denmark, Finland, Germany, Hungary, Norway, Portugal, Slovakia, Spain, Sweden, US, Canada)
Design	Phase III, randomised, parallel group, placebo- and active-controlled study of 1,987 patients	Phase III, randomised, parallel group, placebo-controlled study of 1,329 patients	Phase III, randomised, parallel group, placebo-controlled study of 1,306 patients
Duration of study	• 2-week single-blind placebo run-in • 12 weeks on double-blind randomised treatment		
Method of randomisation	• 1:1:1:1 • Computer-generated randomisation scheme • Randomisation was stratified by country	• 1:1:1 • Computer-generated randomisation scheme	• 1:1:1 • Computer-generated randomisation scheme
Method of blinding (care provider, patient and outcome assessor)	• Study drugs packaged using double-dummy blinding • During placebo run-in, patients were blinded to identity of study drug • During double-blind treatment and follow-up, the investigator, study site personnel, patients, sponsor and sponsor's representatives were blinded to the identity of the randomised drug assignment		
Interventions, N randomised	• 50 mg mirabegron, N=497 • 100 mg mirabegron, N=498	• 50 mg mirabegron, N=442 • 100 mg mirabegron, N=433	• 25 mg mirabegron, N=433 • 50 mg mirabegron, N=440

Study no. (acronym)	178-CL-046 (SCORPIO)	178-CL-047 (ARIES)	178-CL-074 (CAPRICORN)
Comparators/active control, N randomised	• 4 mg tolterodine SR, N=495 • Placebo, N=497	• Placebo, N=454	• Placebo, N=433
Permitted concomitant medications	Alpha blockers; 5-alpha reductase inhibitors; CYP3A4 inducers; Loop diuretics These medications were permitted provided patient had been taking them on a long-term basis (i.e. not stopped, started or changed dose within 30 days prior to study entry)		
Disallowed concomitant medications	• Anticholinergics • Antispasmodics • CYP2D6 substrates with narrow therapeutic indices • Medications recommended not to be used with tolterodine (i.e. strong CYP3A4 inhibitors classified as antibiotics and antivirals, antifungals, antiarrhythmics)	• Anticholinergics • Antispasmodics • CYP2D6 substrates with narrow therapeutic indices	
Discontinuation of study therapy	• Patient request/withdrawn consent • Patient experienced AEs • Patient experienced lack of efficacy • Patient lost to follow-up • Patient was in violation of protocol		
Assessments	Visits at Weeks 4, 8, 12		
Primary outcomes (including scoring methods and timings of assessments)	• CFB to end of treatment (final visit) in mean number of incontinence episodes per 24 hours based on a 3-day micturition diary • CFB to end of treatment (final visit) in mean number of micturitions per 24 hours based on a 3-day micturition diary		

Study no. (acronym)	178-CL-046 (SCORPIO)	178-CL-047 (ARIES)	178-CL-074 (CAPRICORN)
Secondary outcomes (including scoring methods and timings of assessments)	**Key secondary efficacy endpoints** (based on 3-day micturition diary) • CFB to final visit in mean volume voided per micturition • CFB to Week 4 in mean number of incontinence episodes per 24 hours • CFB to Week 4 in mean number of micturitions per 24 hours **Safety endpoints** • Adverse events		**Key secondary efficacy endpoints** (based on 3-day micturition diary) • CFB to final visit in mean volume voided per micturition • CFB to Week 4 in mean number of incontinence episodes per 24 hours • CFB to Week 4 in mean number of micturitions per 24 hours • CFB to final visit in mean level of urgency • CFB to final visit in mean number of urgency incontinence episodes • CFB to final visit in mean number of urgency incontinence episodes (Grade 3/4) **Safety endpoints** Adverse events
Duration of follow-up	30 days after end of treatment phase (contact by telephone)		2 weeks

Abbreviations: AE, adverse event; CFB, change from baseline; EU, European Union; IVRS, interactive voice response system; mg, milligram; OAB, overactive bladder; SR, slow-release.
†142/1,987 patients (7.1%) in the randomised analysis set were from the UK.

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. Highlight any differences between the trials.

The inclusion and exclusion criteria for the relevant RCTs are summarised in Table 9.

Table 9: Eligibility criteria of the primary RCTs

Inclusion criteria	Exclusion criteria
Criteria common to all studies: SCORPIO, ARIES and CAPRICORN	
At screening • Male or female ≥ 18 years • Signed informed consent • Willing and able to complete micturition diary and questionnaires correctly • Symptoms of OAB (urinary frequency and urgency with or without incontinence) for ≥ 3 months **At baseline** • Patient still fulfilled all inclusion criteria and no exclusion criteria from screening visit • Frequency of micturition ≥ 8 times per 24-hour period during the 3-day micturition diary period • ≥ 3 episodes of urgency (Grade 3 or 4) with or without incontinence during the 3-day micturition diary period	**At screening** • Breastfeeding, pregnant, intending to become pregnant during the study, or of childbearing potential, sexually active and not practicing a highly reliable method of birth control • Significant stress incontinence or mixed stress/urgency incontinence where stress was the predominant factor as determined by the investigator (for female patients confirmed by a cough provocation test) • Indwelling catheter or practicing intermittent self-catheterisation • Diabetic neuropathy • Evidence of a symptomatic UTI, chronic inflammation such as interstitial cystitis, bladder stones, previous pelvic radiation therapy or previous or current malignant disease of the pelvic organs • Non-drug treatment including electro-stimulation therapy (bladder training programme or pelvic floor exercises started >30 days prior to entry into study could be continued) • Use of medications intended to treat OAB or prohibited medications listed in the protocol. Patient was excluded if using restricted medications and conditions specified in the protocol were not met • Known or suspected hypersensitivity to mirabegron, other ß-AR agonists, or any of the other inactive ingredients • Any clinically significant condition, which in the opinion of the investigator made the patient unsuitable for the study • Previous treatment with any investigational drug or device within 30 days (90 days in the UK) prior to screening • Employees of the Astellas Group, third parties associated with the study or the study site • Severe hypertension, defined as a sitting average SBP=180 mm Hg and/or average DBP=110 mm Hg **At baseline** • Average total daily urine volume >3000 mL as recorded in the 3-day micturition diary period • Clinically significant increases in laboratory values as assessed in screening samples (e.g. serum creatinine >150 µmol/L, AST and/or ALT >2xULN, or GGT >3xULN) • Abnormal ECG, which in the opinion of the investigator made the patient unsuitable for the study • Severe hypertension, defined as a sitting average SBP ≥ 180

Inclusion criteria	Exclusion criteria
	mm Hg and/or average DBP ≥ 110 mm Hg
Additional criteria for SCORPIO	
	At screening • Clinically significant bladder outflow obstruction at risk of urinary retention • Uncontrolled narrow angle glaucoma, urinary or gastric retention, severe colitis ulcerosa, toxic megacolon, myasthenia gravis or any other medical condition that, in the opinion of the investigator, made the use of anticholinergics contraindicated • Known or suspected hypersensitivity to tolterodine, other anticholinergics
Additional criteria for CAPRICORN	
	At screening • Known or suspected hypersensitivity to tolterodine, other anticholinergics

Abbreviations: ß-AR, beta adrenoreceptor; ALT, alanine amino transferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure; ECG, electrocardiogram; GGT, gamma glutamyl transferase; OAB, overactive bladder; SBP systolic blood pressure; ULN, upper limit of normal; UTI, urinary tract infection.

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups.

Population definitions are defined in Table 16. Although intention-to-treat (ITT) is usually the main data set reported in clinical trials, in non-fatal conditions such as OAB at least one post-dose assessment is required for meaningful data about the study drug. Consistent with studies of other antimuscarinics which do not commonly publish the ITT population, the primary and secondary outcomes have been reported using the full analysis set (FAS) in accordance with ICH E9. In many clinical trials the use of the FAS provides a conservative strategy. Under many circumstances it may also provide estimates of treatment effects which are more likely to mirror those observed in subsequent practice. In addition, the FAS population was required in order to conduct an MTC with the currently available antimuscarinics as the ITT population was not reported across all trials. Sensitivity analyses for the primary Phase III studies were performed on the ITT population for the co-primary endpoint of change from baseline to endpoint in mean number of micturitions per 24 hours and the intent-to-treat – incontinence (ITT-I) population for the co-primary endpoint of change from baseline to endpoint in mean number of incontinence episodes per 24 hours.

A number of datasets, detailed in Table 16 and Table 18 to Table 20, have been analysed throughout SCORPIO, ARIES and CAPRICORN. Baseline characteristics in the FAS datasets are detailed for patient demographics, OAB history and OAB-related characteristics. For incontinence-related characteristics, only patients with incontinence (the FAS-I dataset) are analysed.

Patient demographics of the FAS dataset are summarised in Table 10. Patient demographics were consistent across treatment groups in all three studies. In SCORPIO, ARIES and CAPRICORN, the majority were female (72.0%, 74.8% and

68.5%, respectively), <65 years of age (63.0%, 62.8% and 62.8%, respectively), <75 years of age (91.5%, 84.9% and 90.1%, respectively) and white (99.2%, 88% and 91%, respectively). Similar proportions were observed for the SAS and FAS-I datasets.

Table 10: Patient demographics of participants across randomised groups in the primary RCTs, FAS

178-CL-046 (SCORPIO)	**Placebo N=480**	**Mirabegron**		**Tolterodine SR 4mg N=475**	**Total N=1,906**
		50 mg N=473	**100 mg N=478**		
Sex, n (%)					
Male	134 (27.9)	133 (28.1)	138 (28.9)	129 (27.2)	534 (28.0)
Female	346 (72.1)	340 (71.9)	340 (71.1)	346 (72.8)	1372 (72.0)
Age in years,					
Mean (SD)	59.3 (12.15)	59.2 (12.15)	58.9 (12.69)	59.1 (12.75)	59.1 (12.43)
Age group in years, n (%)					
<65	302 (62.9)	302 (63.8)	306 (64.0)	291 (61.3)	1201 (63.0)
≥ 65	178 (37.1)	171 (36.2)	172 (36.0)	184 (38.7)	705 (37.0)
<75	437 (91.0)	430 (90.9)	435 (91.0)	442 (93.1)	1744 (91.5)
≥ 75	43 (9.0)	43 (9.1)	43 (9.0)	33 (6.9)	162 (8.5)
Race, n (%)					
White	477 (99.4)	468 (98.9)	474 (99.2)	472 (99.4)	1891 (99.2)
Black or African American	2 (0.4)	1 (0.2)	1 (0.2)	2 (0.4)	6 (0.3)
Asian	0	2 (0.4)	2 (0.4)	1 (0.2)	5 (0.3)
Other	1 (0.2)	2 (0.4)	1 (0.2)	0	4 (0.2)
BMI in Kg/m^2	*n=480*	*n=473*	*n=477*	*n=475*	*n=1,905*
Mean (SD)	27.8 (4.97)	27.5 (4.90)	28.0 (4.87)	27.9 (4.97)	27.8 (4.93)
Geographical region[†], n (%)					
Eastern Europe	221 (46.0)	210 (44.4)	221 (46.3)	221 (46.5)	873 (45.8)
Western Europe[†]	259 (54.0)	263 (55.6)	257 (53.8)	254 (53.5)	1033 (54.2)

178-CL-047 (ARIES)	**Placebo N=433**	**Mirabegron**		**Total N=1,270**
		50 mg N=425	**100 mg N=412**	
Sex, n (%)				
Male	101 (23.3)	116 (27.3)	103 (25.0)	320 (25.2)
Female	332 (76.7)	309 (72.7)	309 (75.0)	950 (74.8)
Age in years				
Mean (SD)	60.1 (13.74)	59.6 (13.34)	60.8 (13.02)	NR
Age group in years, n (%)				
<65	261 (60.3)	261 (61.4)	244 (59.2)	766 (60.3)
≥ 65	172 (39.7)	164 (38.6)	168 (40.8)	504 (39.7)

<75	366 (84.5)	367 (86.4)	345 (83.7)	1,078 (84.9)
≥ 75	67 (15.5)	58 (13.6)	67 (16.3)	192 (15.0)
Race, n (%)				
White	378 (87.3)	378 (88.9)	364 (88.4)	1,120 (88.2)
Black or African American	44 (10.2)	29 (6.8)	35 (8.5)	108 (8.5)
Asian	6 (1.4)	11 (2.6)	6 (1.5)	23 (1.8)
Other	5 (1.2)	7 (1.6)	7 (1.7)	19 (1.5)
Ethnicity, n (%)				
Hispanic/ Latino	23 (5.3)	22 (5.2)	31 (7.5)	76 (5.9)
Non-Hispanic/ non-Latino	410 (94.7)	403 (94.8)	381 (92.5)	1,194 (94.0)
BMI in Kg/m^2	*n=432*	*n=425*	*n=412*	
Mean (SD)	30.4 (7.43)	30.0 (6.59)	30.3 (7.09)	NR
Geographical region, n (%)				
Northeastern US	75 (17.3)	72 (16.9)	77 (18.7)	224 (17.6)
Midwestern US	57 (13.2)	56 (13.2)	48 (11.7)	161 (12.7)
Southern US	150 (34.6)	140 (32.9)	139 (33.7)	429 (33.8)
Western US	110 (25.4)	113 (26.6)	106 (25.7)	329 (25.9)
Canada	41 (9.5)	44 (10.4)	42 (10.2)	127 (10.0)
178-CL-074 (CAPRICORN)	**Placebo N=415**	**Mirabegron**		**Total N=1,251**
		25 mg N=410	**50 mg N=426**	
Sex, n (%)				
Male	127 (30.6)	134 (32.7)	133 (31.2)	394 (31.5)
Female	288 (69.4)	276 (67.3)	293 (68.8)	857 (68.5)
Age in years				
Mean (SD)	58.2 (13.83)	58.8 (12.68)	60.4 (12.26)	NR
Age group in years, n (%)				
<65	261 (62.9)	263 (64.1)	262 (61.5)	786 (62.8)
≥ 65	154 (37.1)	147 (35.9)	164 (38.5)	465 (37.2)
<75	371 (89.4)	378 (92.2)	378 (88.7)	1,127 (90.1)
≥ 75	44 (10.6)	32 (7.8)	48 (11.3)	124 (9.9)
Race, n (%)				
White	372 (89.6)	373 (91.0)	389 (91.3)	1,134 (90.6)
Black or African American	34 (8.2)	31 (7.6)	31 (7.3)	96 (7.7)
Asian	7 (1.7)	5 (1.2)	4 (0.9)	16 (1.3)
Other	2 (0.5)	1 (0.2)	2 (0.5)	5 (0.4)

Ethnicity, n (%)				
Hispanic/ Latino	21 (5.1)	22 (5.4)	21 (4.9)	64 (5.1)
Non-Hispanic/ non-Latino	394 (94.9)	388 (94.6)	405 (95.1)	1,187 (94.9)
BMI in Kg/m^2,	*n=415*	*n=410*	*n=426*	
Mean (SD)	29.1 (6.27)	29.6 (6.32)	29.5 (6.52)	NR
Geographical region, n (%)				
Eastern Europe	73 (17.6)	75 (18.3)	74 (17.4)	222 (17.7)
Western Europe	123 (29.6)	117 (28.5)	119 (27.9)	359 (28.7)
Northeastern US	39 (9.4)	38 (9.3)	41 (9.6)	118 (9.4)
Midwestern US	22 (5.3)	24 (5.9)	22 (5.2)	68 (5.4)
Southern US	67 (16.1)	68 (16.6)	74 (17.4)	209 (16.7)
Western US	60 (14.5)	64 (15.6)	65 (15.3)	189 (15.1)
Canada	31 (7.5)	24 (5.9)	31 (7.3)	86 (6.9)

Abbreviations: BMI, body mass index; cm, centimetre; Kg, kilogram; mg, milligram; NR, not reported; SD, standard deviation; SR, slow-release.
[†] For the purposes of this summary, Australia was included within the Western Europe category.

Patient characteristics of OAB history for the FAS datasets are presented in Table 11. OAB history characteristics were comparable across all treatment groups in each of the primary studies. Types of OAB were classified into urgency incontinence (urge incontinence only), mixed (mixed stress/urge incontinence with urge as a predominant factor) and frequency (frequency/urgency without incontinence). The most frequently reported type of OAB varied across the studies; in SCORPIO it was urgency incontinence (40%), in ARIES it was mixed (38%) and in CAPRICORN it was urgency incontinence (35%). Approximately half the patients in each study had received previous medication indicated for OAB. Insufficient effect was the primary reason (61.4–69.4%) cited for discontinuation of previous OAB drugs, while poor tolerability was cited by 20.2–28.6% of patients. Median duration of OAB symptoms ranged from 50.2 to approximately 62 months across the studies.

Table 11: OAB history in participants across randomised groups in the primary RCTs, FAS

178-CL-046 (SCORPIO)	**Placebo N=480**	**Mirabegron**		**Tolterodine SR 4mg N=475**
		50 mg N=473	**100 mg N=478**	
Type of OAB[†], n (%)				
Urgency incontinence	201 (41.9)	192 (40.6)	179 (37.4)	184 (38.7)
Frequency	177 (36.9)	173 (36.6)	183 (38.3)	186 (39.2)
Mixed	102 (21.3)	108 (22.8)	116 (24.3)	105 (22.1)
Prior OAB surgery, n (%)	22 (4.6)	33 (7.0)	28 (5.9)	17 (3.6)
Previous OAB drug, n (%)	238 (49.6)	240 (50.7)	237 (49.6)	231 (48.6)
Reason for previous OAB drug discontinuation[‡], n (%)				

Insufficient effect	159 (66.8)	160 (66.7)	159 (67.1)	155 (67.1)
Poor tolerability	68 (28.6)	65 (27.1)	64 (27.0)	56 (24.2)
Duration of OAB symptoms (months)				
Mean (SD)	76.9 (92.15)	78.7 (85.68)	85.3 (95.24)	76.3 (93.40)
Median	50.5	49.9	53.4	47.2
Range	3 – 688	3 – 637	3 – 567	3 – 711

178-CL-047 (ARIES)	**Placebo N=433**	**Mirabegron**	
		50 mg N=425	**100 mg N=412**
Type of OAB[†], n (%)			
Urgency incontinence	124 (28.6)	135 (31.8)	118 (28.6)
Frequency	133 (30.7)	134 (31.5)	139 (33.7)
Mixed	176 (40.6)	156 (36.7)	155 (37.6)
Prior OAB surgery, n (%)	49 (11.3)	53 (12.5)	46 (11.2)
Previous OAB drug, n (%)	249 (57.5)	242 (56.9)	223 (54.1)
Reason for previous OAB drug discontinuation[‡], n (%)			
Insufficient effect	166 (66.7)	161 (66.5)	137 (61.4)
Poor tolerability	60 (24.1)	49 (20.2)	49 (22.0)
Duration of OAB symptoms (months)			
Mean (SD)	91.9 (108.52)	84.0 (94.61)	91.8 (108.44)
Median	52.4	51.9	52.0
Range	3 − 816	3 − 634	3 − 865

178-CL-074 (CAPRICORN)	**Placebo N=415**	**Mirabegron**	
		25 mg N=410	**50 mg N=426**
Type of OAB[†], n (%)			
Urgency incontinence	117 (28.2)	156 (38.0)	164 (38.5)
Frequency	161 (38.8)	130 (31.7)	114 (26.8)
Mixed	137 (33.0)	124 (30.2)	148 (34.7)
Prior OAB surgery, n (%)	43 (10.4)	25 (6.1)	40 (9.4)
Previous OAB drug, n (%)	217 (52.3)	219 (53.4)	206 (48.4)
Reason for previous OAB drug discontinuation[‡], n (%)			
Insufficient effect	141 (65.0)	149 (68.0)	143 (69.4)
Poor tolerability	57 (26.3)	48 (21.9)	59 (28.6)
Duration of OAB symptoms (months)			
Mean (SD)	91.4 (96.08)	97.4 (115.14)	93.7 (98.94)
Median	63.0	59.8	62.7
Range	3 - 590	3 - 759	3 - 688

Abbreviations: mg, milligram; OAB, overactive bladder; SD, standard deviation; SR, slow-release.

†Types of OAB were defined as follows: urgency incontinence = urge incontinence only, mixed = mixed stress/urge incontinence with urge as a predominant factor, frequency = frequency/urgency without incontinence; ‡Patients could choose >1 reason for discontinuation of previous OAB drug.

OAB-related baseline characteristics for the FAS datasets are presented in Table 12. OAB-related baseline characteristics were consistent across treatment groups in each of the primary studies. The mean number of micturitions per 24 hours was between 11 and 12 in each of the studies. The overall mean level of urgency was approximately 2.4 across all three studies and the mean number of urgency episodes (Grade 3 or 4)[c] was between 5 and 6.

Table 12: OAB-related baseline characteristics in participants across randomised groups in the primary RCTs, FAS

178-CL-046 (SCORPIO)	**Placebo N=480**	**Mirabegron**		**Tolterodine SR 4mg N=475**
		50 mg N=473	**100 mg N=478**	
Mean number of micturitions per 24 hours				
Mean (SD)	11.71 (3.138)	11.65 (2.972)	11.51 (2.703)	11.55 (2.779)
Range	5.3 – 25.0	6.7 – 25.7	6.7 – 23	6.0 – 22.7
Mean volume voided per micturition (mL)				
	n=480	*n=472*	*n=478*	*n=475*
Mean (SD)	156.7 (52.51)	161.1 (58.40)	158.2 (53.14)	158.6 (54.13)
Range	51 – 336	30 – 397	37 – 367	19 – 402
Mean number of urgency episodes (Grade 3 or 4) per 24 hours				
	n=480	*n=473*	*n=477*	*n=474*
Mean (SD)	5.76 (3.994)	5.69 (3.653)	5.94 (3.705)	5.77 (3.446)
Range	0 – 24.3	0 – 20.7	0 – 22.3	0 – 22.7
Mean level of urgency				
	n=480	*n=473*	*n=477*	*n=474*
Mean (SD)	2.37 (0.562)	2.40 (0.543)	2.45 (0.520)	2.41 (0.556)
Range	0 – 4.0	0.5 – 4.0	0.6 – 4.0	0.5 – 4.0
Mean number of nocturia episodes per 24 hours				
Mean (SD)	1.98 (1.412)	1.87 (1.293)	1.90 (1.356)	1.95 (1.412)
Range	0 – 9.7	0 – 6.3	0 – 8.0	0 – 8.3

[c] For each micturition and/or incontinence episode, patients were asked to rate the degree of associated urgency according to the 5-point categorical scale (Patient Perception of Intensity of Urgency Scale):
0. No urgency, I felt no need to empty my bladder, but did so for other reasons.
1. Mild urgency, I could postpone voiding as long as necessary, without fear of wetting myself.
2. Moderate urgency, I could postpone voiding for a short while, without fear of wetting myself.
3. Severe urgency, I could not postpone voiding, but had to rush to the toilet in order not to wet myself.
4. Urge incontinence, I leaked before arriving to the toilet.

178-CL-047 (ARIES)	Placebo N=433	Mirabegron	
		50 mg N=425	100 mg N=412
Mean number of micturitions per 24 hours			
Mean (SD)	11.51 (3.269)	11.80 (3.458)	11.66 (3.389)
Range	3.7 − 40.3	5.7 − 33.3	7.3 − 35.3
Mean volume voided per micturition (mL)			
Mean (SD)	157.5 (58.68)	156.0 (58.69)	157.6 (60.19)
Range	40 − 358	28 − 335	38 − 363
Mean number of urgency episodes (Grade 3 or 4) per 24 hours			
Mean (SD)	5.61 (3.236)	5.88 (3.844)	5.95 (3.608)
Range	0.7 − 16.5	0.0 − 33.3	0.6 − 20.7
Mean level of urgency			
Mean (SD)	2.45 (0.537)	2.45 (0.534)	2.46 (0.544)
Range	0.7 − 4.0	0.3 − 4.0	0.9 − 4.0
Mean number of nocturia episodes per 24 hours			
Mean (SD)	1.93 (1.633)	1.90 (1.613)	2.04 (1.689)
Range	0.0 − 13.0	0.0 − 12.3	0.0 − 11.3
178-CL-074 (CAPRICORN)	**Placebo N=415**	**Mirabegron**	
		25 mg N=410	**50 mg N=426**
Mean number of micturitions per 24 hours			
Mean (SD)	11.48 (2.896)	11.68 (3.099)	11.66 (3.221)
Range	7.3 - 26.3	6.3 - 23.3	7.7 - 37.3
Mean volume voided per micturition (mL)			
Mean (SD)	164.0 (56.87)	165.2 (57.59)	159.3 (52.25)
Range	48 - 356	33 - 349	27 - 357
Mean number of urgency episodes (Grade 3 or 4) per 24 hours			
Mean (SD)	5.40 (3.310)	5.57 (3.617)	5.80 (3.567)
Range	0.3 - 26.0	1.0 - 21.7	1.0 - 18.7
Mean level of urgency			
Mean (SD)	2.36 (0.551)	2.37 (0.563)	2.41 (0.561)
Range	0.8 - 4.0	0.4 - 4.0	0.7 - 4.0
Mean number of nocturia episodes per 24 hours			
Mean (SD)	1.78 (1.274)	1.96 (1.516)	2.03 (1.537)
Range	0.0 - 6.7	0.0 - 9.0	0.0 - 12.0
Mean number of pads used per 24 hours			
Mean (SD)	0.92 (1.804)	0.77 (1.486)	0.83 (1.706)
Range	0.0 - 12.3	0.0 - 11.0	0.0 - 12.0

Abbreviations: mg, milligram; mL, millilitre; OAB, overactive bladder; SD, standard deviation; SR, slow-release.

Incontinence-related baseline characteristics for the FAS-I datasets are presented in Table 13. Incontinence-related characteristics were comparable across all treatment groups in each of the primary studies. The mean number of incontinence episodes per 24 hours and the overall mean number of urgency incontinence episodes per 24 hours ranged from 2.28 to 2.42.

Table 13: Incontinence-related baseline characteristics in participants across randomised groups in the primary RCTs, FAS-I

178-CL-046 (SCORPIO)	**Placebo N=291**	**Mirabegron**		**Tolterodine SR 4mg N=300**
		50 mg N=293	**100 mg N=281**	
Mean number of incontinence episodes per 24 hours				
Mean (SD)	2.67 (2.396)	2.83 (2.827)	2.89 (2.462)	2.63 (2.558)
Range	0.3 − 13.3	0.3 − 16.7	0.3 − 14.0	0.3- 11.7
Mean number of urgency incontinence episodes per 24 hours				
Mean (SD)	2.36 (2.180)	2.46 (2.601)	2.60 (2.305)	2.28 (2.276)
Range	0 − 12.7	0 − 16.7	0 − 12.3	0 − 11.7

178-CL-047 (ARIES)	**Placebo N=325**	**Mirabegron**	
		50 mg N=312	**100 mg N=296**
Mean number of incontinence episodes per 24 hours			
Mean (SD)	3.03 (3.077)	2.77 (2.648)	2.69 (2.438)
Range	0.3 − 25.7	0.3 − 18.0	0.3 − 15.3
Mean number of urgency incontinence episodes per 24 hours			
Mean (SD)	2.51 (2.462)	2.30 (2.365)	2.38 (2.216)
Range	0.0 − 14.7	0.0 − 18.0	0.0 − 12.7

178-CL-074 (CAPRICORN)	**Placebo N=262**	**Mirabegron**	
		25 mg N=254	**50 mg N=257**
Mean number of incontinence episodes per 24 hours			
Mean (SD)	2.43 (2.349)	2.65 (2.544)	2.51 (2.347)
Range	0.3 - 13.7	0.3 - 21.0	0.3 - 13.5
Mean number of urgency incontinence episodes per 24 hours			
Mean (SD)	2.19 (2.202)	2.39 (2.155)	2.27 (2.221)
Range	0.0 - 13.7	0.0 - 13.0	0.0 - 12.5

Abbreviations: mg, milligram; SD, standard deviation; SR, slow-release

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice).

The outcomes investigated were the same across the three primary studies. The timing of assessments and the relevance of the outcomes to the decision problem are presented in Table 14.

The primary studies to support the efficacy of mirabegron were designed to be consistent with Committee for Medicinal Products for Human Use (CHMP) guidance for the clinical investigation of medicinal products for urinary incontinence and included measures of both absolute and relative effect on the patient perception of treatment effect.

The study protocol agreement included co-primary endpoints of frequency and incontinence as per the US Food and Drug administration (FDA) recommendation.

Table 14: Primary and secondary outcomes of the primary RCTs

Outcome	Method of assessment†	Frequency
Co-primary endpoints		
Change from baseline in mean number of micturitions per 24 hours	Micturition diary	E
Change from baseline in mean number of incontinence episodes per 24 hours	Micturition diary	E
Secondary endpoints		
Change from baseline in mean number of micturitions per 24 hours	Micturition diary	4,8,12
Change from baseline in mean volume voided per micturition	Micturition diary	4,8,12,E‡
Change from baseline in mean number of urgency episodes (Grade 3/4) per 24 hours	Micturition diary	4,8,12,E
Change from baseline in level of urgency	Micturition diary	4,8,12,E
Change from baseline in number of urge incontinence episodes per 24 hours	Micturition diary	4,8,12,E
Change from baseline in mean number of incontinence episodes per 24 hours	Micturition diary	4,8,12
Change from baseline in mean number of nocturia episodes per 24 hours	Micturition diary	4,8,12,E
Change from baseline in mean number of pads used per 24 hours	Micturition diary	4,8,12,E
Change from baseline in number of physician visits for patient's bladder condition	eCRF	4,8,12,E
Change from baseline in ICIQ-OAB-q and ICIQ-OABqol	Questionnaire	4,8,12,E
Change from baseline in WPAI:SHP	Questionnaire	12,E
Change from baseline in EQ-5D	Questionnaire	4,8,12,E
Change from baseline in EQ-5D VAS	Questionnaire	4,8,12,E
Change from baseline in PPBC	Questionnaire	12,E
Change from baseline in TS-VAS	Questionnaire	12,E

Abbreviations: 4, from baseline to Week 4; 8, from baseline to Week 8; 12, from baseline to Week 12; E, from baseline to endpoint; EQ-5D, European quality of life - 5 dimensions; OAB, overactive bladder; PPBC, patient perception of bladder condition scale; QoL, quality of life; TS, treatment satisfaction; VAS, visual analogue scale; WPAI:SHP, work productivity and activity impairment: specific health problem.
†Descriptions of the QoL and treatment satisfaction scales can be found in Section 10.14; ‡Endpoint for ARIES and CAPRICORN only.

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a

description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken).

Details of hypotheses and statistical analyses are provided in Table 15. Definitions of populations analysed across all three primary studies are identical and provided in Table 16.

Multiplicity adjustment

In SCORPIO and ARIES, there were two primary and three key secondary efficacy variables. The multiplicity between these variables was controlled at a type I error rate at the alpha = 0.05 level using a stepwise parallel gatekeeping procedure.

- Incontinence episodes at the final visit were evaluated at Stage 1, and the difference in mean change from baseline between a mirabegron dose group and placebo had to be statistically significant before a mirabegron dose group proceeded to Stage 2.
- Micturitions at the final visit were evaluated at Stage 2, and the difference in mean change from baseline between a mirabegron dose group and placebo had to be statistically significant before a mirabegron dose group proceeded to Stage 3.
- Volume voided per micturition at the final visit was evaluated at Stage 3 for the mirabegron dose groups that achieved statistical significance in Stages 1 and 2.

Since two mirabegron groups were compared with placebo, the Hochberg procedure was performed at the alpha = 0.05 level to adjust for multiplicity within each Stage described above. If only one of the mirabegron dose groups proceeded to the next stage for any efficacy variable, then the comparison between mirabegron and placebo was assessed at the alpha = 0.025 level.

No adjustment for multiplicity was necessary in SCORPIO for the comparison between tolterodine and placebo as this was a secondary analysis.

All presented P-values were nominal P-values; however, their statistical significance was based on the multiplicity adjustment method as described above.

In CAPRICORN, The primary comparisons were between the mirabegron 25 mg and 50 mg treatment groups compared with placebo. In order to control the type I error rate at alpha = 0.05, Hochberg's procedure was applied to adjust for multiplicity. Based on Hochberg's procedure, hypothesis testing was performed at the alpha = 0.025 level for comparison of one of the mirabegron treatment groups versus placebo for either of the coprimary efficacy variables.

Table 15: Summary of statistical analyses in the primary RCTs

Study no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
178-CL-046 (SCORPIO)	• Assess the efficacy and safety of mirabegron 50 mg and 100 mg OD vs placebo. • Compare the efficacy, safety and tolerability of mirabegron with tolterodine SR 4 mg OD.	• All statistical comparisons were made using 2-sided tests at the 0.05 significance level. • All data processing, summaries and analyses were performed using SAS Version 9.1 or above in a UNIX environment.	• Sample size of 362 evaluable patients per treatment group provides ~90% power to detect a reduction of 0.7 in the mean number of micturitions per 24 hours over placebo in either mirabegron group at a 2-sided significance level of 0.05 • Assuming ≥ 85% of randomised patients were evaluable, 430 patients were to be randomised to each treatment group. Assuming a dropout rate of 20% during placebo run-in, a total of 1,620 patients were to be enrolled into the study for SCORPIO and 2,160 for ARIES. Sample size calculations to adjust for Dunnett's method (which takes into account multiplicity) were performed using an SAS macro.	• Missing values handled using LOCF (for final visit) and MMRM methodology • Missing items from OAB-q were handled using the half-scale rule[†] • If any subscale score was missing, the HRQoL total score was set to missing • Missing values were not imputed for all other QoL-related questionnaires • Laboratory data values below the LLOQ were set to the value of the LLOQ
178-CL-047 (ARIES)	Assess the efficacy, safety and tolerability of mirabegron 50 mg and 100 mg OD vs placebo.			
178-CL-074 (CAPRICORN)	Assess the efficacy, safety and tolerability of mirabegron 25 mg and 50 mg OD vs placebo.	• To control the type I error rate at alpha = 0.05, Hochberg's procedure was applied to adjust for multiplicity. • Based on Hochberg's procedure, hypothesis testing was performed at the alpha = 0.025 level for comparison of each mirabegron group vs placebo for either coprimary endpoint.	• Sample size of 371 evaluable patients per treatment group would provide 90% power to detect a reduction of 0.7 in the mean number of micturitions per 24 hours over placebo in the mirabegron 25 mg group and/or mirabegron 50 mg group at a 2-sided significance level of 0.025. • Assuming ≥ 85% randomised patients were evaluable, 437 patients were to be randomised to each treatment group. Assuming a dropout rate of about 28% during the placebo run-in period, a total number of 1,821 patients were to be enrolled.	• Values for final visit handled using LOCF methodology • Missing items from OAB-q were handled using the half-scale rule[†] • If any subscale score was missing, the HRQoL total score was set to missing • Missing values were not imputed for all other QoL-related questionnaires

Abbreviations: HRQoL, health-related quality of life; LLOQ, lower limit of quantification; LOCF, last observation carried forward; mg, milligram; MMRM, mixed model repeated measures; OABq, overactive bladder questionnaire; OD, once daily; QoL, quality of life; SR, slow-release; vs, versus.

†Half-scale rule: a subscale score was calculated when ≤ 50% of the items within a subscale were missing. If >50% of the items within a subscale were missing, the score was set to missing.

Table 16: Definitions and summary of populations analysed across the primary RCTs

Population	Abbreviation	Definition
Run-in Period Analysis Set	RPAS	All patients who took ≥ 1 dose of single-blind placebo run-in study drug.
Randomised Analysis Set	RAS	All randomised patients.
Full Analysis Set	FAS	All randomised patients who took ≥ 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and ≥ 1 postbaseline visit diary with a micturition measurement.
FAS Incontinence Analysis Set	FAS-I	All FAS patients who had ≥ 1 incontinence episode at baseline.
Per Protocol Set	PPS	All FAS patients who did not deviate from the list of pre-specified major protocol violations.
PPS Incontinence Analysis Set	PPS-I	All PPS patients who had ≥ 1 incontinence episode at baseline.
Intent-to-Treat Analysis Set	ITT	All randomised patients who took ≥ 1 dose of double-blind study drug and who had a baseline diary with micturition measurements.
ITT Incontinence Analysis Set	ITT-I	All randomised patients who took ≥ 1 dose of double-blind study drug and who had micturition measurements and ≥ 1 incontinence episode in the baseline diary.
Safety Analysis Set	SAS	All randomised patients who took ≥ 1 dose of double-blind study drug.

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Pre-planned subgroup analyses

In the three primary studies, subgroup analyses were conducted on the coprimary efficacy variables using the FAS-I and the FAS populations for the following: sex, age group (<65, ≥ 65 and <75, ≥ 75), race and geographical region. Interpretation of the results of these analyses is limited due to disproportionate numbers of patients in the subgroups for some variables and the influence of sample size on results.

Pre-planned pooled analyses

Pre-specified pooled analyses were conducted on the three primary studies using the FAS populations, including subgroup analyses of gender and previous treatment with antimuscarinics.

Post-hoc analyses

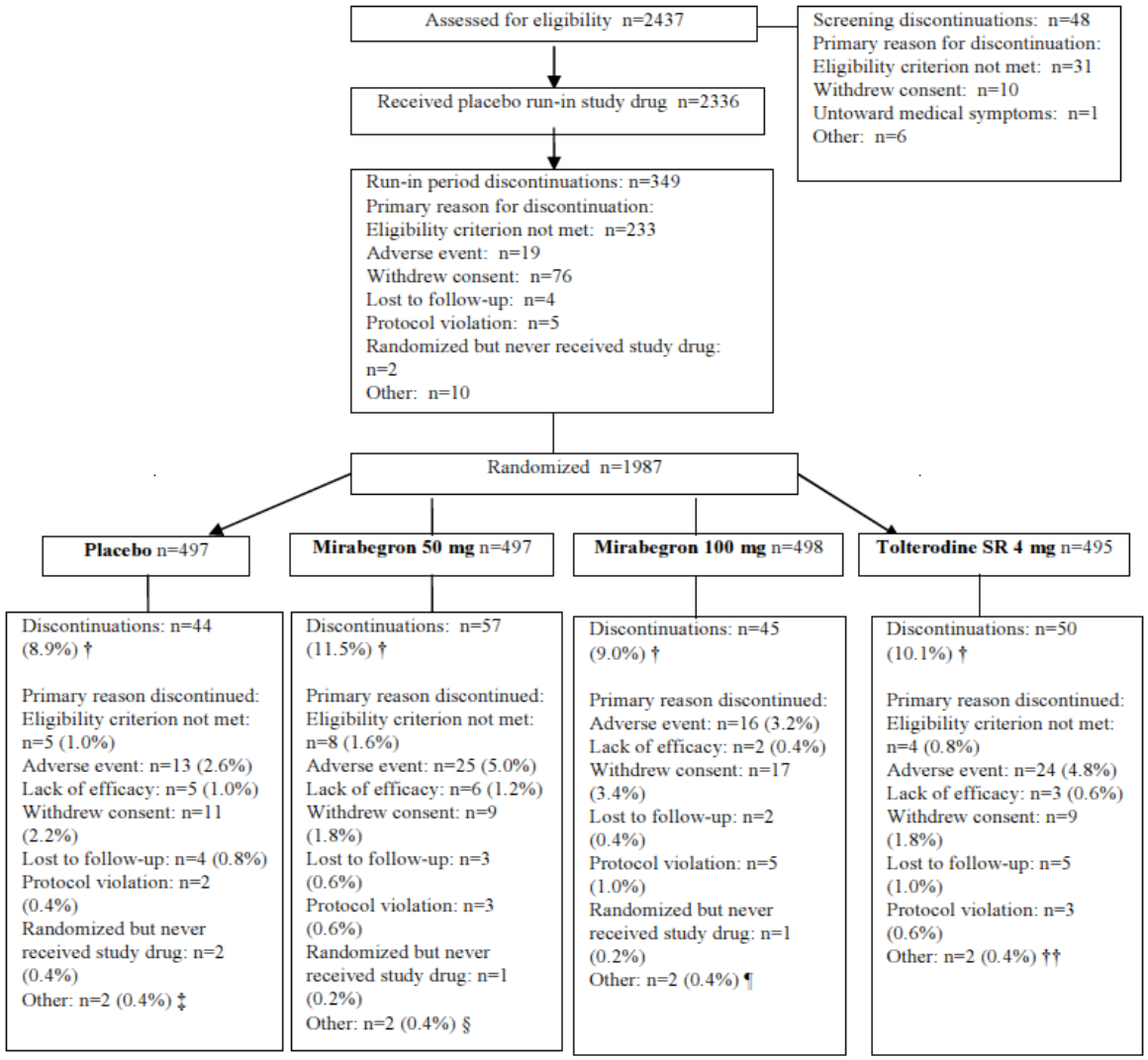
A post-hoc analysis of the EQ-5D results was performed on the pooled data from the three primary studies.

Participant flow

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

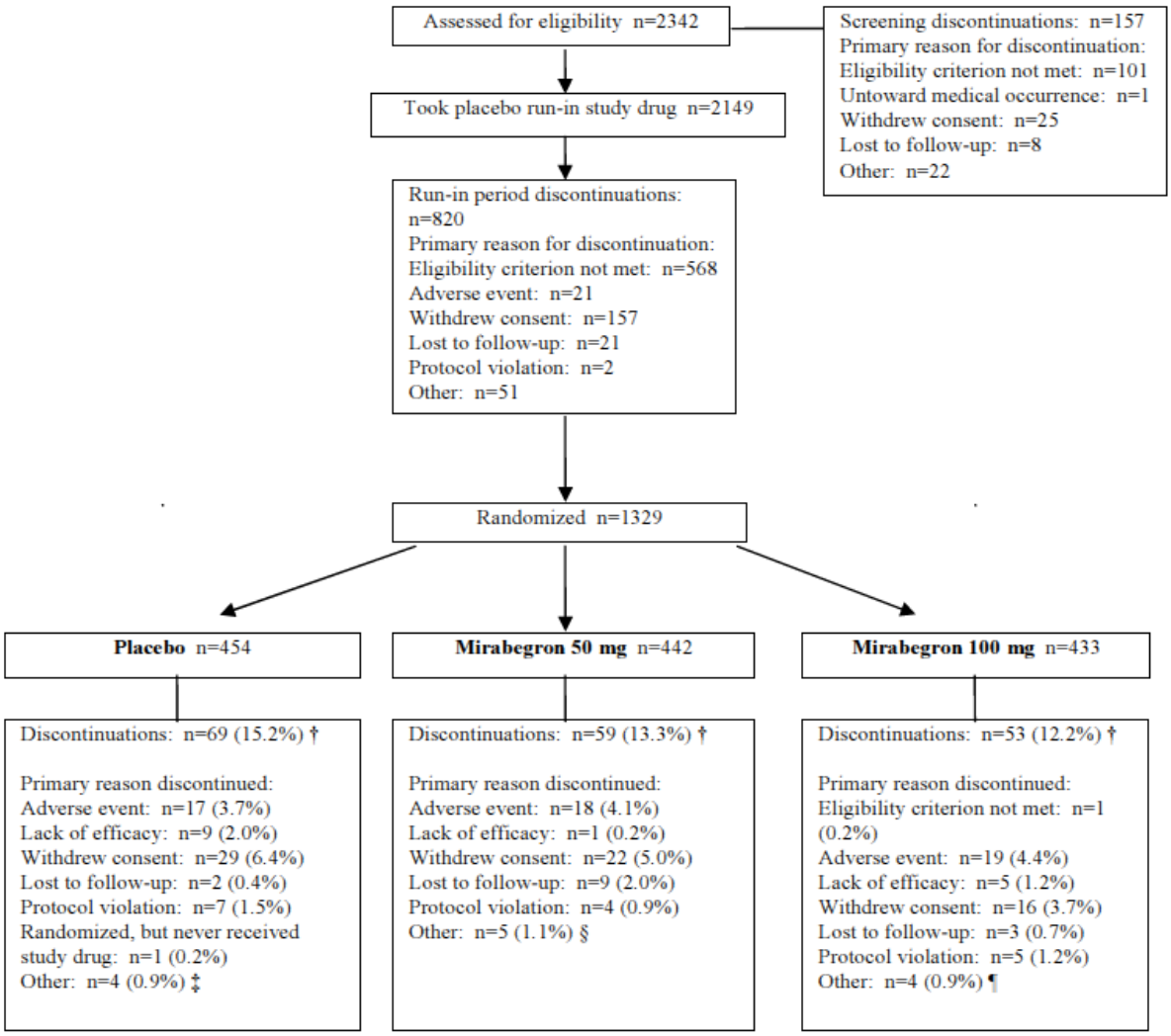
CONSORT flow charts showing the numbers of patients who were eligible to enter the relevant RCTs, and who were randomised and allocated to each treatment are presented in Figure 3 to Figure 5 for SCORPIO, ARIES and CAPRICORN.

Figure 3: Patient flow in SCORPIO



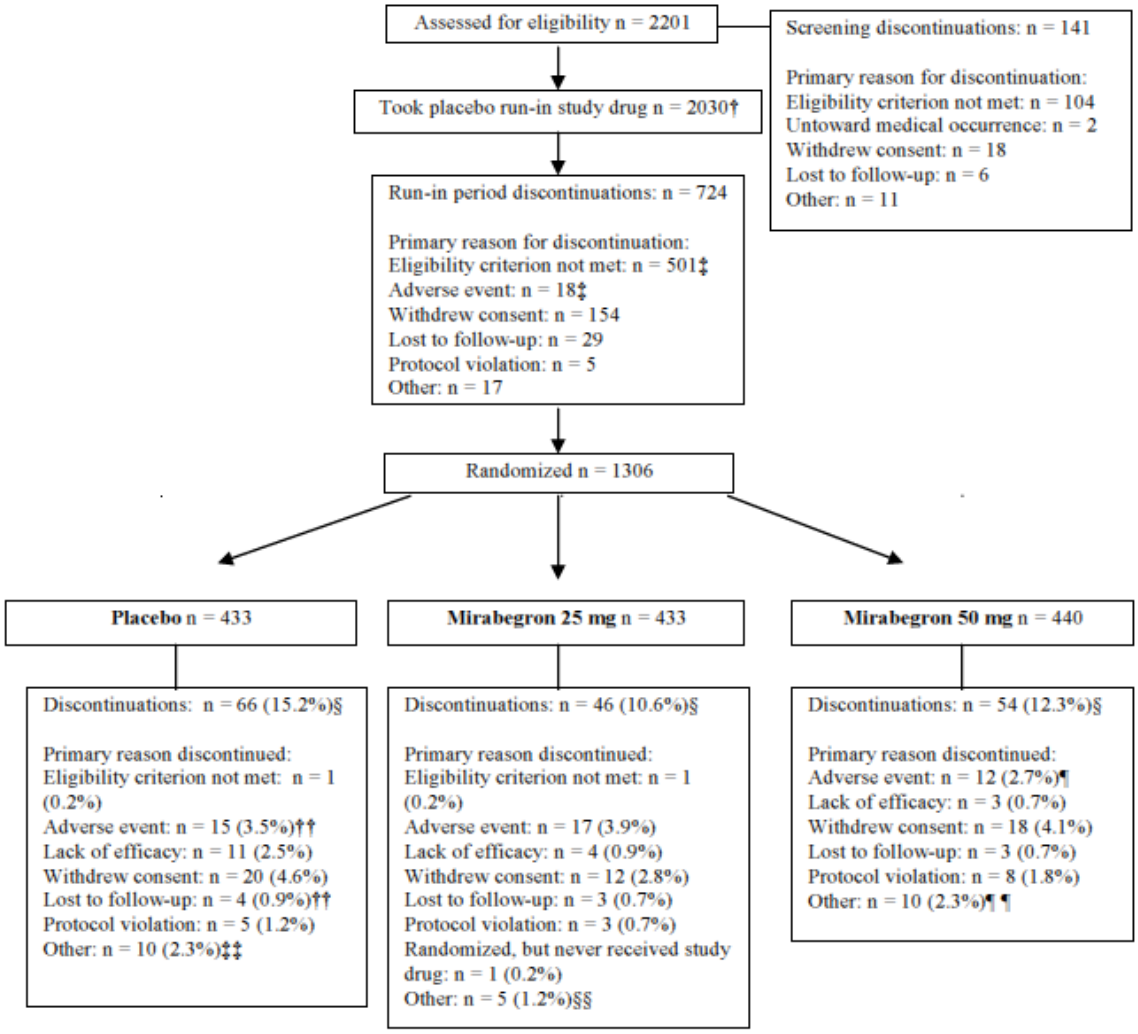
Abbreviations: mg, milligram; SR, slow-release.
†Discontinuations are those reported for patients in the RAS; ‡Other reasons for discontinuation in the placebo group were personal reasons and blood pressure was too difficult to measure; §Other reasons for discontinuation in the mirabegron 50 mg group were unable to commit to study schedule due to work commitments and patient wanted to go to Italy for family reasons and could not return in time to begin the study; ¶Other reasons for discontinuation in the mirabegron 100 mg group were patient was excluded in error and patient had to move to another town in Spain; ††Other reasons for discontinuation in the tolterodine SR 4 mg group were personal reasons and family troubles.

Figure 4: Patient flow in ARIES



Abbreviations: mg, milligram.
†Discontinuations are those reported for patients in the RAS; ‡Other reasons for discontinuation in the placebo group were noncompliance with diary completion; inability to complete diary correctly; error by study site personnel and investigator decision to withdraw patient; §Other reasons for discontinuation in the mirabegron 50 mg group were extreme weather and hazardous travel conditions precluded attendance at site visits; noncompliance with study schedule, diary completion and study drug; family emergency caused patient to run out of study drug; withdrawal by investigator due to visit delay such that patient had not taken study drug for 12 days and average urinary output exceeded baseline exclusion criterion; ¶Other reasons for discontinuation in the mirabegron 100 mg group were withdrawal by investigator; scheduling for excluded procedure; withdrawal by investigator due to noncompliance with protocol and incarceration with concomitant noncompliance with study drug.

Figure 5: Patient flow in CAPRICORN



Abbreviations: mg, milligram; SR, slow-release.
†Thirty patients returned full medication kits at baseline visit (visit 2) indicating that they did not take any study medication and thus were considered run-in failures; ‡One patient in the run-in period experienced an AE of UTI that led to permanent discontinuation of study drug . This patient is included as discontinued due to eligibility criterion not met; §Discontinuations are those reported for patients in the Randomized Analysis Set; ¶One patient in the mirabegron 50 mg group reported an AE prior to start of double-blind study drug that led to permanent discontinuation of study drug; ††One patient in the placebo group experienced a TEAE of chest pain that led to permanent discontinuation of study drug. This patient is included as discontinued due to lost to follow-up; ‡‡Other reasons for discontinuation were medications that were considered exclusionary by the medical monitor, early termination due to medical history, possibility of patient missing safety assessments at visits 5 and 6, and initial ECG conducted on wrong machine which was initially read as abnormal (and was later reread and assessed as normal after the patient was discontinued); §§Other reasons for discontinuation were medications that were considered exclusionary, either by the protocol or by the medical monitor and concomitant leukopenia and thrombocytopenia; ¶ ¶Other reasons for discontinuation were medications that were considered exclusionary either by the protocol or the medical monitor, cannabis use and multiple prior UTIs.

6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion

should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- ***Was the method used to generate random allocations adequate?***
- ***Was the allocation adequately concealed?***
- ***Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?***
- ***Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?***
- ***Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?***
- ***Is there any evidence to suggest that the authors measured more outcomes than they reported?***
- ***Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?***

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See Section 10.3, appendix 3 for a suggested format.

A complete quality assessment for each RCT is provided in Section 10.3.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria.

Critical appraisals of the relevant RCTs are presented in Table 17.

Table 17: Quality assessment results for mirabegron primary RCTs

Study no. (acronym)	178-CL-046 (SCORPIO)	178-CL-047 (ARIES)	178-CL-074 (CAPRICORN)
Was randomisation carried out appropriately?	yes	yes	yes
Was the concealment of treatment allocation adequate?	yes	yes	yes
Were the groups similar at the outset of the study in terms of prognostic factors?	yes	yes	yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	yes	yes	yes
Were there any unexpected imbalances in drop-outs between groups?	no	no	no
Is there any evidence to suggest that the authors measured more outcomes than they reported?	no	no	no
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	yes	yes	yes

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one RCT, tabulate the responses.

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- ***The unit of measurement.***
- ***The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio in an equivalent statistic. Both absolute and relative data should be presented.***
- ***A 95% confidence interval.***
- ***Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.***
- ***When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of***

that RCT. Analytical adjustments should be described to cater for the interim nature of the data.

- ***Other relevant data that may assist in the interpretation of the results may be included, such as adherence to medication and/or study protocol.***
- ***Discuss and justify definitions of any clinically important differences.***
- ***Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.***

6.5.4 Primary RCTs: Studies 178-CL-046 (SCORPIO), 178-CL-047 (ARIES) and 178-CL-074 (CAPRICORN)

Summary of efficacy

- RCT evidence for mirabegron is based on three primary Phase III studies; 178-CL-046 (SCORPIO), 178-CL-047 (ARIES) and 178-CL-074 (CAPRICORN).
  - Significant improvements were observed in the co-primary endpoint of change from baseline to endpoint for mirabegron and placebo in mean number of micturitions (SCORPIO, placebo = -1.34, mirabegron = -1.93; ARIES, placebo = -1.05, mirabegron = -1.66; CAPRICORN, placebo = -1.18, mirabegron = -1.60) and mean number of incontinence episodes per 24 hours (SCORPIO, placebo = -1.17, mirabegron = -1.57; ARIES, placebo = -1.13, mirabegron = -1.47; CAPRICORN, placebo = -0.96, mirabegron = -1.38)
    - The change in mean number of micturitions was significant versus placebo in SCORPIO ($p<0.001$), ARIES ($p=0.001$) and CAPRICORN ($p=0.015$)
    - The change in mean number of incontinence episodes per 24 hours was significant versus placebo in SCORPIO ($p=0.003$), ARIES ($p=0.026$) and CAPRICORN ($p=0.001$).
  - Statistically significant improvements in placebo subtracted change from baseline to final visit were observed for mirabegron 50 mg groups in the secondary efficacy endpoints of:
    - mean volume voided per micturition (SCORPIO, 11.9 mL, $p<0.001$; ARIES, 11.1 mL, $p=0.001$; CAPRICORN, 12.4 mL, $p<0.001$)
    - mean number of urgency episodes (Grade 3 or 4) per 24 hours (SCORPIO, -0.60, $p=0.005$; ARIES, -0.75, $p=0.001$)
    - mean level of urgency (SCORPIO, -0.09, $p=0.018$; ARIES, -0.01, $p=0.004$)
    - mean number of urge incontinence episodes per 24 hours (SCORPIO, -0.35, $p=0.003$; ARIES, -0.43, $p=0.005$)
    - mean number of nocturia episodes per 24 hours (SCORPIO, -0.15, $p=0.022$; ARIES, -0.18, $p=0.043$).
  - Statistically significant improvements were observed in treatment satisfaction scores using the TS VAS in the 50 mg mirabegron groups across all three primary studies.

- Using a more refined, disease specific, health-related quality of life instrument; the OAB-q, statistically significant improvements at 12 weeks for the 50 mg mirabegron groups compared with placebo were observed in:
  - symptom bother score (SCORPIO, placebo = -14.9, mirabegron = -19.6, p<0.001; ARIES, placebo = -11, mirabegron = -17, p<0.001; CAPRICORN, placebo = -16.0, mirabegron = -18.8, p=0.028)
  - HRQoL score (SCORPIO, placebo = 13.7, mirabegron = 16.1, p=0.031) and ARIES, placebo = 10.7, mirabegron = 14.8, p=0.001).
- Long-term evidence from safety study 178-CL-049 (TAURUS) shows that the treatment effect trends continued up to 52 weeks, although no statistical comparisons of efficacy between treatment groups were performed.

Datasets analysed

Dataset definitions have previously been described in Table 16. The number of patients in the datasets presented in this submission are detailed in Table 18 to Table 20 for studies SCORPIO, ARIES and CAPRICORN.

Table 18: Overview of analysis sets in SCORPIO

Analysis set, n (%)	Placebo	Mirabegron		Tolterodine SR 4 mg	Total
		50 mg	100 mg		
RAS	497 (100.0)	497 (100.0)	498 (100.0)	495 (100.0)	1987 (100.0)
FAS	480 (96.6)	473 (95.2)	478 (96.0)	475 (96.0)	1906 (95.9)
FAS-I	291 (58.6)	293 (59.0)	281 (56.4)	300 (60.6)	1165 (58.6)
ITT	493 (99.2)	492 (99.0)	496 (99.6)	495 (100.0)	1976 (99.4)
ITT-I	299 (60.2)	309 (62.2)	294 (59.0)	311 (62.8)	1213 (61.0)
SAS	494 (99.4)	493(99.2)	496 (99.6)	495 (100.0)	1978 (99.5)

Abbreviations: FAS, full analysis set; FAS-I, full analysis set-incontinence; ITT, intent-to-treat; ITT-I, intent-to-treat-incontinence set; mg, milligram; RAS, randomised analysis set; SAS, safety analysis set; SR, slow-release.

Table 19: Overview of analysis sets in ARIES

Analysis set, n (%)	Placebo	Mirabegron		Total
		50 mg	100 mg	
RAS	454 (100.0)	442 (100.0)	433 (100.0)	1329 (100.0)
FAS	433 (95.4)	425 (96.2)	412 (95.2)	1270 (95.6)
FAS-I	325 (71.6)	312 (70.6)	296 (68.4)	933 (70.2)
ITT	453 (99.8)	442 (100.0)	433 (100.0)	1328 (99.9)
ITT-I	339 (74.7)	326 (73.8)	309 (71.4)	974 (73.3)
SAS	453 (99.8)	442 (100.0)	433 (100.0)	1328 (99.9)

Abbreviations: FAS, full analysis set; FAS-I, full analysis set-incontinence; ITT, intent-to-treat; ITT-I, intent-to-treat-incontinence set; mg, milligram; RAS, randomised analysis set; SAS, safety analysis set.

Table 20: Overview of analysis sets in CAPRICORN

Analysis set, n (%)	Placebo	Mirabegron		Total
		25 mg	50 mg	
RAS	433 (100.0)	433 (100.0)	440 (100.0)	1306 (100.0)
FAS	415 (95.8)	410 (94.7)	426 (96.8)	1251 (95.8)
FAS-I	262 (60.5)	254 (58.7)	257 (58.4)	773 (59.2)
ITT	433 (100.0)	432 (99.8)	440 (100.0)	1305 (99.9)
ITT-I	276 (63.7)	271 (62.6)	268 (60.9)	815 (62.4)
SAS	433 (100.0)	432 (99.8)	440 (100.0)	1305 (99.9)

Abbreviations: FAS, full analysis set; FAS-I, full analysis set-incontinence; ITT, intent-to-treat; ITT-I, intent-to-treat-incontinence set; mg, milligram; RAS, randomised analysis set; SAS, safety analysis set.

Co-primary efficacy results

Change from baseline to endpoint in mean number of micturitions per 24 hours

The change from baseline to endpoint in the mean number of micturitions per 24 hours was a co-primary endpoint in SCORPIO, ARIES and CAPRICORN. Significant differences in the mean number of micturitions were observed in the mirabegron groups compared with placebo in all three studies (Table 21).

Table 21: Co-primary efficacy result: Change from baseline to endpoint in mean number of micturitions per 24 hours for the primary RCTs, FAS

178-CL-046 (SCORPIO)	Placebo N=480	Mirabegron		Tolterodine SR 4 mg N=475
		50 mg N=473	100 mg N=478	
Adjusted mean CFB	-1.34	-1.93	-1.77	-1.59
SE	0.110	0.111	0.110	0.111
95% CI	-1.55, -1.12	-2.15, -1.72	-1.99, -1.56	-1.80, -1.37
Mean difference vs placebo	N/A	-0.60	-0.44	-0.25
SE	N/A	0.156	0.156	0.156
95% CI	N/A	-0.90, -0.29	-0.74, -0.13	-0.55, 0.06
p-value	N/A	<0.001	0.005	0.11
178-CL-047 (ARIES)	**Placebo N=433**	**Mirabegron**		
		50 mg N=425	**100 mg N=412**	
Adjusted mean CFB	-1.05	-1.66	-1.75	
SE	0.132	0.133	0.135	
95% CI	-1.31, -0.79	-1.92, -1.40	-2.01, -1.48	
Mean difference vs placebo	N/A	-0.61	-0.70	
SE	N/A	0.188	0.189	
95% CI	N/A	-0.98, -0.24	-1.07, -0.33	
p-value	N/A	0.001	<0.001	

178-CL-074 (CAPRICORN)	Placebo N=415	Mirabegron	
		25 mg N=410	50 mg N=426
Adjusted mean CFB	-1.18	-1.65	-1.60
SE	0.124	0.125	0.122
95% CI	-1.42, -0.94	-1.90, -1.41	-1.84, -1.36
Mean difference vs placebo	N/A	-0.47	-0.42
SE	N/A	0.176	0.174
95% CI	N/A	-0.82, -0.13	-0.76, -0.08
p-value	N/A	0.007	0.015

Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SE, standard error; SR slow-release.

A further analysis of the ITT dataset was performed (Table 22). As with the FAS dataset analysis, significant differences in the mean number of micturitions were observed in the mirabegron groups compared with placebo in all three studies

Table 22: Co-primary efficacy result secondary analyses: Change from baseline to final visit in mean number of micturitions per 24 hours for the primary RCTs, ITT

178-CL-046 (SCORPIO)	Placebo N=493	Mirabegron		Tolterodine SR 4 mg N=495
		50 mg N=492	100 mg N=496	
Adjusted mean CFB	-1.30	-1.86	-1.71	-1.53
SE	0.108	0.108	0.107	0.107
95% CI	-1.51,-1.09	-2.07,-1.65	-1.92,-1.50	-1.74,-1.32
Mean difference vs placebo	N/A	-0.56	-0.41	-0.23
SE	N/A	0.152	0.152	0.152
95% CI	N/A	-0.86,-0.26	-0.71,-0.11	-0.53,0.07
p-value	N/A	<0.001	0.007	0.14
178-CL-047 (ARIES)	**Placebo N=453**	**Mirabegron**		
		50 mg N=442	**100 mg N=433**	
Adjusted mean CFB	-1.00	-1.60	-1.65	
SE	0.128	0.129	0.131	
95% CI	-1.26, -0.75	-1.86, -1.35	-1.91, -1.40	
Mean difference vs placebo	N/A	-0.60	-0.65	
SE	N/A	0.182	0.183	
95% CI	N/A	-0.96, -0.24	-1.01, -0.29	
p-value	N/A	0.001	<0.001	
178-CL-074 (CAPRICORN)	**Placebo N=433**	**Mirabegron**		
		25 mg N=432	**50 mg N=440**	

Adjusted mean CFB	-1.12	-1.58	-1.55
SE	0.120	0.120	0.119
95% CI	-1.35,-0.88	-1.82,-1.35	-1.79,-1.32
Mean difference vs placebo	N/A	-0.46	-0.43
SE	N/A	0.170	0.169
95% CI	N/A	-0.80,-0.13	-0.77,-0.10
p-value	N/A	0.007	0.010

Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SE, standard error; SR slow-release.

Change from baseline to endpoint in mean number of incontinence episodes per 24 hours

The change from baseline to endpoint in the mean number of incontinence episodes per 24 hours was a co-primary endpoint in SCORPIO, ARIES and CAPRICORN. Significant differences in the mean number of incontinence episodes were observed in all mirabegron groups compared with placebo in all three studies (Table 23).

Table 23: Co-primary efficacy result: Change from baseline to endpoint in mean number of incontinence episodes per 24 hours for the primary RCTs, FAS-I

178-CL-046 (SCORPIO)	**Placebo N=291**	**Mirabegron**		**Tolterodine SR 4 mg N=300**
		50 mg N=293	**100 mg N=281**	
Adjusted mean CFB	-1.17	-1.57	-1.46	-1.27
SE	0.113	0.113	0.115	0.112
95% CI	-1.39, -0.95	-1.79, -1.35	-1.68, -1.23	-1.49, -1.05
Mean difference vs placebo	N/A	-0.41	-0.29	-0.10
SE	N/A	0.160	0.162	0.159
95% CI	N/A	-0.72, -0.09	-0.61, 0.03	-0.42, 0.21
p-value	N/A	0.003	0.010	0.11
178-CL-047 (ARIES)	**Placebo N=325**	**Mirabegron**		
		50 mg N=312	**100 mg N=296**	
Adjusted mean CFB	-1.13	-1.47	-1.63	
SE	0.112	0.114	0.117	
95% CI	-1.35, -0.91	-1.69, -1.25	-1.86, -1.40	
Mean difference vs placebo	N/A	-0.34	-0.50	
SE	N/A	0.160	0.162	
95% CI	N/A	-0.66, -0.03	-0.82, -0.18	
p-value	N/A	0.026	<0.001	
178-CL-074 (CAPRICORN)	**Placebo N=262**	**Mirabegron**		
		25 mg N=254	**50 mg N=257**	

Adjusted mean CFB	-0.96	-1.36	-1.38
SE	0.122	0.124	0.123
95% CI	-1.19, -0.72	-1.60, -1.11	-1.62, -1.14
Mean difference vs placebo	N/A	-0.40	-0.42
SE	N/A	0.174	0.173
95% CI	N/A	-0.74, -0.06	-0.76, -0.08
p-value	N/A	0.005	0.001

Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SE, standard error; SR, slow-release.

Table 24: Co-primary efficacy result secondary analyses: Change from baseline to final visit in mean number of incontinence episodes per 24 hours for the primary RCTs, ITT-I

178-CL-046 (SCORPIO)	**Placebo N=299**	**Mirabegron**		**Tolterodine SR 4 mg N=311**
		50 mg N=309	**100 mg N=294**	
Adjusted mean CFB	-1.15	-1.52	-1.34	-1.23
SE	0.112	0.110	0.113	0.110
95% CI	-1.37,-0.93	-1.73,-1.30	-1.57,-1.12	-1.45,-1.02
Mean difference vs placebo	N/A	-0.36	-0.19	-0.08
SE	N/A	0.157	0.159	0.157
95% CI	N/A	-0.67,-0.06	-0.50,0.12	-0.39,0.23
p-value	N/A	0.015	0.047	0.19
178-CL-047 (ARIES)	**Placebo N=339**	**Mirabegron**		
		50 mg N=326	**100 mg N=309**	
Adjusted mean CFB	-1.07	-1.40	-1.58	
SE	0.109	0.111	0.115	
95% CI	-1.29, -0.86	-1.62, -1.18	-1.80, -1.35	
Mean difference vs placebo	N/A	-0.32	-0.50	
SE	N/A	0.156	0.158	
95% CI	N/A	-0.63, -0.02	-0.81, -0.19	
p-value	N/A	0.041	<0.001	
178-CL-074 (CAPRICORN)	**Placebo N=276**	**Mirabegron**		
		25 mg N=271	**50 mg N=268**	
Adjusted mean CFB	-0.91	-1.25	-1.34	
SE	0.119	0.120	0.120	
95% CI	-1.14,-0.67	-1.49,-1.02	-1.58,-1.11	
Mean difference vs placebo	N/A	-0.34	-0.44	
SE	N/A	0.169	0.169	
95% CI	N/A	-0.67,-0.01	-0.77,-0.10	

p-value	N/A	0.015	<0.001

Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SE, standard error; SR, slow-release.

Secondary efficacy results

Change from baseline to Weeks 4, 8, 12 in mean number of micturitions per 24 hours

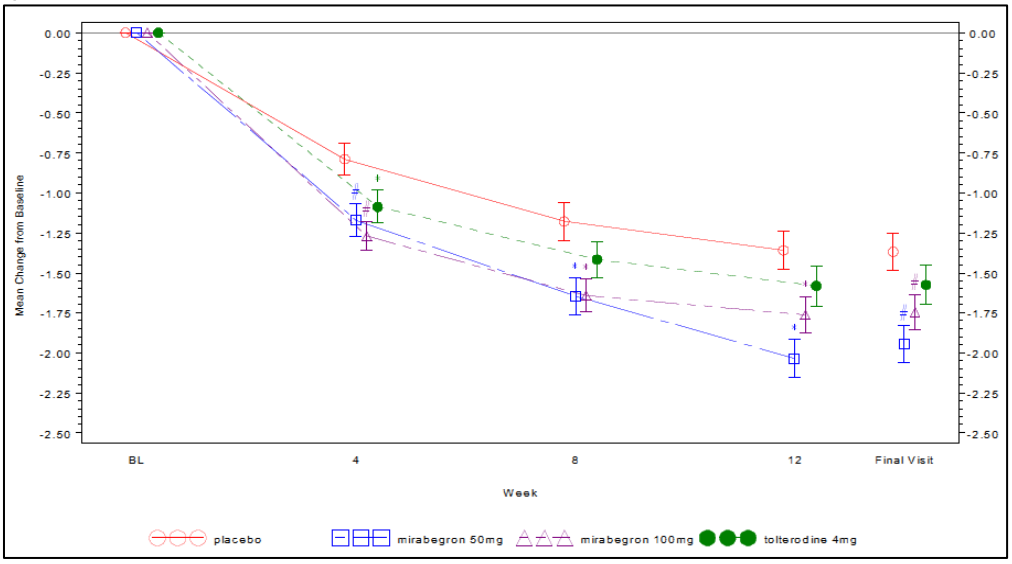
Change from baseline in mean number of micturitions per 24 hours in SCORPIO, ARIES and CAPRICORN are presented in Figure 6.

- In SCORPIO all three active treatment groups (mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg) demonstrated statistically significant differences from baseline to Week 4 in the reduction in the mean number of micturitions per 24 hours compared with placebo. At Weeks 8 and 12, mirabegron 50 mg and 100 mg continued to demonstrate statistically significant differences, however, the difference was not statistically significant for the tolterodine SR 4 mg group after Week 4.
- In ARIES, efficacy for mirabegron 50 mg and 100 mg versus placebo was observed as early as Week 4; both mirabegron groups demonstrated a statistically significant difference from baseline to Week 4 in the reduction in the mean number of micturitions per 24 hours compared with placebo. At Weeks 8 and 12, mirabegron 50 mg and 100 mg continued to demonstrate statistically significant differences from baseline in the reduction in the mean number of micturitions per 24 hours compared with placebo.
- In CAPRICORN, neither mirabegron group demonstrated a statistically significant difference in reduction from baseline to Week 4 in the mean number of micturitions per 24 hours compared with placebo due to multiplicity adjustment (25 mg, p=0.30; 50 mg, p=0.035). The mirabegron 50 mg group achieved a numerically greater adjusted mean difference versus placebo than the mirabegron 25 mg group. Efficacy for mirabegron 25 mg and 50 mg versus placebo was observed at Week 8. A numerical advantage was maintained in both groups at Week 12 relative to placebo; however, the difference was not statistically significant, likely due to the magnitude of the placebo effect on micturition frequency at Week 12.

Figure 6: Change from baseline in mean number of micturitions per 24 hours for the primary RCTs, FAS

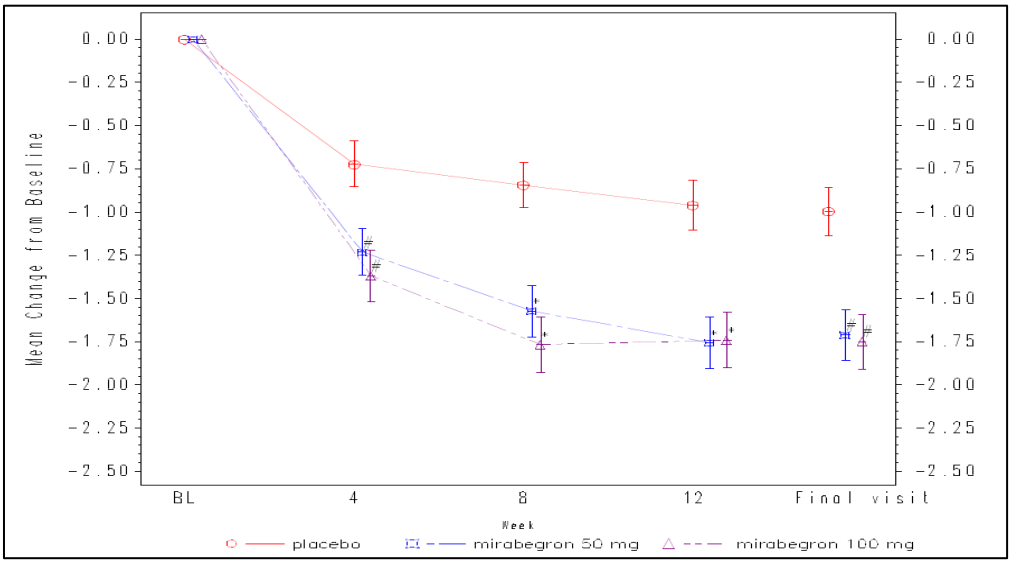
178-CL-046

(SCORPIO)



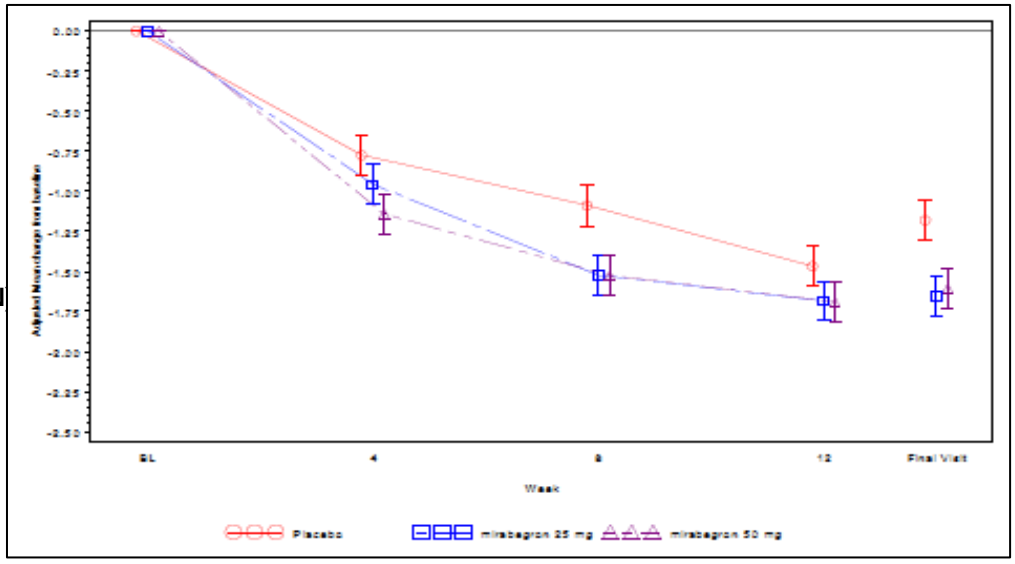
178-CL-047

(ARIES)



178-CL-074

(CAPRICORN



Abbreviations: mg, milligram.

Change from baseline to Weeks 4, 8, 12 in mean number of incontinence episodes per 24 hours,

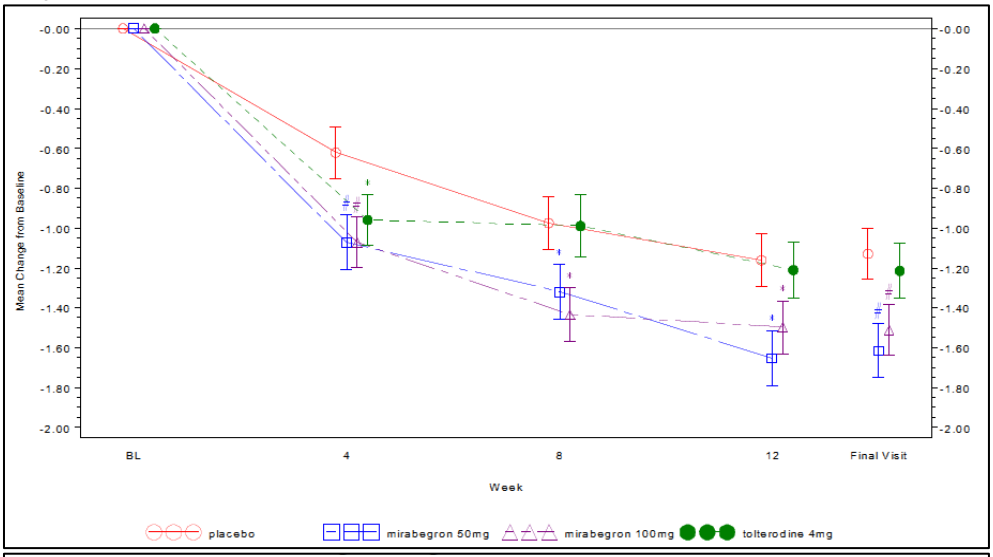
Change from baseline in the mean number of incontinence episodes per 24 hours are presented in Figure 7 for the FAS-I datasets in SCORPIO, ARIES and CAPRICORN.

- In SCORPIO, efficacy of mirabegron 50 mg and 100 mg and tolterodine SR 4 mg versus placebo was demonstrated as early as Week 4. Both mirabegron doses and tolterodine demonstrated statistically significant decreases in the mean number of incontinence episodes per 24 hours compared with placebo. This efficacy was maintained over time (statistically significant at Weeks 8 and 12) for mirabegron 50 mg and 100 mg but was not statistically significant for the tolterodine SR 4 mg group after Week 4.
- In ARIES, both mirabegron groups demonstrated statistically significant differences in the reduction in the mean number of incontinence episodes per 24 hours compared with placebo as early as Week 4. At Weeks 8 and 12, mirabegron 50 mg and 100 mg continued to demonstrate statistically significant differences from baseline compared with placebo.
- In CAPRICORN, efficacy of mirabegron 50 mg versus placebo was demonstrated at the first measured time point at Week 4. At Weeks 8 and 12, both mirabegron 25 mg and 50 mg demonstrated statistically significant differences from baseline versus placebo.

Figure 7: Change from baseline in mean number of incontinence episodes per 24 hours for the primary RCTs, FAS-I

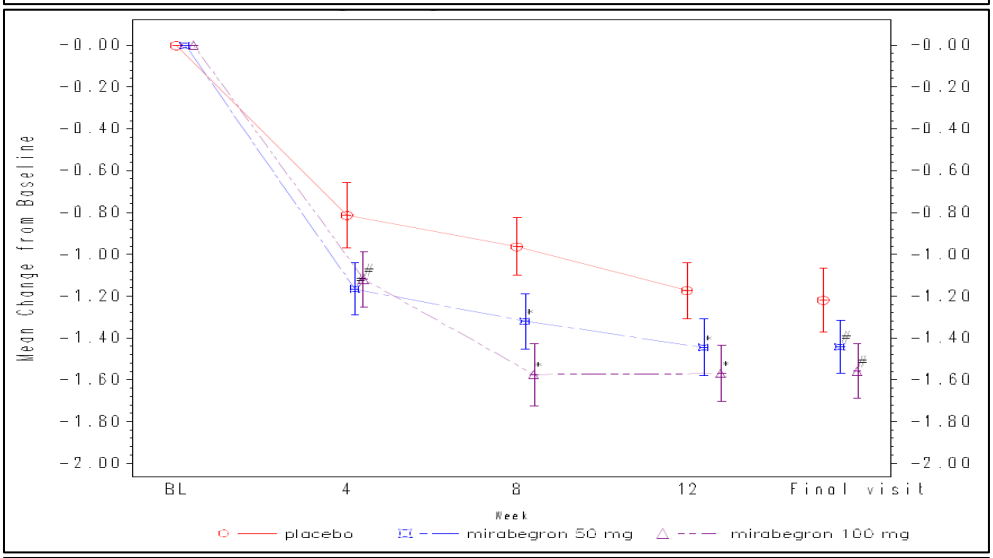
178-CL-046

(SCORPIO)



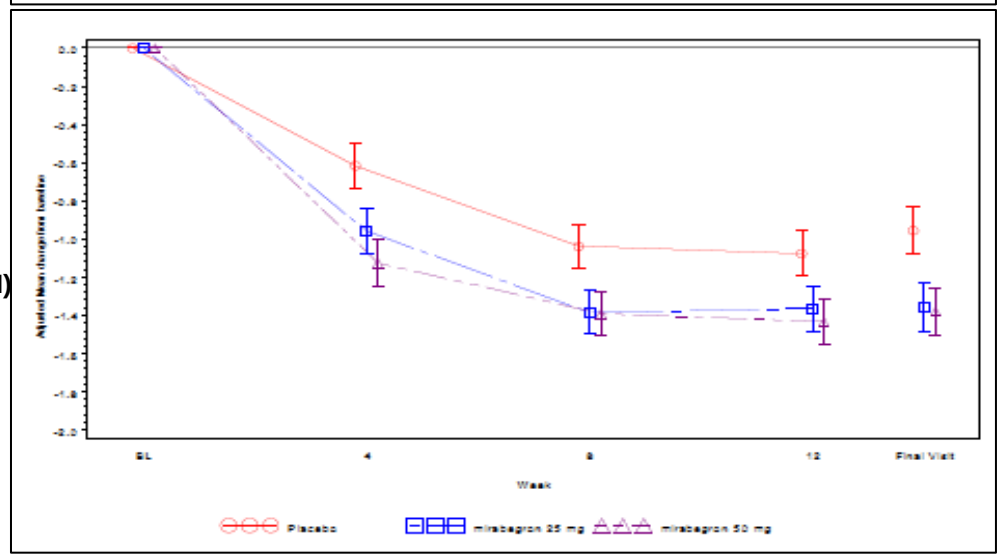
178-CL-047

(ARIES)



178-CL-074

(CAPRICORN)



Abbreviations: mg, milligram.

Change from baseline in mean volume voided per micturition, mean number of urgency episodes (Grade 3/4) per 24 hours, mean level of urgency, mean number of urge incontinence episodes per 24 hours and mean number of nocturia episodes per 24 hours

Results of the secondary outcomes; change from baseline in mean volume voided per micturition, mean number of urgency episodes (Grade 3/4) per 24 hours, mean level of urgency, mean number of urge incontinence episodes per 24 hours and mean number of nocturia episodes per 24 hours are provided in Table 25.

Table 25: Secondary outcomes; change from baseline in mean volume voided per micturition, mean number of urgency episodes (Grade 3/4) per 24 hours, mean level of urgency, mean number of urge incontinence episodes per 24 hours and mean number of nocturia episodes per 24 hours

	178-CL-046 (SCORPIO)				178-CL-047 (ARIES)			178-CL-074 (CAPRICORN)		
	Placebo N=480	Mirabegron		Tolterodine SR 4 mg N=475	Placebo N=433	Mirabegron		Placebo N=415	Mirabegron	
		50 mg N=473	100 mg N=478			50 mg N=425	100 mg N=412		25 mg N=410	50 mg N=426
Mean volume voided (mL) per micturition, FAS										
n	*480*	*472*	*478*	*475*	*433*	*424*	*412*	*415*	*410*	*426*
Adjusted mean CFB to final visit	12.3	24.2	25.6	25.0	7.0	18.2	18.0	8.3	12.8	20.7
SE	1.99	2.01	2.00	2.00	2.41	2.44	2.47	2.23	2.24	2.20
Estimated difference vs placebo	N/A	11.9	13.2	12.6	N/A	11.1	11.0	N/A	4.6	12.4
95% CI	N/A	6.3, 17.4	7.7, 18.7	7.1, 18.2	N/A	4.4, 17.9	4.2, 17.7	N/A	-1.6, 10.8	6.3, 18.6
p-value	N/A	<0.001	<0.001	<0.001	N/A	0.001	0.002	N/A	0.15	<0.001
Significant after multiplicity adjustment?	N/A	Yes	Yes	NR	N/A	Yes	Yes	N/A	No	Yes
Mean number urgency episodes (Grade 3/4) per 24 hours, FAS										
n	*479*	*470*	*474*	*472*	*432*	*424*	*411*	*413*	*410*	*426*
Adjusted mean CFB to final visit	-1.65	-2.25	-1.96	-2.07	-0.82	-1.57	-1.76	-1.35	-1.68	-1.94

SE	0.151	0.152	0.151	0.152	0.161	0.162	0.165	0.154	0.155	0.152
Estimated difference vs placebo	N/A	-0.60	-0.31	-0.42	N/A	-0.75	-0.94	N/A	-0.33	-0.59
95% CI	N/A	-1.02, -0.18	-0.73, 0.11	-0.84, -0.00	N/A	-1.20, -0.30	-1.40, -0.49	N/A	-0.76, 0.10	-1.01, -0.16
p-value	N/A	0.005	0.14	0.050	N/A	0.001	<0.001	N/A	0.13	0.007
Significant after multiplicity adjustment?	N/A	NR	NR	NR	N/A	NR	NR	N/A	No	No
Mean level of urgency, FAS										
n	NR	NR	NR	NR	*432*	*425*	*411*	*413*	*410*	*426*
Adjusted mean CFB to final visit	-0.22	-0.31	-0.30	-0.29	-0.08	-0.19	-0.21	-0.15	-0.22	-0.29
SE	0.028	0.028	0.028	0.028	0.026	0.026	0.027	0.028	0.029	0.028
Estimated difference vs placebo	N/A	-0.09	-0.08	-0.07	N/A	-0.11	-0.13	N/A	-0.07	-0.14
95% CI	N/A	-0.17, -0.02	-0.16, -0.01	-0.15, 0.01	N/A	-0.18, -0.04	-0.20, -0.05	N/A	-0.15, 0.01	-0.22, -0.06
p-value	N/A	0.018	0.037	0.085	N/A	0.004	<0.001	N/A	0.083	<0.001
Significant after multiplicity adjustment?	N/A	NR	NR	NR	N/A	NR	NR	N/A	No	No
Mean number of nocturia episodes per 24 hours, FAS										
n	*428*	*423*	*422*	*433*	*366*	*348*	*356*	*362*	*362*	*378*
Adjusted mean CFB to final visit	-0.41	-0.56	-0.50	-0.45	-0.38	-0.57	-0.57	-0.48	-0.49	-0.52
SE	0.047	0.047	0.047	0.047	0.063	0.065	0.064	0.058	0.058	0.057
Estimated difference vs placebo	N/A	-0.15	-0.09	-0.04	N/A	-0.18	-0.19	N/A	-0.01	-0.04
95% CI	N/A	-0.28, -0.02	-0.22, 0.04	-0.17, 0.09	N/A	-0.36, -0.01	-0.37, -0.01	N/A	-0.17, 0.15	-0.20, 0.12
p-value	N/A	0.022	0.20	0.52	N/A	0.043	0.036	N/A	0.93	0.63

Significant after multiplicity adjustment?	N/A	NR	NR	NR	N/A	NR	NR	N/A	No	No
Mean number of urge incontinence episodes per 24 hours, FAS-I										
n	*283*	*286*	*276*	*289*	*319*	*297*	*291*	*256*	*247*	*251*
Adjusted mean CFB to final visit	-1.11	-1.46	-1.33	-1.18	-0.89	-1.32	-1.45	-0.95	-1.31	-1.33
SE	0.110	0.109	0.111	0.109	0.100	0.104	0.105	0.110	0.112	0.111
Estimated difference vs placebo	N/A	-0.35	-0.22	-0.07	N/A	-0.43	-0.56	N/A	-0.36	-0.39
95% CI	N/A	-0.65, -0.05	-0.53, 0.09	-0.38, 0.23	N/A	-0.72, -0.15	-0.85, -0.28	N/A	-0.67, -0.05	-0.69, -0.08
p-value	N/A	0.003	0.024	0.26	N/A	0.005	<0.001	N/A	0.004	0.002
Significant after multiplicity adjustment?	N/A	NR	NR	NR	N/A	NR	NR	N/A	No	No

Abbreviations: CFB, change from baseline; CI, confidence interval; FAS, full analysis set; FAS-I, full analysis set – incontinence; mg, milligrams; mL, milli-litre; N/A, not applicable; NR, not reported; SR, slow-release; vs, versus.

Change from baseline in mean number of pads used per 24 hours

Within the three studies, SCORPIO, ARIES and CAPRICORN, the mean number of pads used per 24 hours was comparable across all treatment groups at baseline. In all treatment groups, there was a reduction in the mean number of pads used per 24 hours from baseline to final visit.

- In SCORPIO, all three active treatment groups demonstrated a statistically significant difference from baseline to Week 4, 8 and 12 in the reduction in the mean number of pads used per 24 hours compared with placebo. At Week 4, the adjusted mean difference versus placebo was -0.28, -0.36 and -0.22 pads for the mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg groups, respectively. Mirabegron 100 mg demonstrated statistically significant decreases versus placebo in the mean number of pads used at Week 4. The magnitude of the decrease in mean number of pads relative to placebo observed at Week 4 was maintained at Weeks 8 and 12 for the mirabegron 50 mg group only.
- In ARIES, both mirabegron groups demonstrated statistically significant differences from baseline to Weeks 4, 8, 12 and final visit in the reduction in the mean number of pads used per 24 hours compared with placebo. At Week 4, the adjusted mean difference versus placebo was -0.38 (mirabegron 50 mg) and -0.37 (mirabegron 100 mg). The magnitude of reduction in mean number of pads relative to placebo observed at Week 4 was maintained at Weeks 8 and 12 for both mirabegron groups.
- In CAPRICORN, the adjusted mean difference from placebo for the mirabegron 25 mg and 50 mg groups at final visit was 0.16 (more pad use) and -0.17 (less pad use), respectively. At Weeks 4, 8 and 12, respectively, the adjusted mean difference versus placebo was +0.13, +0.18 and +0.17 for the mirabegron 25 mg group and was -0.09, -0.19 and -0.11 for the mirabegron 50 mg group. There was no statistically significant difference from placebo in either mirabegron group at any time point in mean number of pads used per 24 hours.

HRQoL and treatment satisfaction

HRQoL and treatment satisfaction was assessed using generic scales such as EQ-5D, EQ-5D VAS, TS-VAS and WPAI:SHP, and disease specific scales OABq, PPBC (described in Section 10.15).

QoL assessment using OAB-q symptom bother and OAB-q HRQoL

Assessment of HRQoL was also conducted using the disease specific scale: OAB-q with domains for symptom bother (Table 26), concern (Table 27), coping (Table 28), social (Table 29), sleep (Table 30) and total HRQoL (Table 31).

Table 26: OAB-q symptom bother score for the primary RCTs

178-CL-046 (SCORPIO)	**Placebo N=480**	**Mirabegron**		**Tolterodine SR 4 mg N=475**
		50 mg N=473	**100 mg N=478**	
n	*475*	*465*	*473*	*469*
Adjusted mean CFB to final visit	-14.9	-19.6	-19.9	-18.4
Estimated difference vs placebo	N/A	-4.7	-5.0	-3.5
95% CI	N/A	-7.1, -2.4	-7.3, -2.6	-5.9, -1.2
p-value	N/A	<0.001	<0.001	0.003
178-CL-047 (ARIES)	**Placebo N=433**	**Mirabegron**		
		50 mg N=425	**100 mg N=412**	
n	*356*	*350*	*344*	
Adjusted mean CFB to final visit	-10.8	-17.0	-20.2	
Estimated difference vs placebo	N/A	-6.2	-9.3	
95% CI	N/A	-8.9, -3.5	-12.1, -6.6	
p-value	N/A	<0.001	<0.001	
178-CL-074 (CAPRICORN)	**Placebo N=415**	**Mirabegron**		
		25 mg N=410	**50 mg N=426**	
n	*405*	*407*	*422*	
Adjusted mean CFB to final visit	16.0	-17.9	-18.8	
Estimated difference vs placebo	N/A	-1.8	-2.8	
95% CI	N/A	-4.3, 0.7	-5.3, -0.3	
p-value	N/A	0.15	0.028	

Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SR, slow-release.

Table 27: OAB-q concern score for the primary RCTs

178-CL-046 (SCORPIO)	**Placebo N=480**	**Mirabegron**		**Tolterodine SR 4 mg N=475**
		50 mg N=473	**100 mg N=478**	
n	*474*	*469*	*474*	*470*
Adjusted mean CFB to final visit	15.7	18.4	19.0	16.2
Estimated difference vs placebo	N/A	2.6	3.2	0.4
95% CI	N/A	0.2, 5.0	0.8, 5.6	-2.0, 2.8
p-value	N/A	0.033	0.008	0.74

178-CL-047 (ARIES)	Placebo N=433	Mirabegron	
		50 mg N=425	100 mg N=412
n	*356*	*350*	*344*
Adjusted mean CFB to final visit	12.7	18.0	20.5
Estimated difference vs placebo	N/A	5.3	7.7
95% CI	N/A	2.4, 8.2	4.8, 10.6
p-value	N/A	<0.001	<0.001
178-CL-074 (CAPRICORN)	**Placebo N=415**	**Mirabegron**	
		25 mg N=410	**50 mg N=426**
n	*407*	*408*	*421*
Adjusted mean CFB to final visit	14.7	15.8	16.2
Estimated difference vs placebo	N/A	1.0	1.5
95% CI	N/A	-1.5, 3.6	-1.0, 4.0
p-value	N/A	0.43	0.24

Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SR, slow-release.

Table 28: OAB-q coping score for the primary RCTs

178-CL-046 (SCORPIO)	Placebo N=480	Mirabegron		Tolterodine SR 4 mg N=475
		50 mg N=473	100 mg N=478	
n	*474*	*468*	*473*	*470*
Adjusted mean CFB to final visit	15.5	18.5	19.9	17.8
Estimated difference vs placebo	N/A	2.9	4.3	2.3
95% CI	N/A	0.4, 5.5	1.8, 6.9	-0.3, 4.8
p-value	N/A	0.025	<.001	0.083
178-CL-047 (ARIES)	**Placebo N=433**	**Mirabegron**		
		50 mg N=425		**100 mg N=412**
n	*355*	*350*		*344*
Adjusted mean CFB to final visit	12.8	16.9		19.1
Estimated difference vs placebo	N/A	4.1		6.3
95% CI	N/A	1.1, 7.1		3.4, 9.3
p-value	N/A	0.007		<0.001

178-CL-074 (CAPRICORN)	Placebo N=415	Mirabegron	
		25 mg N=410	50 mg N=426
n	*406*	*408*	*419*
Adjusted mean CFB to final visit	14.7	16.9	16.4
Estimated difference vs placebo	N/A	2.2	1.7
95% CI	N/A	-0.5, 4.9	-0.9, 4.4
p-value	N/A	0.10	0.20

Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SR, slow-release.

Table 29: OAB-q social score for the primary RCTs

178-CL-046 (SCORPIO)	Placebo N=480	Mirabegron		Tolterodine SR 4 mg N=475
		50 mg N=473	100 mg N=478	
n	*475*	*469*	*472*	*470*
Adjusted mean CFB to final visit	8.7	10.1	10.9	8.8
Estimated difference vs placebo	N/A	1.4	2.2	0.1
95% CI	N/A	-0.5, 3.3	0.3, 4.1	-1.7, 2.0
p-value	N/A	0.15	0.024	0.88
178-CL-047 (ARIES)	**Placebo N=433**	**Mirabegron**		
		50 mg N=425		**100 mg N=412**
n	*355*	*350*		*344*
Adjusted mean CFB to final visit	6.0	7.4		9.6
Estimated difference vs placebo	N/A	1.4		3.7
95% CI	N/A	-0.7, 3.6		1.5, 5.8
p-value	N/A	0.19		<0.001
178-CL-074 (CAPRICORN)	**Placebo N=415**	**Mirabegron**		
		25 mg N=410		**50 mg N=426**
n	*406*	*409*		*420*
Adjusted mean CFB to final visit	7.1	8.2		7.7
Estimated difference vs placebo	N/A	1.1		0.6
95% CI	N/A	-0.8, 3.0		-1.3, 2.5
p-value	N/A	0.25		0.54

Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SR, slow-release.

Table 30: OAB-q sleep score for the primary RCTs

178-CL-046 (SCORPIO)	**Placebo N=480**	**Mirabegron**		**Tolterodine SR 4 mg N=475**
		50 mg N=473	**100 mg N=478**	
n	*475*	*469*	*474*	*470*
Adjusted mean CFB to final visit	13.2	15.1	15.8	13.9
Estimated difference vs placebo	N/A	1.9	2.6	0.7
95% CI	N/A	-0.5, 4.3	0.2, 5.0	-1.7, 3.1
p-value	N/A	0.12	0.034	0.56
178-CL-047 (ARIES)	**Placebo N=433**	**Mirabegron**		
		50 mg N=425	**100 mg N=412**	
n	*356*	*350*	*344*	
Adjusted mean CFB to final visit	9.7	14.6	17.5	
Estimated difference vs placebo	N/A	4.9	7.8	
95% CI	N/A	1.9, 7.9	4.8, 10.8	
p-value	N/A	0.001	0.001	
178-CL-074 (CAPRICORN)	**Placebo N=415**	**Mirabegron**		
		25 mg N=410	**50 mg N=426**	
n	*407*	*408*	*421*	
Adjusted mean CFB to final visit	14.0	14.3	14.5	
Estimated difference vs placebo	N/A	0.3	0.4	
95% CI	N/A	-2.4, 2.9	-2.2, 3.1	
p-value	N/A	0.84	0.76	

Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SR, slow-release.

Table 31: OAB-q HRQoL total score for the primary RCTs

178-CL-046 (SCORPIO)	**Placebo N=480**	**Mirabegron**		**Tolterodine SR 4 mg N=475**
		50 mg N=473	**100 mg N=478**	
n	*473*	*468*	*472*	*470*
Adjusted mean CFB to final visit	13.7	16.1	17.0	14.8
Estimated difference vs placebo	N/A	2.3	3.3	1.1
95% CI	N/A	0.2, 4.5	1.2, 5.4	-1.1, 3.2
p-value	N/A	0.031	0.002	0.32

178-CL-047 (ARIES)	Placebo N=433	Mirabegron	
		50 mg N=425	100 mg N=412
n	*355*	*350*	*344*
Adjusted mean CFB to final visit	10.7	14.8	17.3
Estimated difference vs placebo	N/A	4.1	6.5
95% CI	N/A	1.6, 6.6	4.1, 9.0
p-value	N/A	0.001	<0.001
178-CL-074 (CAPRICORN)	**Placebo N=415**	**Mirabegron**	
		25 mg N=410	**50 mg N=426**
n	*406*	*408*	*419*
Adjusted mean CFB to final visit	13.0	14.3	14.2
Estimated difference vs placebo	N/A	1.3	1.2
95% CI	N/A	-0.9, 3.5	-1.0, 3.4
p-value	N/A	0.26	0.28

Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SR, slow-release.

HRQoL assessment using EQ-5D and EQ-5D VAS

Assessment of HRQoL was conducted using the generic scale the European quality of life-five dimensions (EQ-5D). Across all three primary studies, there were no evident differences between treatment groups in the percentages of patients shifting from baseline to final visit from one level to another.

In addition to the EQ-5D questions, HRQoL was assessed using the EQ-5D visual analogue scale (EQ-5D VAS) (Table 32). Positive change from baseline indicates improvement.

- In SCORPIO, the mirabegron 100 mg group had a numerically higher change from baseline to final visit than the placebo, mirabegron 50 mg and tolterodine groups, which were comparable.
- In ARIES, both mirabegron groups had numerically higher changes from baseline to final visit than placebo.
- In CAPRICORN, both mirabegron groups had numerically higher changes from baseline to final visit than placebo.

Table 32: EQ-5D VAS results for the primary RCTs

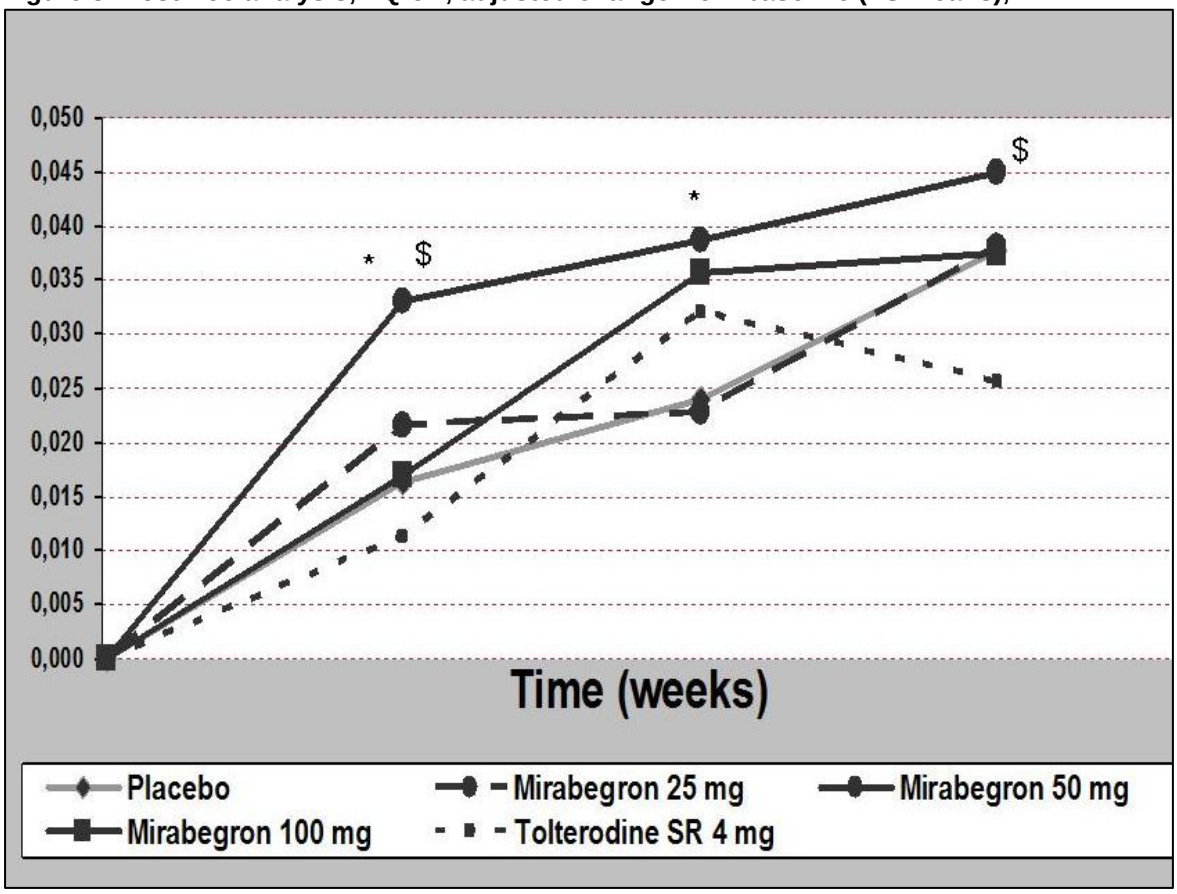
178-CL-046 (SCORPIO)	**Placebo N=480**	**Mirabegron**		**Tolterodine SR 4 mg N=475**
		50 mg N=473	**100 mg N=478**	
n	*470*	*466*	*472*	*467*
Mean CFB to final visit	6.4	6.5	8.1	6.4
SD	19.03	18.67	17.74	18.23
178-CL-047 (ARIES)	**Placebo N=433**	**Mirabegron**		
		50 mg N=425	**100 mg N=412**	
n	*424*	*417*	*410*	
Mean CFB to final visit	1.46	3.04	3.52	
SD	13.090	12.142	12.184	
178-CL-074 (CAPRICORN)	**Placebo N=415**	**Mirabegron**		
		25 mg N=410	**50 mg N=426**	
n	*404*	*406*	*419*	
Mean CFB to final visit	3.43	4.12	4.96	
SD	16.076	15.082	17.225	

Abbreviations: CFB, change from baseline; mg, milligram; SD, standard deviation; SR, slow-release.

Data were pooled from the three primary studies, SCORPIO, ARIES and CAPRICORN for a post-hoc analysis of EQ-5D results using the EQ-5D modified-intent-to-treat (m-ITT) population of 3,741 patients (all study patients who were randomised, received at least one dose of double-blind study medication and completed the EQ-5D questionnaire at baseline and at least once post-baseline, excluding any patients who presented serious deviations from the protocol or for whom the EQ-5D questionnaire data was not available at 12 weeks) .

After adjusting for baseline confounding factors, mirabegron 50 mg was found to be superior to tolterodine 4mg in terms of change from baseline utility score after 12 weeks (mean change of 0.045 vs 0.026, respectively; $p \leq 0.05$) (Figure 8). Significant differences vs placebo were observed at 4 weeks (mean change of 0.033 vs 0.016, respectively; $p<0.05$) and at 8 weeks (mean change of 0.039 vs 0.024, respectively; $p<0.05$). A similar trend was also observed at 12 weeks, though between-group differences were not statistically significant (mean change for mirabegron 50mg and placebo: 0.045 vs 0.038, respectively; $p=0.30$).

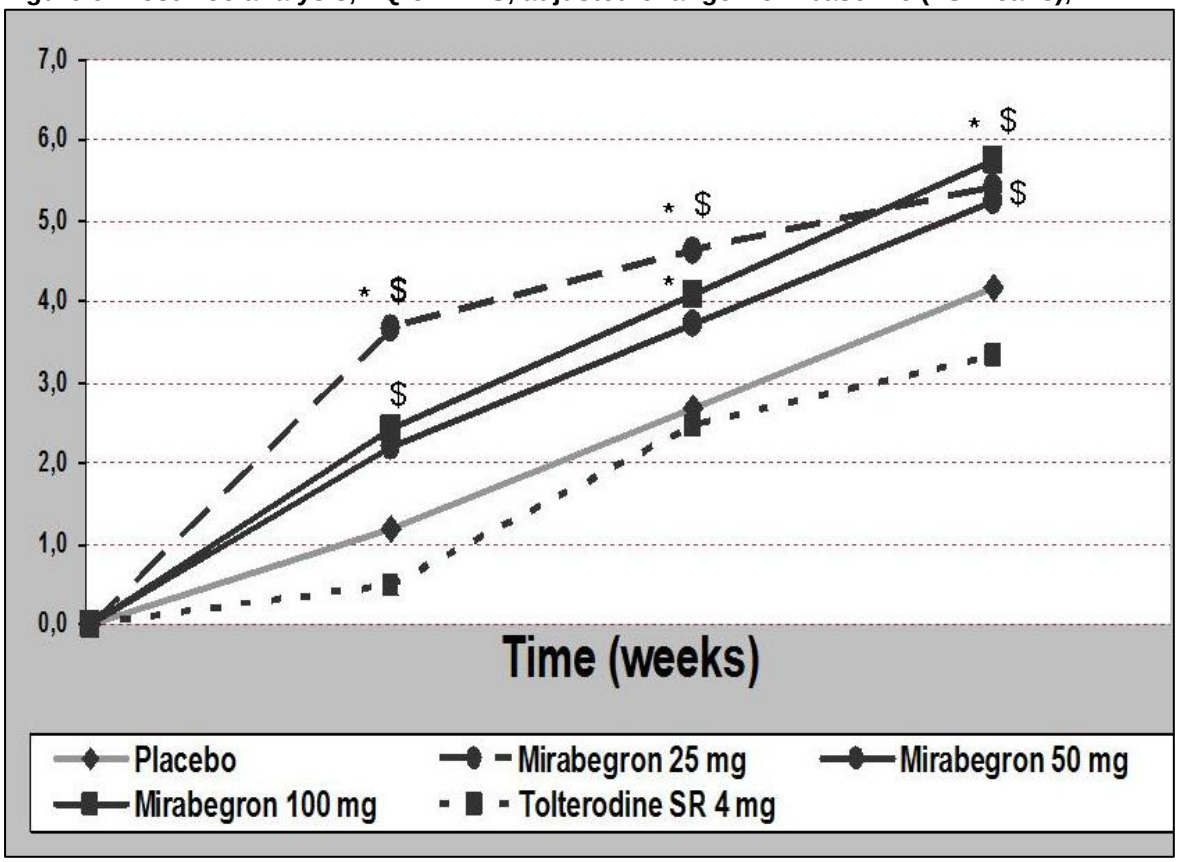
Figure 8: Post-hoc analysis, EQ-5D, adjusted change from baseline (LS means), m-ITT



* p value vs placebo <0.05; $ p value vs tolterodine <0.05.

Figure 9 shows the results on the EQ-VAS. Adjusted estimates of change from baseline were significantly higher in the mirabegron 100 mg group with respect to placebo at 8 and 12 weeks (change at 12 weeks of +5.7 vs +4.2, respectively; $p<0.05$). A similar trend was observed for the mirabegron 50 mg dose group, though the difference with placebo was not statistically significant. All mirabegron doses showed larger improvements on the EQ-VAS than tolterodine 4 mg at 12 weeks with changes of 5.7, 5.3, and 5.4 points on the EQ-VAS for mirabegron 100 mg, 50 mg, and 25 mg, respectively, compared with a change of 3.3 points for tolterodine 4 mg. The differences in the change scores between the 3 mirabegron doses and tolterodine were all statistically significant at $p<0.01$ mirabegron 100 mg) or $p<0.05$ (mirabegron 50 mg and 25 mg).

Figure 9: Post-hoc analysis, EQ-5D VAS, adjusted change from baseline (LS means), m-ITT



* p value vs placebo <0.05; $ p value vs tolterodine <0.05.

Treatment satisfaction assessment using TS VAS, PPBC and WPAI:SHP

Treatment satisfaction was assessed using the treatment satisfaction visual analogue scale (TS VAS). In each of the three studies, all active treatment groups (mirabegron 50 mg, mirabegron 100 mg and tolterodine 4 mg SR) demonstrated statistically significant differences in the change from baseline to final visit in the increase in TS VAS score compared with placebo.

When assessment was made using the patient perception of bladder condition (PPBC) scale both mirabegron groups had statistically significantly higher changes from baseline to final visit than placebo in SCORPIO and ARIES, but the differences vs placebo were not statistically significant in either mirabegron group in CAPRICORN.

When assessment of work and impairment was conducted using the work productivity and activity impairment: specific health problem scale (WPAI:SHP). In SCORPIO, the magnitude of negative change from baseline to final visit was greater for both mirabegron groups than placebo in all four parameters. In ARIES, the negative mean change from baseline to final visit was greater in both mirabegron groups compared with placebo for all four parameters. In CAPRICORN, the negative mean change from baseline to final visit was greater in the mirabegron 50 mg group compared with placebo for all parameters except overall work impairment.

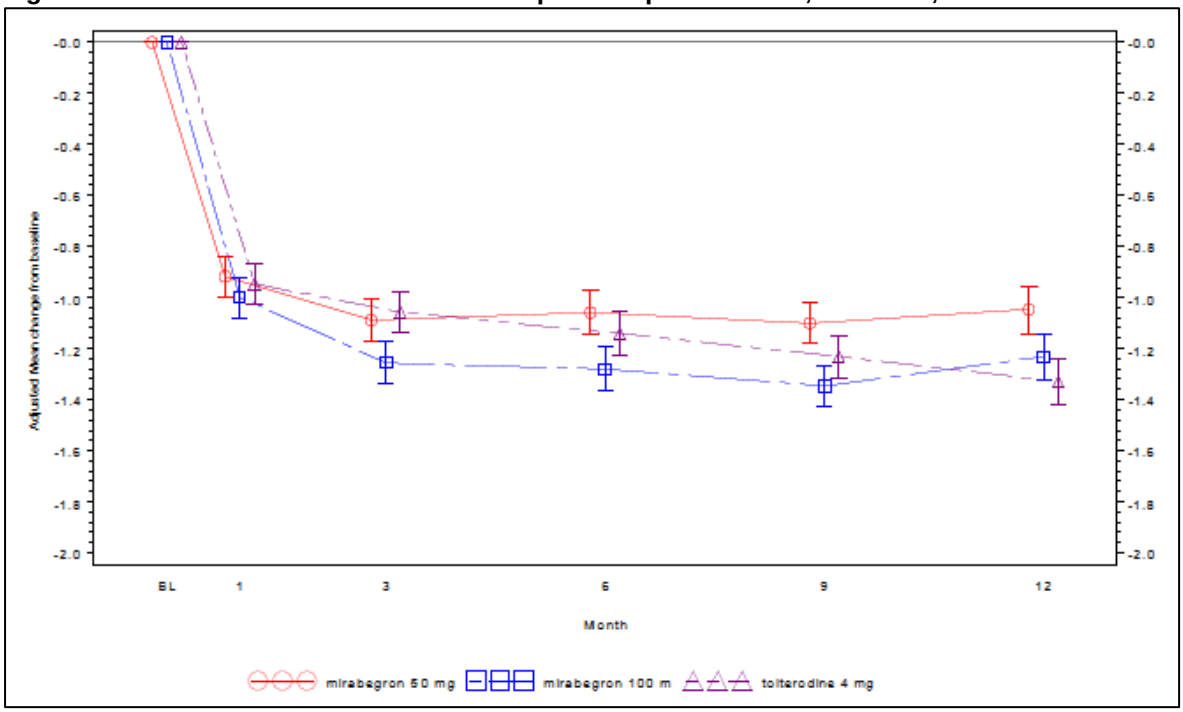
6.5.5 Long-term efficacy results from study 178-CL-049 (TAURUS)

As TAURUS was a study designed to primarily assess safety, the methodology has been presented in Section 6.9.1. All efficacy results from TAURUS were secondary to the safety results. TAURUS was not a placebo-controlled study, but an active control was included for contextualisation of the mirabegron efficacy results. No direct statistical comparisons of efficacy between treatment groups were performed.

Mean number of incontinence episodes per 24 hours, FAS-I

At baseline, the mean number of incontinence episodes per 24 hours was 2.66, 2.49 and 2.42 for the mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg treatment groups, respectively. At final visit, the adjusted mean change (95% CI) from baseline at Month 12 was -1.01 (-1.18; -0.84), -1.24 (-1.41; -1.07), -1.26 (-1.43; -1.10) for the mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively, as assessed by means of an ANCOVA analysis (Figure 10).

Figure 10: Mean number of incontinence episodes per 24 hours, TAURUS, FAS-I

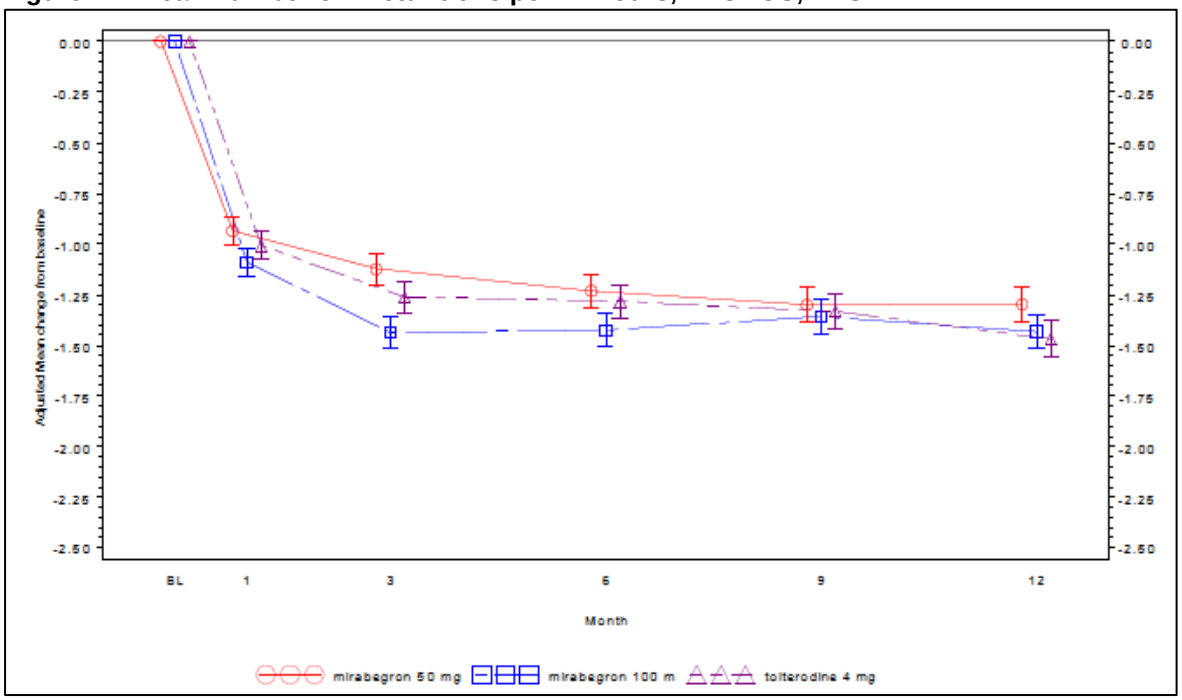


Abbreviations: mg, milligram.

Mean number of micturitions per 24 hours, FAS

At baseline, the mean number of micturitions per 24 hours was 11.13, 11.16 and 10.94 for the mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively. At final visit, as assessed by means of an ANCOVA analysis, the adjusted mean change (95% CI) from baseline in mean number of micturitions per 24 hours was -1.27 (-1.44, -1.11) and -1.41 (-1.57, -1.25), -1.39 (-1.56, -1.23) for the mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively (Figure 11).

Figure 11: Mean number of micturitions per 24 hours, TAURUS, FAS

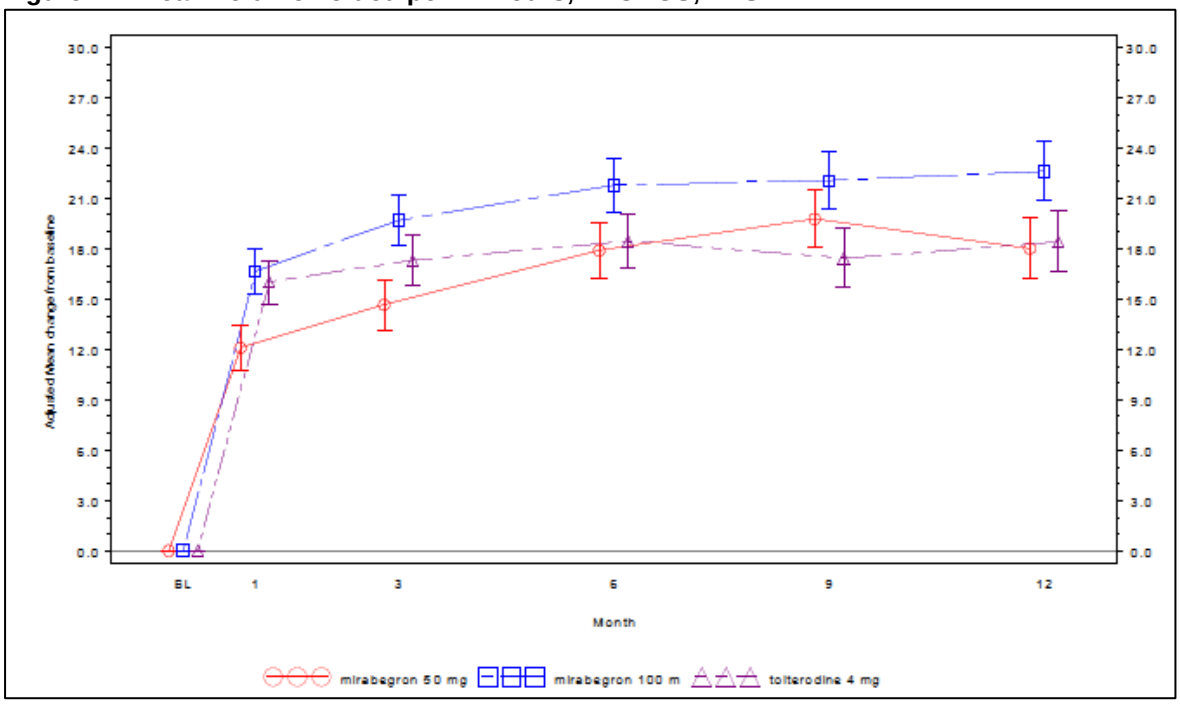


Abbreviations: mg, milligram.

Mean volume voided per 24 hours, FAS

At baseline, the mean volumes voided per 24 hours were 160.1 mL, 164.9 mL and 160.1 mL for the mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively. At final visit, as assessed by means of an ANCOVA analysis, the adjusted mean change (95% CI) from baseline in mean volumes voided per 24 hours were 17.5 (14.3, 20.7) and 21.5 (18.3, 24.7), 18.1 (14.8, 21.3) for the mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively (Figure 12).

Figure 12: Mean volume voided per 24 hours, TAURUS, FAS



Abbreviations: mg, milligram.

Additional efficacy analyses

Numeric reductions in change from baseline to final visit in the mean number of urgency incontinence episode per 24 hours, Grade 3 or 4 urgency episodes per 24 hours, mean level of urgency, mean number of pads used and mean number of nocturia episodes per 24 hours were observed for patients on mirabegron and tolterodine (Table 33).

Treatment satisfaction, HRQoL and PPBC were also numerically improved in all treatment groups.

Table 33: Additional efficacy analyses, TAURUS

Outcome	Mirabegron		Tolterodine ER 4 mg
	50 mg	100 mg	
Mean number of urgency incontinence episodes per 24 hours, FAS-I			
Baseline, mean	2.46	2.27	2.26
Final visit, adjusted mean CFB	-1.01	-1.23	-1.21
Mean number of urgency episodes (Grades 3 or 4) per 24 hours, FAS			
Baseline, mean	5.67	5.63	5.45
Final visit, adjusted mean CFB	-1.62	-1.80	-1.63
Mean level of urgency, FAS			
Baseline, mean	2.45	2.44	2.44
Final visit, adjusted mean CFB	-0.29	-0.29	-0.27
Mean number of pads used, FAS			
Baseline, mean	2.62	2.60	2.44

Final visit, adjusted mean CFB	-0.81	-0.88	-1.02
Mean number of nocturia episodes per 24 hours, FAS			
Baseline, mean	2.08	2.11	2.02
Final visit, adjusted mean CFB	-0.46	-0.39	-0.43
Treatment satisfaction: TS VAS, FAS			
Baseline, mean	4.87	4.88	5.01
Final visit, adjusted mean CFB[†] (95% CI)	2.08 (1.75, 2.41)	2.11 (1.79, 2.43)	2.27 (1.94, 2.59)
HRQoL – OAB-q, FAS			
Symptom bother score, adjusted mean CFB	-13.1	-14.8	-14.3
HRQoL total score, adjusted mean CFB	10.7	11.7	11.4
Coping, adjusted mean CFB	12.2	13.6	13.3
Concern, adjusted mean CFB	11.8	13.3	12.5
Sleep, adjusted mean CFB	10.7	10.8	11.2
Social, adjusted mean CFB	6.5	7.2	7.2
PPBC, FAS			
Baseline, mean	3.9	3.9	3.8
Final visit, adjusted mean CFB	-0.8	-0.9	-0.8
Proportion of patients with ≥ 1 point improvement, %	52.9	59.6	54.4
Proportion of patients with major (≥ 2 point) improvement, %	26.2	28.2	26.6

Abbreviations: CFB, change from baseline; ER, extended-release; FAS, full analysis set; FAS-I, full analysis set – incontinence; HRQoL, health-related quality of life; mg, milligram; OAB-q, overactive bladder questionnaire; PPBC, patient perception of bladder condition; TS, treatment satisfaction; VAS, visual analogue scale.

Efficacy conclusions

Across all three primary studies, SCORPIO, ARIES and CAPRICORN, the mirabegron groups demonstrated statistically significant greater reductions from baseline to final visit compared with placebo in the mean number of incontinence episodes per 24 hours and the mean number of micturitions per 24 hours (the co-primary efficacy endpoints).

For the secondary endpoints in SCORPIO and ARIES, both mirabegron groups and the tolterodine group had statistically significant greater increases from baseline compared with placebo in the mean volume voided per micturition to final visit, the mean number of incontinence episodes per 24 hours to Week 4, and the mean number of micturitions per 24 hours to Week 4. The 50 mg groups were statistically significantly improved for the outcomes of mean number of Grade 3 and 4 urgency episodes and the mean level of urgency in both trials.

For the secondary endpoints in CAPRICORN, the mirabegron 50 mg group had a statistically significant greater increase from baseline to final visit compared with placebo in the mean volume voided per micturition; mirabegron 25 mg was not statistically significant compared with placebo. Since the mirabegron 25 mg group did not meet

significance for mean volume voided with multiplicity adjustment, subsequent endpoints for the mirabegron 50 mg group were evaluated at the 0.025 significance level as part of the gatekeeping procedure. Subsequent endpoints for the mirabegron 25 mg group were excluded from further hypothesis testing. The mirabegron 50 mg group had a statistically significant greater reduction from baseline to Week 4 compared with placebo in mean number of incontinence episodes per 24 hours. Mean number of incontinence episodes per 24 hours in the mirabegron 25 mg group did not reach statistical significance. Neither the mean number of Grade 3 and 4 urgency episodes nor the mean level of urgency reached statistical significance after multiplicity adjustment.

For the patient reported outcomes, all mirabegron groups demonstrated statistically significant greater increases from baseline to final visit compared with placebo in the TS-VAS and OABq symptom bother scale (with the exception of the CAPRICORN 25 mg group for OABq). In SCORPIO and ARIES, both mirabegron groups demonstrated statistically significant greater improvements from baseline to final visit compared with placebo in the OAB-q HRQoL dimensions of coping, concern and total HRQoL score.

The long-term safety study, TAURUS, showed that mirabegron (50 mg and 100 mg) demonstrated numeric reductions from baseline to final visit in the mean number of micturitions per 24 hours, mean number of incontinence episodes per 24 hours and numeric improvements in mean volume voided per micturition. Improvements in these symptoms were observed by Week 4 with continued improvement until at least Week 12 and maintenance of the effect through Month 12.

6.6 Meta-analysis

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- ***Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.***
- ***Statistically combine (pool) the results for the both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).***
- ***Provide an adequate description of the methods of statistical combination and justify their choice.***
- ***Undertake sensitivity analysis when appropriate.***
- ***Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).***

No meta-analysis of the data obtained through the mirabegron clinical study programme has been conducted, but a mixed treatment comparison was conducted and the results are presented in Section 6.7. The information provided throughout this section relates to a pre-specified pooled analysis of the three primary studies, SCORPIO, ARIES and CAPRICORN.

6.6.1.1 Methodology

Primary evidence for the efficacy of mirabegron in the treatment of patients with symptoms of OAB comes from the individual Phase III studies, SCORPIO, ARIES and CAPRICORN. These studies were similar in design and therefore suitable for pooling of data, as determined in the statistical analysis plan.

Data were pooled for the placebo and mirabegron 50 mg treatment groups from all three studies, as well as the mirabegron 100 mg groups from SCORPIO and ARIES. Data from the mirabegron 25 mg treatment group in CAPRICORN was not pooled as this dose was not evaluated in more than one Phase III study.

Multiplicity adjustments in analysis of co-primary efficacy endpoints and key secondary efficacy endpoints

Methods for multiplicity adjustment for the pre-specified pooled analyses are based on those established in the statistical analysis plans (SAPs) for SCORPIO, ARIES and CAPRICORN.

A stepwise parallel gatekeeping procedure was performed to control the Type I error rate at the 0.05 significance level for the co-primary efficacy endpoints of:

- change from baseline to final visit in mean number of incontinence episodes per 24 hours
- change from baseline to final visit in mean number micturitions of per 24 hours

and the key secondary efficacy endpoints of:

- change from baseline to final visit in mean volume voided per micturition

- change from baseline to week 4 in mean number of incontinence episodes per 24 hours
- change from baseline to week 4 in mean number of micturitions per 24 hours
- change from baseline to final visit in mean level of urgency
- change from baseline to final visit in mean number of urgency incontinence episodes per 24 hours
- change from baseline to final visit in mean number of urgency episodes (Grade 3 or 4) per 24 hours.

Statistical testing was performed in eight stages, evaluating the primary and key secondary endpoints in the order indicated above. Within each stage, the Hochberg procedure was used to control the overall Type I error rate at the alpha =0.05 level for comparisons of the two mirabegron treatment groups with placebo. In each stage the endpoint was evaluated and the difference between a mirabegron dose group and placebo must have been statistically significant before that mirabegron dose group proceeded to the next stage. If one mirabegron treatment group succeeded in Stage 1, then only that treatment group proceeded to Stage 2 and the comparison of that treatment group versus placebo was assessed at alpha=0.025. If both mirabegron treatment groups failed at a particular stage, then neither mirabegron treatment group was tested in subsequent stages.

Univariate analysis: analysis of covariance model for integrated analysis

Data was pooled from the primary studies as indicated above. Change from baseline for the following efficacy endpoints was analysed using analysis of covariance (ANCOVA) with treatment group, gender and study as factors and baseline values as a covariate.

Change from baseline to final visit in:

- mean number of micturitions per 24 hours
- mean volume voided per micturition
- mean level of urgency per 24 hours
- mean number of urgency episodes (Grade 3 or 4) per 24 hours
- TS-VAS score
- mean number of nocturia episodes per 24 hours.

Change from baseline to Week 4, Week 8 and Week 12 in:

- mean number of micturitions per 24 hours
- mean volume voided per micturition.

Based on the ANCOVA, least squares (LS) mean estimates and 2-sided 95% CIs for mean changes from baseline within treatment group and differences between each mirabegron treatment group and placebo were derived. These LS means were used to obtain p-values for each mirabegron treatment group comparison versus placebo.

Univariate analysis: stratified rank ANCOVA model for integrated analysis

For change from baseline to final visit in mean number of incontinence episodes per 24 hours, change from baseline to Week 4, Week 8 and Week 12 in mean number of incontinence episodes per 24 hours and change from baseline to final visit in mean number of urgency incontinence episodes, stratified rank ANCOVA was used for hypothesis testing. For each endpoint variable the stratified rank ANCOVA was performed twice, once each for the pairwise comparisons of mirabegron 50 mg vs placebo and mirabegron 100 mg vs placebo. The following steps were performed for each stratified rank ANCOVA:

1. Standardised ranks within each study were derived across the two treatment groups for the baseline value and the change from baseline value

2. A linear regression model with baseline standardised ranks and gender effect as factors was fitted separately for each study and corresponding residuals were derived from the model

3. The stratified mean score test was performed using the values of the residuals as scores and study as strata to obtain a p-value for each comparison.

The LS mean estimates and 2-sided 95% CIs for mean changes from baseline within treatment group, as well as the difference between each mirabegron treatment group and placebo with respect to the mean change from baseline, were derived from the ANCOVA model described previously for other endpoints.

Univariate analysis: logistic regression

Logistic analysis was performed to compare treatments with respect to the proportion of patients with at least one incontinence episode at baseline (FAS-I) who experienced zero incontinence episodes at final visit and who had a 50% reduction in incontinence episodes at final visit. The logistic regression model included treatment group, gender, study and baseline measurement. The odds ratio of mirabegron over placebo, the corresponding 2-sided 95% CI of the odds ratio, and the p-value for the null hypothesis that the odds ratio was equal to one are presented.

Repeated measures analysis

Repeated measures ANCOVA was performed on selected endpoints to assess treatment effect over time. The model for repeated measures was similar to the model used for the individual primary study reports. This model included terms for treatment group, time (each relevant visit), baseline measurement (nested within time), time by treatment interaction, gender, gender by time interaction and study. Endpoints on which repeated measures analysis were performed are:

- mean number of incontinence episodes per 24 hours
- mean number of micturitions per 24 hours
- mean volume voided per micturition.

Differences between LS means based on the ANCOVA model were used to obtain p-values for each mirabegron treatment group vs placebo at each visit. In addition, the

p-value for treatment-by-time interaction was calculated to indicate whether the treatment effects changed over time.

6.6.1.2 Statistical assessment of heterogeneity

This is a pre-specified pooled analysis of study data from SCORPIO, ARIES and CAPRICORN and no statistical assessment of heterogeneity was performed.

6.6.1.3 Sensitivity analyses

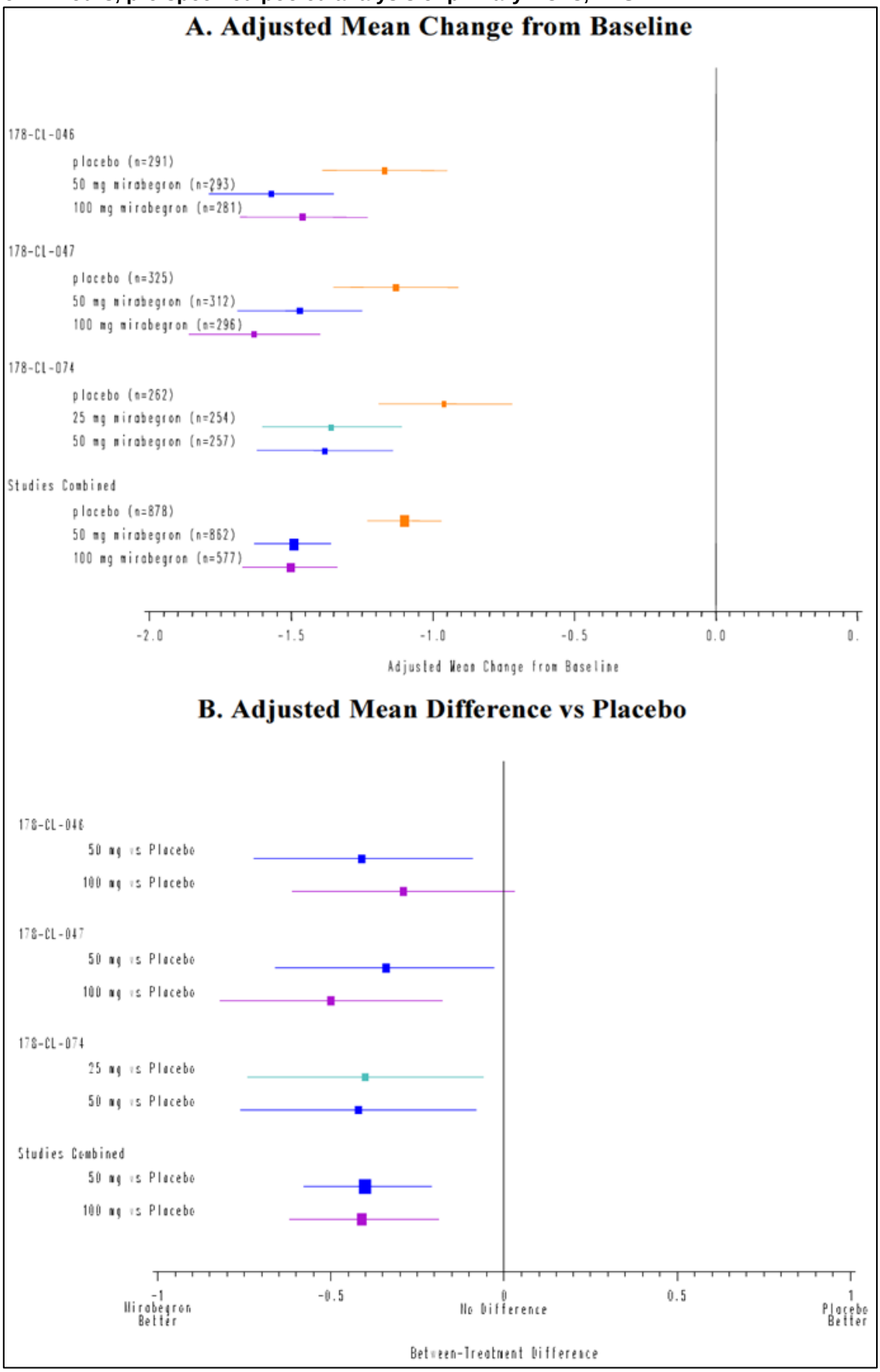
In addition to the analyses of the FAS and FAS-I population, sensitivity analyses were performed in each of the primary studies to assess the robustness of the primary efficacy analyses. Sensitivity analyses were performed on the PPS, PPS-I, ITT and ITT-I populations.

6.6.1.4 Results: General OAB population (all patients)

Mean number of incontinence episodes per 24 hours

The mean number of incontinence episodes per 24 hours at baseline was comparable across all treatment groups in the pooled primary studies. The adjusted mean changes from baseline to final visit were -1.10, -1.49 and -1.50 for the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively (Figure 13, Table 34). The adjusted mean differences versus placebo were -0.40 (mirabegron 50 mg) and -0.41 (mirabegron 100 mg). Both mirabegron groups demonstrated statistically significant reductions from baseline to final visit in mean number of incontinence episodes per 24 hours compared with placebo with multiplicity adjustment.

Figure 13: Change from baseline to final visit in mean number of incontinence episodes per 24 hours, pre-specified pooled analysis of primary RCTs, FAS-I



Abbreviations: mg, milligram.

Table 34: Change from baseline to final visit in mean number of incontinence episodes per 24 hours, pre-specified pooled analysis of primary RCTs, FAS-I

Outcome	Placebo N=878	Mirabegron	
		50 mg N=862	100 mg N=577
Adjusted mean CFB (SE)	-1.10 (0.067)	-1.49 (0.068)	-1.50 (0.085)
95% CI	-1.23, -0.97	-1.63, -1.36	-1.67, -1.34
Adjusted mean difference vs placebo (SE)	N/A	-0.40 (0.094)	-0.41 (0.110)
95% CI	N/A	-0.58, -0.21	-0.62, -0.19
p-value	N/A	<0.001	<0.001

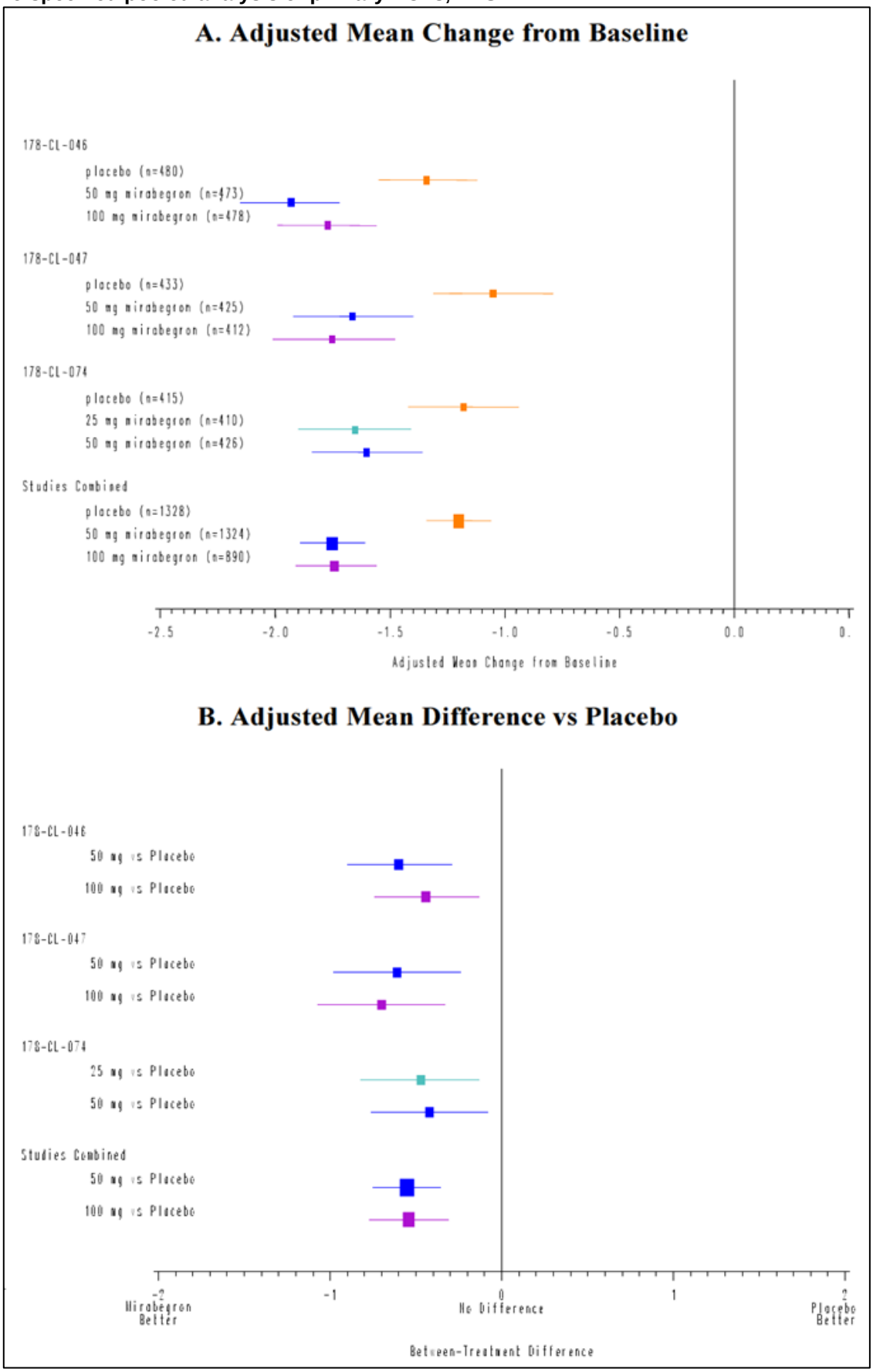
Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SE, standard error.

In the repeated measures analysis, change from baseline to week 12 in mean number of incontinence episodes per 24 hours demonstrated adjusted mean differences versus placebo for both treatment groups that were similar to the primary analysis. Both mirabegron 50 and 100 mg demonstrated statistically significantly superior mean reduction of incontinence episodes compared with the placebo group as early as Week 4 (the first measured time point) and their effectiveness was maintained throughout the treatment period (Weeks 8 and 12).

Mean number of micturitions per 24 hours

The mean number of micturitions per 24 hours at baseline was comparable across all treatment groups in the pooled primary studies. The adjusted mean changes from baseline to final visit were -1.20, -1.75 and -1.74 for the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively (Figure 14, Table 35). The adjusted mean differences versus placebo were -0.55 (mirabegron 50 mg) and -0.54 (mirabegron 100 mg). Each mirabegron group demonstrated a statistically significant reduction from baseline to final visit in mean number of micturitions per 24 hours compared with placebo with multiplicity adjustment.

Figure 14: Change from baseline to final visit in mean number of micturitions per 24 hours, pre-specified pooled analysis of primary RCTs, FAS



Abbreviations: mg, milligram.

Table 35: Change from baseline to final visit in mean number of micturitions per 24 hours, pre-specified pooled analysis of primary RCTs, FAS

Outcome	Placebo N=1,328	Mirabegron	
		50 mg N=1,324	100 mg N=890
Adjusted mean CFB (SE)	-1.20 (0.071)	-1.75 (0.071)	-1.74 (0.089)
95% CI	-1.34, -1.06	-1.89, -1.61	-1.91, -1.56
Adjusted mean difference vs placebo (SE)	N/A	-0.55 (0.099)	-0.54 (0.115)
95% CI	N/A	-0.75, -0.36	-0.77, -0.31
p-value	N/A	<0.001	<0.001

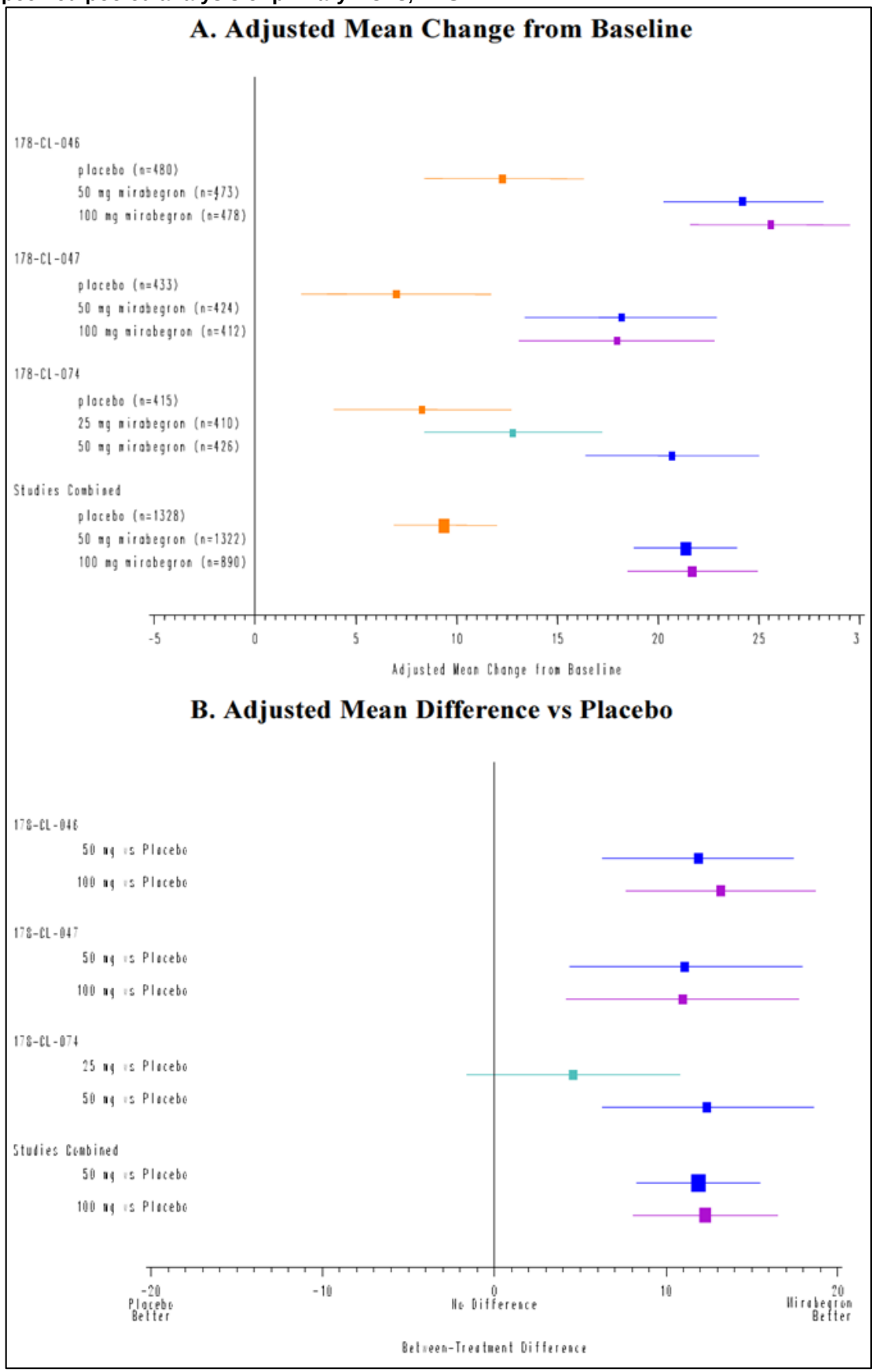
Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SE, standard error.

In repeated measures analysis, change from baseline to week 12 in mean number of micturitions per 24 hours demonstrated adjusted mean differences versus placebo for both treatment groups that were similar to the primary analysis. Both mirabegron 50 and 100 mg demonstrated statistically significantly superior mean reduction in micturitions per 24 hours compared with the placebo group as early as Week 4 (the first measured time point) and their effectiveness was maintained throughout the treatment period (Weeks 8 and 12).

Mean volume voided per micturition

The mean volume voided per micturition at baseline was comparable across all treatment groups in the pooled primary studies. The adjusted mean changes from baseline to final visit were 9.4, 21.4 and 21.7 mL for the placebo, mirabegron 50 mg and 100 mg groups, respectively (Figure 15, Table 36). The adjusted mean differences versus placebo were 11.9 mL (mirabegron 50 mg) and 12.3 mL (mirabegron 100 mg). Each mirabegron group demonstrated a statistically significant increase from baseline to final visit in mean volume voided per micturition compared with placebo with multiplicity adjustment.

Figure 15: Change from baseline to final visit in mean volume voided per micturition, pre-specified pooled analysis of primary RCTs, FAS



Abbreviations: mg, milligram.

Table 36: Change from baseline to final visit in mean volume voided per micturition, pre-specified pooled analysis of primary RCTs, FAS

Outcome	Placebo N=1,328	Mirabegron	
		50 mg N=1,324	100 mg N=890
n at baseline	*1,328*	*1,322*	*890*
Adjusted mean CFB (SE)	9.4 (1.29)	21.4 (1.30)	21.7 (1.64)
95% CI	6.9, 12.0	18.8, 23.9	18.5, 24.9
Adjusted mean difference vs placebo (SE)	N/A	11.9 (1.82)	12.3 (2.12)
95% CI	N/A	8.3, 15.5	8.1, 16.5
p-value	N/A	<0.001	<0.001

Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SE, standard error.

In repeated measures analysis, change from baseline to week 12 in mean volume voided per micturition demonstrated adjusted mean differences versus placebo of 12.6 mL for both the mirabegron 50 and 100 mg treatment groups. Both mirabegron 50 and 100 mg demonstrated statistically significantly superior increase in mean volume voided per micturition compared with the placebo group as early as Week 4 (the first measured time point), and their effectiveness was maintained throughout the treatment period (Weeks 8 and 12).

Mean level of urgency

The mean level of urgency at baseline was comparable across all treatment groups in the pooled primary studies. The adjusted mean changes from baseline to final visit were -0.15, -0.26 and -0.26 for the placebo, mirabegron 50 mg and 100 mg groups, respectively (Table 37). The adjusted mean differences versus placebo were -0.11 (mirabegron 50 mg) and -0.11 (mirabegron 100 mg) for mean level of urgency. Each mirabegron group demonstrated a statistically significant reduction from baseline to final visit in the mean level of urgency compared with placebo with multiplicity adjustment.

Table 37: Change from baseline to final visit in mean level of urgency, pre-specified pooled analysis of primary RCTs, FAS

Outcome	Placebo N=1,328	Mirabegron	
		50 mg N=1,324	100 mg N=890
n at baseline	*1,325*	*1,323*	*866*
Adjusted mean CFB (SE)	-0.15 (0.016)	-0.26 (0.016)	-0.26 (0.021)
95% CI	-0.18, -0.12	-0.30, -0.23	-0.30, -0.22
Adjusted mean difference vs placebo (SE)	N/A	-0.11 (0.023)	-0.11 (0.027)
95% CI	N/A	-0.16, -0.07	-0.16, -0.06
p-value	N/A	<0.001	<0.001

Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SE, standard error.

Mean number of urgency incontinence episodes per 24 hours

The mean number of urgency incontinence episodes at baseline was comparable across all treatment groups in the pooled primary studies. The adjusted mean changes from baseline to final visit were -0.98, -1.38 and -1.38 for the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively (Table 38). The adjusted mean differences versus placebo were -0.40 (mirabegron 50 mg) and -0.40 (mirabegron 100 mg). Each mirabegron group demonstrated a statistically significant reduction from baseline to final visit in mean number of urgency incontinence episodes compared with placebo.

Table 38: Change from baseline to final visit in mean number of urgency incontinence episodes per 24 hours, pre-specified pooled analysis of primary RCTs, FAS-I

Outcome	Placebo N=878	Mirabegron	
		50 mg N=862	100 mg N=577
n at baseline	*858*	*834*	*567*
Adjusted mean CFB (SE)	-0.98 (0.062)	-1.38 (0.063)	-1.38 (0.078)
95% CI	(-1.10, -0.86	(-1.50, -1.26	(-1.53, -1.23)
Adjusted mean difference vs placebo (SE)	N/A	-0.40 (0.087)	-0.40 (0.101)
95% CI	N/A	-0.57, -0.23	-0.60, -0.20
p-value	N/A	<0.001	<0.001

Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SE, standard error.

Mean number of urgency episodes (Grade 3 or 4) per 24 hours

The mean number of urgency episodes per 24 hours at baseline was comparable across all treatment groups in the pooled primary studies. The adjusted mean changes from baseline to final visit were -1.29, -1.93 and -1.89 for the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively (Table 39). The adjusted mean differences versus placebo were -0.64 (mirabegron 50 mg) and -0.60 (mirabegron 100 mg). Each mirabegron group demonstrated a statistically significant difference in reduction from baseline to final visit in mean number of urgency episodes per 24 hours compared with placebo with multiplicity adjustment.

Table 39: Change from baseline to final visit in mean number of urgency episodes (Grade 3 or 4) per 24 hours, pre-specified pooled analysis of primary RCTs, FAS

Outcome	Placebo N=1,328	Mirabegron	
		50 mg N=1,324	100 mg N=890
n at baseline	*1,324*	*1,320*	*885*
Adjusted mean CFB (SE)	-1.29 (0.091)	-1.93 (0.092)	-1.89 (0.116)
95% CI	-1.47, -1.11	-2.11, -1.75	-2.11, -1.66
Adjusted mean difference vs placebo (SE)	N/A	-0.64 (0.128)	-0.60 (0.150)
95% CI	N/A	-0.89, -0.39	-0.89, -0.31
p-value	N/A	<0.001	<0.001

Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SE, standard error.

Mean number of nocturia episodes per 24 hours

In the primary studies, nocturia was defined as waking at night one or more times to void (i.e. any voiding associated with sleep disturbance between the time the patient goes to bed with the intention to sleep until the time the patient gets up in the morning with the intention to stay awake). The mean number of nocturia episodes per 24 hours at baseline was comparable across all treatment groups in the pooled primary studies. The adjusted mean changes from baseline to final visit were -0.42, -0.55 and -0.54 for the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively (Table 40). The adjusted mean differences versus placebo were -0.14 (mirabegron 50 mg) and -0.12 (mirabegron 100 mg). Both mirabegron groups demonstrated statistically significant reductions compared with placebo.

Table 40: Change from baseline to final visit in mean number of nocturia episodes per 24 hours, pre-specified pooled analysis of primary RCTs, FAS

Outcome	Placebo N=1,328	Mirabegron	
		50 mg N=1,324	100 mg N=890
n at baseline	*1,156*	*1,149*	*778*
Adjusted mean CFB (SE)	-0.42 (0.033)	-0.55 (0.033)	-0.54 (0.042)
95% CI	-0.48, -0.35	-0.62, -0.49	-0.62, -0.46
Adjusted mean difference vs placebo (SE)	N/A	-0.14 (0.046)	-0.12 (0.054)
95% CI	N/A	-0.23, -0.05	-0.23, -0.02
p-value	N/A	0.003	0.023

Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SE, standard error.

Mean TS-VAS score

The mean TS-VAS score at baseline was comparable across all treatment groups. The adjusted mean changes from baseline to final visit were 1.25, 2.01 and 2.33 for the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively (Table 41). The adjusted mean differences versus placebo were 0.76 (mirabegron 50 mg) and 1.08 (mirabegron 100 mg). Both mirabegron groups demonstrated statistically significant increases from baseline to final visit in TS-VAS score compared with placebo.

Table 41: Change from baseline to final visit in TS-VAS, pre-specified pooled analysis of primary RCTs, FAS

Outcome	Placebo N=1,328	Mirabegron	
		50 mg N=1,324	100 mg N=890
n at baseline	*1,195*	*1,189*	*800*
Adjusted mean CFB (SE)	1.25 (0.089)	2.01 (0.089)	2.33 (0.112)
95% CI	1.08, 1.42	1.84, 2.19	2.11, 2.55
Adjusted mean difference vs placebo (SE)	N/A	0.76 (0.125)	1.08 (0.145)
95% CI	N/A	0.52, 1.01	0.80, 1.37
p-value	N/A	<0.001	<0.001

Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SE, standard error.

6.6.1.5 Results: Subgroup analyses

As per the NICE scope, subgroup analyses were performed for the male vs female populations and also the previously treated vs treatment-naïve populations.

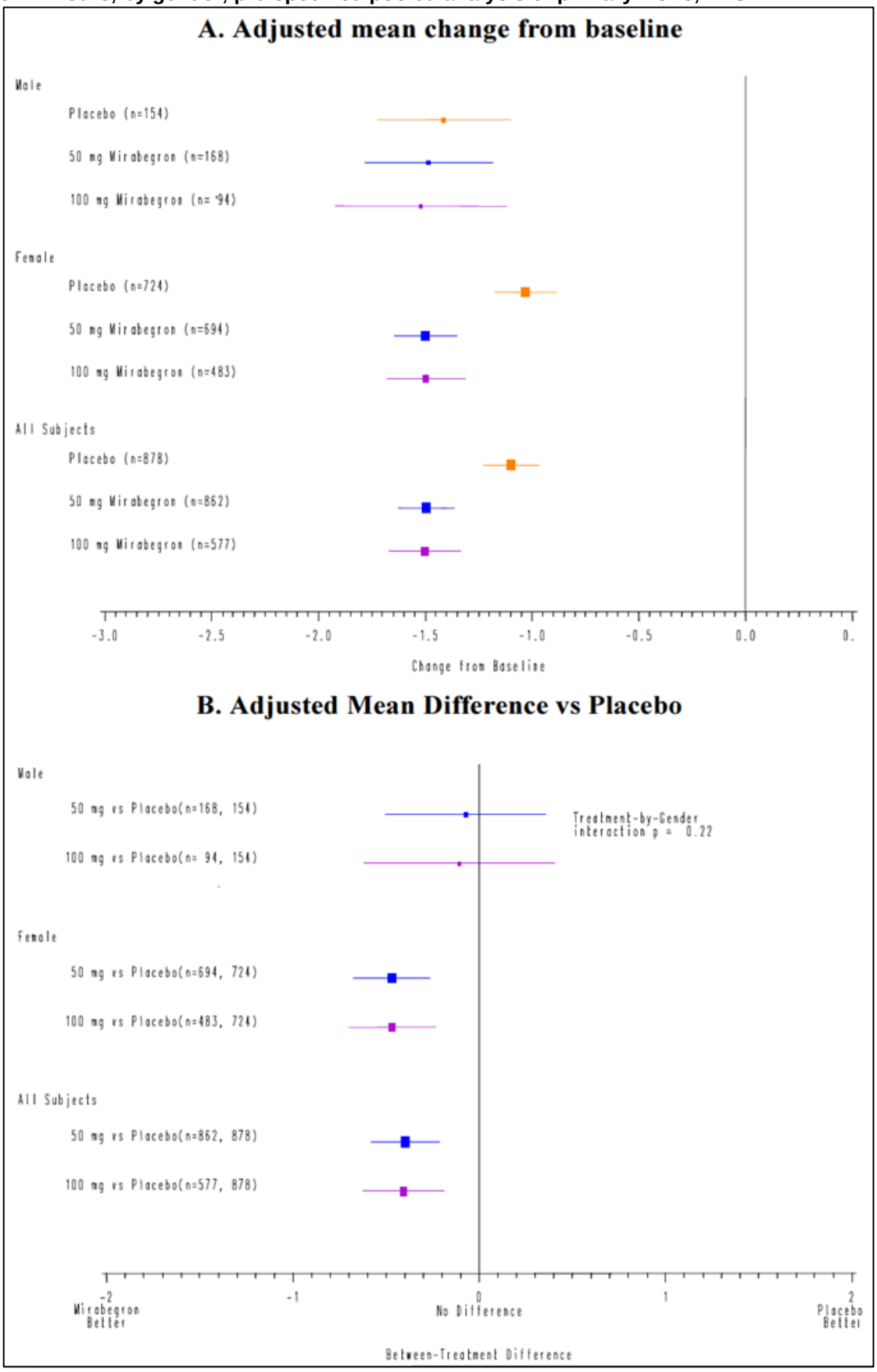
Male and female subgroups

Mean number of incontinence episodes per 24 hours

In the subpopulation analysis of gender, mirabegron 50 and 100 mg showed a reduction in the mean number of incontinence episodes per 24 hours from baseline to final visit for both male and female patients. The treatment by gender interaction p-value was 0.22; numerically larger reductions versus placebo were observed in female patients (adjusted mean difference from placebo: -0.47 and -0.47, mirabegron 50 and 100 mg groups, respectively) compared with male patients (adjusted mean difference from placebo: -0.07 and -0.11, mirabegron 50 and 100 mg groups, respectively). Due to the small sample sizes for male patients in the FAS-I the CIs were larger than those observed in female patients.

Baseline mean values for incontinence episodes were lower in male patients (2.12, 2.25 and 2.01 episodes per 24 hours in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively) than in female patients (2.86, 2.83 and 2.94 episodes per 24 hours in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively). The adjusted mean change from baseline is similar in male and female patients treated with mirabegron. The magnitude of the adjusted mean difference versus placebo in male patients is influenced by the low baseline values and a higher placebo response. As male patients were less likely than female patients to have incontinence at baseline and also demonstrated a higher placebo adjusted mean change from baseline, the findings in male patients with incontinence reflect a limited ability to demonstrate an appreciable reduction from baseline in incontinence episodes per 24 hours compared with placebo.

Figure 16: Change from baseline to final visit in mean number of incontinence episodes per 24 hours, by gender, pre-specified pooled analysis of primary RCTs, FAS-I



Abbreviations: mg, milligram.

Table 42: Change from baseline to final visit in mean number of incontinence episodes per 24 hours, by gender, pre-specified pooled analysis of primary RCTs, FAS-I

Outcome	Placebo N=878	Mirabegron	
		50 mg N=862	100 mg N=577
Males			
n at baseline	*154*	*168*	*94*
Adjusted mean CFB (SE)	-1.41 (0.159)	-1.48 (0.152)	-1.52 (0.205)
95% CI	(-1.72, -1.10	(-1.78, -1.18	(-1.92, -1.12
Adjusted mean difference vs placebo (SE)	N/A	-0.07 (0.220)	-0.11 (0.260)
95% CI	N/A	(-0.50, 0.36)	(-0.62, 0.40
Females			
n at baseline	*724*	*694*	*483*
Adjusted mean CFB (SE)	-1.03 (0.074)	-1.50 (0.075)	-1.50 (0.093)
95% CI	(-1.17, -0.89	(-1.65, -1.35	(-1.68, -1.32
Adjusted mean difference vs placebo (SE)	N/A	-0.47 (0.105)	-0.47 (0.120)
95% CI	N/A	0.67, -0.26	(-0.70, -0.23
Gender interaction p-value	**0.22**		

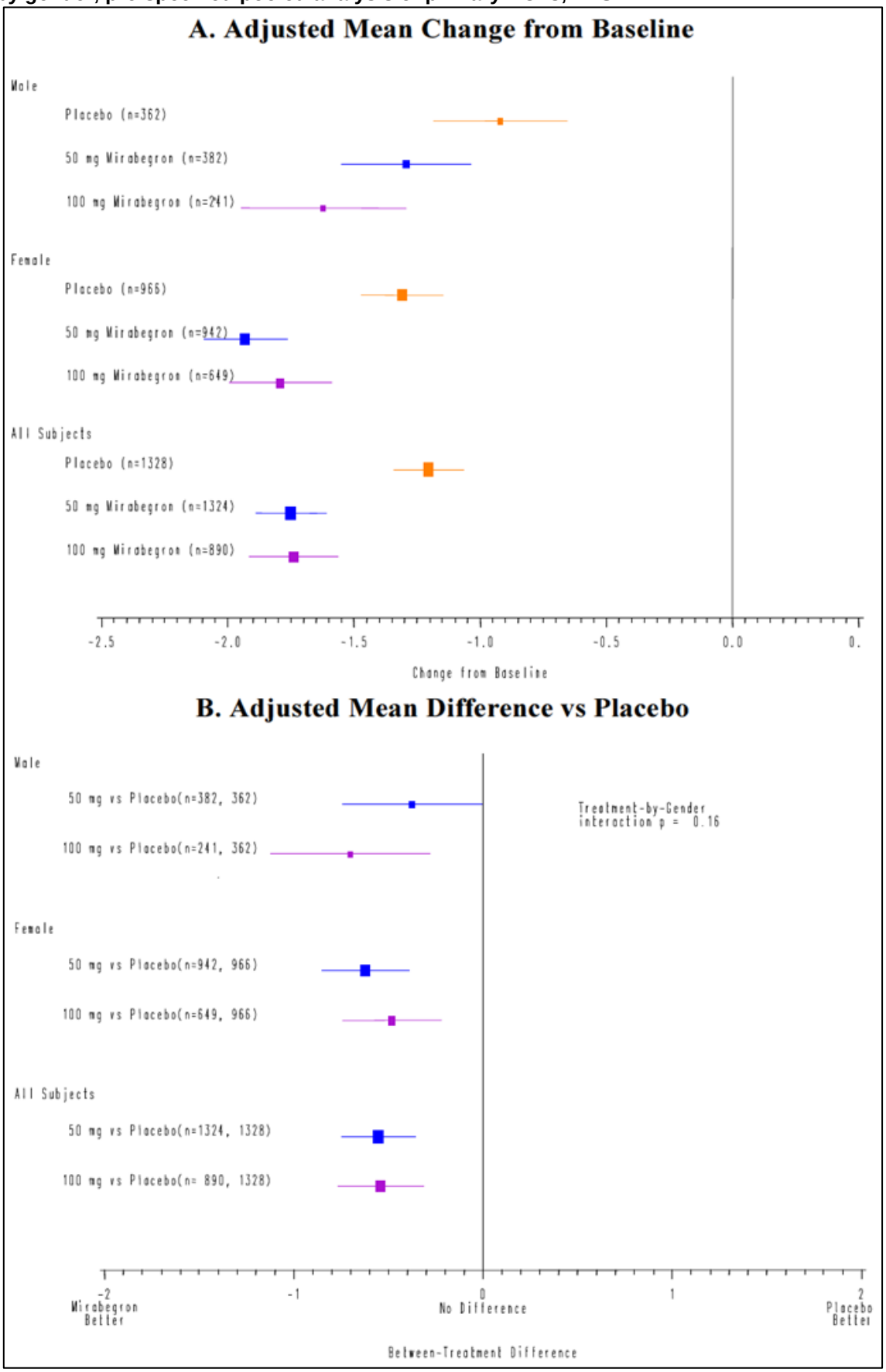
Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SE, standard error.

Mean number of micturitions per 24 hours

In the subpopulation analysis by gender, mirabegron 50 and 100 mg were effective in reducing the mean number of micturitions per 24 hours from baseline to final visit for both male and female patients. The treatment by gender interaction p-value was 0.16.

The baseline mean number of micturitions per 24 hours for male and female patients was similar across treatment groups. In the placebo, mirabegron 50 mg and mirabegron 100 mg groups, the adjusted mean change from baseline to final visit in male patients was -0.92, -1.29 and -1.62, respectively and -1.31, -1.93 and -1.79, respectively, in female patients. Among male patients, the adjusted mean difference versus placebo was -0.37 (95% CI: -0.74, -0.01) in the mirabegron 50 mg group and -0.70 (95% CI: -1.12, -0.28) in the mirabegron 100 mg group. Among female patients, the adjusted mean difference versus placebo was -0.62 (95% CI: -0.85, -0.39) in the mirabegron 50 mg group and -0.48 (95% CI: -0.74, 0.22) in the mirabegron 100 mg group.

Figure 17: Change from baseline to final visit in mean number of micturitions per 24 hours, by gender, pre-specified pooled analysis of primary RCTs, FAS



Abbreviations: mg, milligram.

Table 43: Change from baseline to final visit in mean number of micturitions per 24 hours, by gender, pre-specified pooled analysis of primary RCTs, FAS

	Placebo N=1,328	Mirabegron	
		50 mg N=1,324	100 mg N=890
Males			
n at baseline	*362*	*382*	*241*
Adjusted mean CFB (SE)	-0.92 (0.135)	-1.29 (0.131)	-1.62 (0.166)
95% CI	-1.18, -0.66	1.55, -1.04	-1.95, -1.29
Adjusted mean difference vs placebo (SE)	N/A	-0.37 (0.187)	-0.70 (0.215)
95% CI	N/A	-0.74, -0.01	-1.12, -0.28
Females			
n at baseline	*966*	*942*	*649*
Adjusted mean CFB (SE)	-1.31 (0.082)	-1.93 (0.084)	-1.79 (0.103)
95% CI	-1.47, -1.15	-2.09, -1.77	(-1.99, -1.59)
Adjusted mean difference vs placebo (SE)	N/A	-0.62 (0.117)	-0.48 (0.133)
95% CI	N/A	-0.85, -0.39	-0.74, -0.22
Gender interaction p-value	**0.16**		

Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SE, standard error.

Previously treated and treatment-naïve subgroups

In the primary studies, patients who received prior antimuscarinic OAB medications could be enrolled (patients were asked to indicate whether they had taken prior medication for OAB (yes/no). Antimuscarinics included tolterodine, solifenacin, oxybutynin, trospium, darifenacin, propiverine, fesoterodine and emepronium.

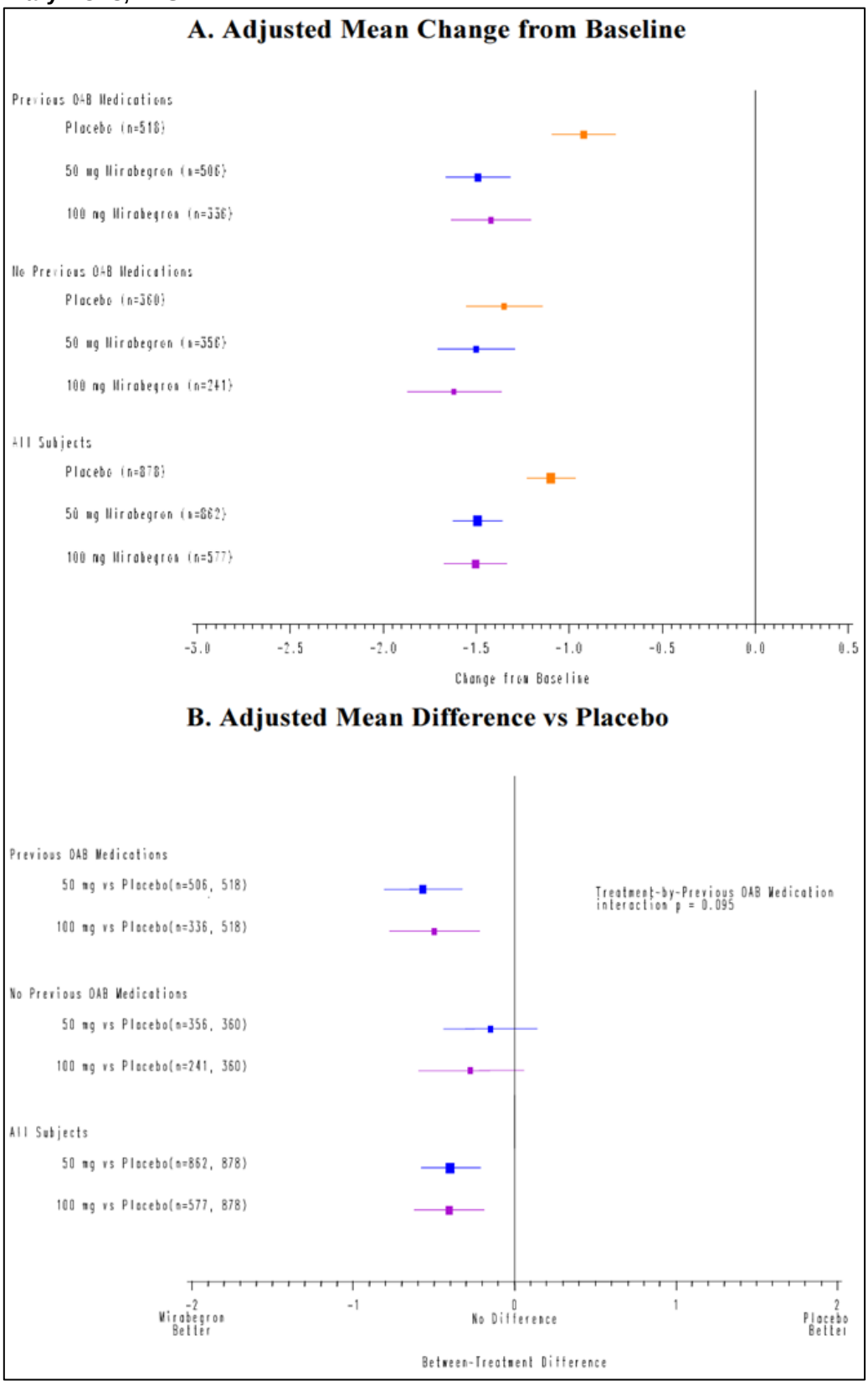
Mean number of incontinence episodes per 24 hours

Mirabegron 50 and 100 mg were effective in reducing the mean number of incontinence episodes per 24 hours from baseline to final visit in both patients who received previous OAB medication (i.e. previously treated) and in patients who did not receive previous OAB therapy (i.e. treatment-naïve). The treatment by subpopulation interaction p-value was 0.095.

The adjusted mean change from baseline to final visit for previously treated patients was -0.92, -1.49 and -1.42 for placebo, mirabegron 50 mg and mirabegron 100 mg, respectively, and -1.35, -1.50, and -1.62, respectively, for treatment-naïve patients. For previously treated patients, the reduction was larger for the mirabegron 50 mg group compared with the mirabegron 100 mg group (adjusted mean difference versus placebo: -0.57 and -0.50, respectively). For treatment-naïve patients, the reduction was smaller for mirabegron 50 mg compared with mirabegron 100 mg (adjusted mean difference versus placebo: -0.15 and -0.27, respectively). The adjusted mean change from baseline in mean number of incontinence episodes per 24 hours is similar between previously

treated and treatment-naïve patients. The magnitude of the adjusted mean difference versus placebo in treatment-naïve patients is influenced by the higher placebo response.

Figure 18: Change from baseline to final visit in mean number of incontinence episodes per 24 hours, previously treated vs treatment-naïve patients, pre-specified pooled analysis of primary RCTs, FAS-I



Abbreviations: mg, milligram.

Table 44: Change from baseline to final visit in mean number of incontinence episodes per 24 hours, previously treated vs treatment-naïve patients, pre-specified pooled analysis of primary RCTs, FAS-I

Outcome	Placebo	Mirabegron	
		50 mg	100 mg
Previously treated			
n	*518*	*506*	*336*
Adjusted mean CFB (SE)	-0.92 (0.087)	-1.49 (0.088)	-1.42 (0.110)
95% CI	-1.09, -0.75	-1.66, -1.32	-1.64, -1.21
Adjusted mean difference vs placebo (SE)	N/A	-0.57	-0.50
95% CI	N/A	-0.81, -0.33	-0.77, -0.22
Treatment-naïve			
n	*360*	*356*	*241*
Adjusted mean CFB (SE)	-1.35 (0.104)	-1.50 (0.105)	-1.62 (0.129)
95% CI	-1.55, -1.14	-1.71, -1.29	-1.87, -1.36
Adjusted mean difference vs placebo (SE)	N/A	-0.15	-0.27
95% CI	N/A	-0.44, 0.14	-0.60, 0.06
Population interaction p-value	**0.095**		

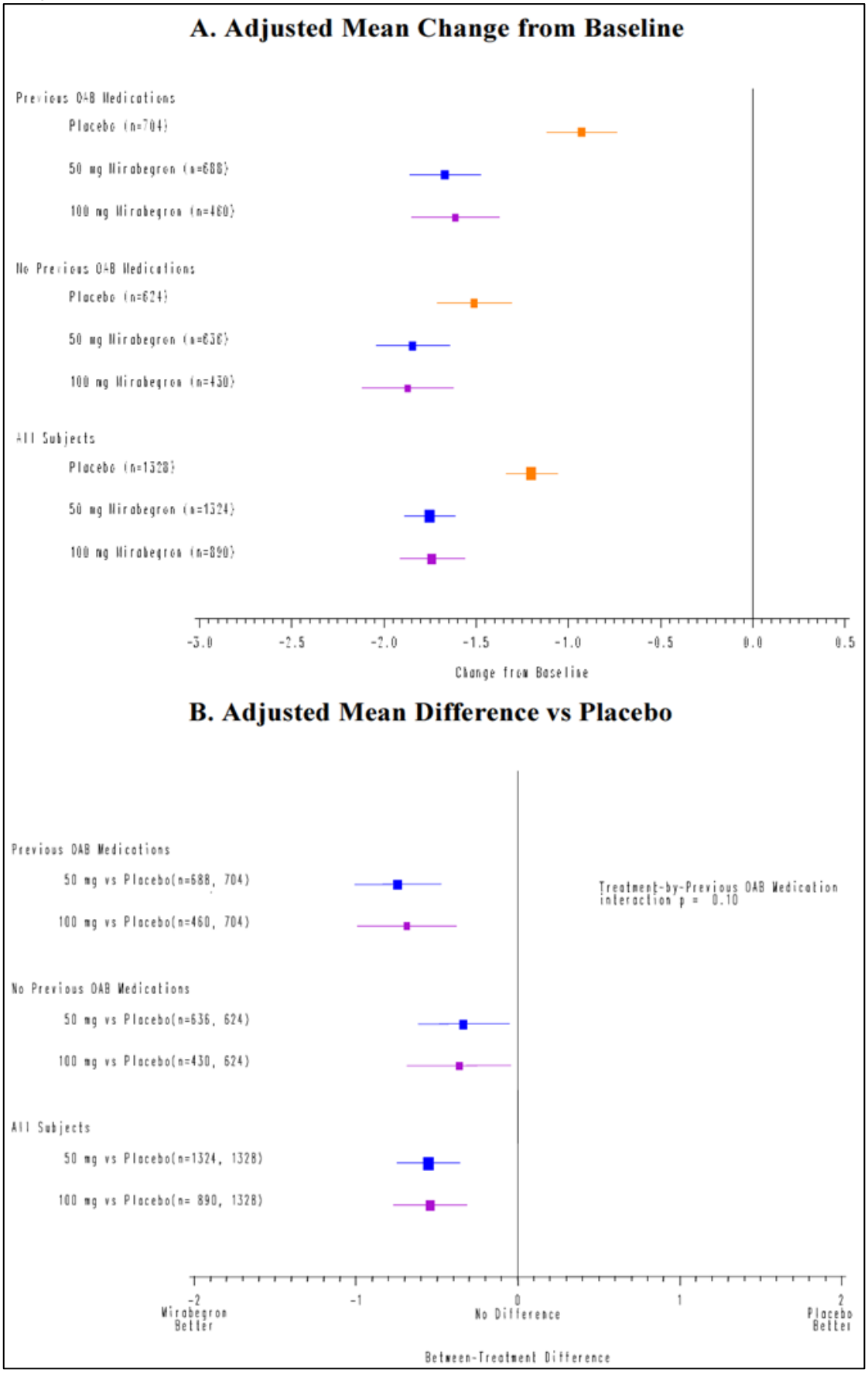
Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SE, standard error.

Mean number of micturitions per 24 hours

In the subpopulation analysis of previously treated vs treatment-naïve patients, mirabegron 50 and 100 mg were effective in reducing the mean number of micturitions per 24 hours from baseline to final visit in both populations. The treatment by subpopulation interaction p-value was 0.10.

The adjusted mean change from baseline to final visit in previously treated patients was -0.93, -1.67 and -1.61 for placebo, mirabegron 50 mg and mirabegron 100 mg, respectively, and -1.51, -1.84, and -1.87, respectively, for treatment-naïve patients. The reduction from baseline to final visit was less for treatment-naïve patients for the mirabegron 50 and 100 mg groups (adjusted mean difference versus placebo: -0.33 and -0.36, respectively) compared with previously treated patients (adjusted mean difference versus placebo: -0.74 and -0.69, respectively). The adjusted mean change from baseline is similar in previously treated and treatment-naïve patients. The magnitude of the adjusted mean difference versus placebo in treatment-naïve patients is influenced by the higher placebo response.

Figure 19: Change from baseline to final visit in mean number of micturitions per 24 hours, previously treated vs treatment-naïve patients, pre-specified pooled analysis of primary RCTs, FAS



Abbreviations: mg, milligram.

Table 45: Change from baseline to final visit in mean number of micturitions per 24 hours, previously treated vs treatment-naïve patients, pre-specified pooled analysis of primary RCTs, FAS

Outcome	Placebo	Mirabegron	
		50 mg	100 mg
Previously treated			
n	*704*	*688*	*460*
Adjusted mean CFB (SE)	-0.93 (0.097)	-1.67 (0.098)	-1.61 (0.122)
95% CI	-1.12, -0.74	-1.86, -1.48	-1.85, -1.37
Adjusted mean difference vs placebo (SE)	N/A	-0.74	-0.69
95% CI	N/A	-1.01, -0.47	-0.99, -0.38
Treatment-naïve			
n	*624*	*636*	*430*
Adjusted mean CFB (SE)	-1.51 (0.103)	-1.84 (0.102)	-1.87 (0.126)
95% CI	-1.71, -1.31	-2.04, -1.64	-2.12, -1.63
Adjusted mean difference vs placebo (SE)	N/A	-0.33	-0.36
95% CI	N/A	-0.62, -0.05	-0.68, -0.04
Population interaction p-value	**0.10**		

Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; SE, standard error.

6.6.1.6 Summary of pre-specified pooled analyses

General OAB population

Data for patients treated with mirabegron 50 and 100 mg showed similar statistically significant improvements compared with placebo for the co-primary efficacy endpoints of change from baseline to final visit in mean number of incontinence episodes and micturitions per 24 hours. Furthermore the clinical relevance of these improvements can be seen in significant improvements in quality of life reporting. Repeated measures analyses demonstrated adjusted mean differences versus placebo for both treatment groups that were very similar to the primary analyses. Both mirabegron 50 and 100 mg also demonstrated similar statistically significant improvements versus placebo for the key secondary efficacy endpoint of change from baseline to final visit in mean volume voided per micturition.

Male and female subgroups

Mirabegron 50 and 100 mg doses were effective in reducing the mean number of incontinence episodes and micturitions per 24 hours from baseline to final visit for both male and female patients. A larger reduction was observed in female patients compared with male patients, an effect which could be attributed to the lower baseline values observed in male patients and the higher placebo response observed in male patients compared with female patients.

Previously treated and treatment-naïve subgroups

Mirabegron 50 and 100 mg doses were effective in reducing the mean number of incontinence episodes and micturitions per 24 hours from baseline to final visit for both previously treated and treatment-naïve patients.

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

No meta-analysis of the data obtained through the mirabegron clinical study programme has been conducted, but a mixed treatment comparison was conducted and the results are presented in Section 6.7.

6.6.3 If any of the relevant RCTs listed in response to Section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

Three out of the seven RCTs identified in Section 6.2.4 were included in the pre-specified pooled analysis. Four studies were excluded. The rationale for excluding these studies is provided in Table 46.

Table 46: List of identified RCTs included/excluded from the pre-specified pooled analysis

Study no. (acronym)	Included	Excluded	Rationale for exclusion
178-CL-044 (DRAGON)		✓	• This study was intended to be supportive • The endpoint of mean number of incontinence episodes per 24 hours was not considered a primary endpoint in this study • This study has differences from the primary studies in the derivations of micturition-based endpoints
178-CL-045		✓	• This study was conducted only in Japan and are supportive for this submission • The endpoint of mean number of incontinence episodes per 24 hours was not considered a primary endpoint in this study • The inclusion and exclusion criteria for defining the OAB population differ from the primary studies • Urinary urgency was captured based on whether a patient had urgency or not with an episode. Therefore, the key secondary endpoints of mean level of urgency, mean number of urgency incontinence episodes (Grade 3 or 4)/24 hr and mean number of urgency episodes (Grade 3 or 4)/24 hr) in the primary studies cannot be summarised • Collection of data for mean number of nocturia episodes/24 hr differs between this study and the primary studies
178-CL-046 (SCORPIO)	✓		

Study no. (acronym)	Included	Excluded	Rationale for exclusion
178-CL-047 (ARIES)	✓		
178-CL-048		✓	• This study was conducted only in Japan and are supportive for this submission • The endpoint of mean number of incontinence episodes per 24 hours was not considered a primary endpoint in this study • The inclusion and exclusion criteria for defining the OAB population differ from the primary studies • Urinary urgency was captured based on whether a patient had urgency or not with an episode. Therefore, the key secondary endpoints of mean level of urgency, mean number of urgency incontinence episodes (Grade 3 or 4)/24 hr and mean number of urgency episodes (Grade 3 or 4)/24 hr) in the primary studies cannot be summarised • Collection of data for mean number of nocturia episodes/24 hr differs between this study and the primary studies
178-CL-049 (TAURUS)		✓	• Differences in duration of treatment • Lack of placebo control
178-CL-074 (CAPRICORN)	✓		

6.7 Indirect and mixed treatment comparisons

6.7.1 *Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in Section 10.4, appendix 4.*

Please see Section 6.1 for the methods used to identify studies for use in the mixed treatment comparison (MTC).

6.7.2 *Please follow the instructions specified in Sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in Section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.*

Eligibility criteria and a flow diagram of included and excluded studies can be found in Section 6.2. Of the 115 studies identified at e3 in the flow diagram in Section 6.2.2, 40 studies in total matched the inclusion criteria for the MTC. The full inclusion/exclusion criteria for the MTC were:

Inclusion criteria:

- Study duration of 4-16 weeks for safety analysis
- Study duration of 8-16 weeks for efficacy
- Appropriate measures of variability
- Primary analysis
- Outcomes as per the final scope.

Exclusion criteria:

- Sub-analysis
- Pooled analysis
- Inappropriate study duration
- No relevant outcome reported
- Not a major publication
- Inadequate reporting
- Not relevant doses/treatments compared
- Non-RCT/ not relevant study design
- Not appropriate population for analysis.

For critical appraisal of RCTs for the MTC, refer to Section 10.5.

6.7.3 Provide a summary of the trials used to conduct the indirect comparison.

A summary of the trials used to inform the MTC is provided in Table 47.

Table 47: Summary of the trials used to conduct the MTC

Study (primary ref)	Intervention	Trial design	Patient population	No randomised patients	Trial length (wks)
Mirabegron studies					
DRAGON (35)	• Mirabegron 25 mg • Mirabegron 50 mg • Mirabegron 100 mg • Mirabegron 200 mg • Tolterodine ER 4 mg • Placebo	Phase IIb, RCT, double-blind, double dummy, multicentre (Europe)	OAB, ≥ 18 years	928	12
SCORPIO (37)	• Mirabegron 50 mg • Mirabegron 100 mg • Tolterodine ER 4 mg • Placebo	Phase III, RCT, double-blind, multicentre (Europe, Australia)	OAB, ≥ 18 years	1987	12
ARIES (39)	• Mirabegron 50 mg • Mirabegron 100 mg • Placebo	Phase III, RCT, double-blind, double dummy, multicentre (US and Canada)	OAB, ≥ 18 years	1329	12
CAPRICORN (42)	• Mirabegron 25 mg • Mirabegron 50 mg • Placebo	Phase III, RCT, double-blind, double dummy, multicentre (Europe, US, Canada)	OAB, ≥ 18 years	1306	12
178-CL-045 (36)	• Mirabegron 25 mg • Mirabegron 50 mg • Mirabegron 100 mg • Placebo	Phase II, RCT, double-blind, multicentre (Japan)	OAB, 20–80 years	842	12
178-CL-048 (40)	• Mirabegron 50 mg • Tolterodine tartrate 4 mg • Placebo	RCT, double-blind, multicentre (Japan)	OAB , ≥ 20 years	1139	12
Comparator studies					
BLOSSOM† (44)	• Mirabegron 150 mg • Mirabegron 100 mg • Tolterodine ER 4 mg • Placebo	Phase II, RCT, double-blind, multicentre (Europe)	OAB, ≥ 18 years	262	4
Abrams 2006 (45)	• Oxybutynin 5 mg TDS • Propiverine 20 mg • Propiverine 45 mg • Placebo	RCT, double-blind, multicentre (UK)	Idiopathic OAB, >18 years	77	4
Appell 2001 (46)	• Tolterodine IR 2 mg BD • Oxybutynin ER 10 mg	RCT, double-blind, multicentre (USA)	OAB	378	12

Study (primary ref)	Intervention	Trial design	Patient population	No randomised patients	Trial length (wks)
Birns 2000 (47)	• Oxybutynin ER 10 mg • Oxybutynin IR 5 mg BD	RCT, double-blind, double dummy, multicentre (UK)	Patients with voiding problems, 18–76 years	130	6
Cardozo 2004 (48)	• Solifenacin 5 mg • Solifenacin 10 mg • Solifenacin 20 mg	RCT, double-blind, multicentre	OAB, ≥ 18 years	907	12
Chapple 2007 (49)	• Tolterodine ER 4 mg • Fesoterodine 4 mg • Fesoterodine 8 mg • Placebo	Phase III RCT, double-blind, double dummy, multicentre	OAB, ≥ 18 years	1135	12
Chapple 2004 (50)	• Solifenacin 2.5 mg • Solifenacin 5 mg • Solifenacin 10 mg • Solifenacin 20 mg • Tolterodine IR 2 mg BD • Placebo	Phase II, RCT, double-blind, multicentre (Europe)	Idiopathic detrusor overactivity, 18–80 years	225	4
Chapple 2004 (51)	• Solifenacin 5 mg • Solifenacin 10 mg • Tolterodine 2 mg BD • Placebo	Phase IIIa RCT, double-blind, multicentre (North America & Europe)	OAB, ≥ 18 years	1081	12
Choo 2008 (52)	• Solifenacin 5 mg • Solifenacin 10 mg • Tolterodine IR 2 mg BD	Phase III RCT, double-blind, multicentre (Korea)	OAB, ≥ 18 years	329	12
Chu 2009 (53)	• Solifenacin 10 mg • Placebo	Phase III RCT, double-blind, multicentre (USA)	OAB, ≥ 18 years	672	12
Corcos 2006 (54)	• Oxybutynin ER 5 mg • Oxybutynin ER 10 mg • Oxybutynin ER 15 mg	RCT, double-blind, multicentre (Canada)	Urge urinary incontinence ≥ 18 years	237	4
Diokno 2003 (55)	• Oxybutynin ER 10 mg • Tolterodine ER 4 mg	RCT, double-blind, multicentre (USA)	Women with OAB, ≥ 18 years	790	12
Dmochowski 2003 (56)	• Oxybutynin TDS • Long-acting tolterodine • Placebo	RCT, double blind, double dummy	≥ 18 years, taking pharmacologic treatment for OAB	361	12
Herschorn 2008 (56)	• Tolterodine ER 4 mg • Placebo	RCT, double-blind, multicentre (Canada, Europe)	OAB, ≥ 18 years	617	12

Study (primary ref)	Intervention	Trial design	Patient population	No randomised patients	Trial length (wks)
Herschorn 2010 (57)	• Solifenacin 5 mg • Oxybutynin IR 5 mg TDS	RCT, double-blind, double dummy, multicentre (Canada)	OAB, ≥ 18 years	132	8
Herschorn 2010 (58)	• Fesoterodine 4/8 mg • Tolterodine ER 4 mg • Placebo	RCT, double-blind, double dummy, multicentre (USA)	OAB, ≥ 18 years	1712	12
Ho 2010 (59)	• Solifenacin 5 mg • Tolterodine ER 4 mg	Randomised, open-label, single centre (Taiwan)	OAB, ≥ 18 years	75	12
Homma 2003 (60)	• Tolterodine ER 4 mg • Oxybutynin 3 mg TDS • Placebo	RCT, double-blind, multicentre (Japan)	OAB, ≥ 20 years	608	12
Jacquetin 2001 (61)	• Tolterodine IR 1 mg BD • Tolterodine IR 2 mg BD • Placebo	Phase III RCT, double-blind, multicentre (France & Belgium)	OAB, ≥ 18 years	251	4
Kaplan 2011 (62)	• Fesoterodine 4/8 mg • Tolterodine ER 4 mg • Placebo	RCT, double-blind, double dummy, multicentre (North & South America, Europe, Asia, Africa)	OAB, ≥ 18 years	2417	12
Khullar 2004 (63)	• Tolterodine ER 4 mg • Placebo	RCT, double-blind, multicentre (Europe)	Women ≥ 18 years with urge-predominant mixed incontinence	854	8
Lackner 2008 (64)	• Oxybutynin ER 5 mg • Placebo	RCT, double-blind	Women ≥ 65 years with urge-incontinence and cognitive impairment	50	4
Lee 2002 (65)	• Tolterodine IR 2 mg BD • Oxybutynin 5 mg BD	RCT, double-blind, multicentre (Korea)	OAB, ≥ 18 years	228	8

Study (primary ref)	Intervention	Trial design	Patient population	No randomised patients	Trial length (wks)
Malone-Lee 2001 (66)	• Tolterodine IR 1 mg BD • Tolterodine IR 2 mg BD • Placebo	RCT, double-blind, multicentre (UK, France, Ireland)	≥ 65 years with symptoms of urinary urgency, increased frequency of micturition and/or urge incontinence	177	4
Nitti 2007 (67)	• Fesoterodine 4 mg • Fesoterodine 8 mg • Placebo	RCT, double-blind, multicentre (USA)	OAB, ≥ 18 years	836	12
Nitti 2010 (68)	• Fesoterodine 4 mg • Fesoterodine 8 mg • Fesoterodine 12 mg • Placebo	Phase II RCT, double-blind, multicentre	OAB, 18–78 years	173	8
Rackley 2006 (69)	• Tolterodine ER 4 mg • Placebo	RCT, double-blind, multicentre (USA)	OAB, ≥ 18 years	850	12
Rogers 2008 (70)	• Tolterodine ER 4 mg • Placebo	RCT, double-blind, multicentre (USA)	Sexually active women ≥ 18 years with OAB	413	12
Rudy 2006 (71)	• Trospium chloride 20 mg BD • Placebo	RCT, double-blind, multicentre (USA)	OAB, ≥ 18 years	658	12
Staskin 2007 (72)	• Trospium chloride 60 mg • Placebo	RCT, double-blind, multicentre (USA)	Subjects with OAB	601	12
Van Kerrebroeck 2001 (73)	• Tolterodine IR 2 mg BD • Tolterodine ER 4 mg • Placebo	RCT, double-blind, multicentre (Australasia, Europe, North America)	OAB, ≥ 18 years	1529	12
Yamaguchi 2007 (74)	• Solifenacin 5 mg • Solifenacin 10 mg • Propiverine 20 mg • Placebo	Phase III RCT, double-blind, multicentre (Japan)	OAB, ≥ 20 years	1584	12
Yamaguchi 2011 (75)	• Fesoterodine 4 mg • Fesoterodine 8 mg • Placebo	Phase III RCT, double-blind, multicentre (Asia)	OAB, ≥ 20 years	951	12

Study (primary ref)	Intervention	Trial design	Patient population	No randomised patients	Trial length (wks)
Zinner 2002 (76)	• Tolterodine ER 4 mg • Placebo	RCT, multicentre (Europe, USA, Canada, Australia, New Zealand)	OAB, ≥ 18 years	1015	12

Abbreviations: BD, twice daily; ER, extended-release; IR, immediate-release; OAB, overactive bladder; RCT, randomised controlled trial; TDS, three times daily; wks, weeks.
†The Blossom study has been included as a comparator study only as the mirabegron doses analysed (50 mg BD and 100 mg BD) are not of interest for the submission.

6.7.4 For the selected trials, provide a summary of the data used in the analysis.

A summary of trials used for the outcomes of micturition, incontinence, urge incontinence, dry mouth, constipation and blurred vision are provided in Table 48 to Table 53.

Table 48: Overview of included studies evaluating micturition

Study	Placebo	Mirabegron 50 mg	Tolterodine 4 mg	Oxybutynin 5 mg	Solifenacin 5mg	Solifenacin 10mg	Fesoterodine 4mg	Fesoterodine 8mg
Kaplan 2011 (62)	✓		✓					✓
Herschorn 2010 (58)	✓		✓					✓
Chu 2009 (53)	✓					✓		
Herschorn 2008 (77)	✓		✓					
Choo 2008 (52)			✓		✓	✓		
Nitti 2007 (67)	✓						✓	✓
Chapple 2007 (49)	✓		✓				✓	✓
Yamaguchi 2007 (74)	✓				✓	✓		
Cardozo 2004 (48)	✓				✓	✓		
Khullar 2004 (63)	✓		✓					
Chapple 2004 (50)	✓		✓		✓	✓		
Lee 2002 (65)			✓	✓				
Appell 2001 (46)			✓	✓				
Van Kerrebroeck 2001 (73)	✓		✓					
Dmochowski 2003 (56)	✓		✓					

Study	Placebo	Mirabegron 50 mg	Tolterodine 4 mg	Oxybutynin 5 mg	Solifenacin 5mg	Solifenacin 10mg	Fesoterodine 4mg	Fesoterodine 8mg
Staskin 2007 (72)	✓							
SCORPIO (37)	✓	✓	✓					
ARIES (39)	✓	✓						
CAPRICORN (42)	✓	✓						
DRAGON (35)	✓	✓	✓					
178-CL-045 (36)	✓	✓						
178-CL-048 (40)	✓	✓	✓					
Yamaguchi 2011 (75)	✓						✓	✓

Table 49: Overview of included studies evaluating incontinence

Study	Placebo	Mirabegron 50 mg	Tolterodine 4 mg	Oxybutynin 5 mg	Solifenacin 5mg	Solifenacin 10mg	Fesoterodine 4mg	Fesoterodine 8mg
Chu 2009 (53)	✓					✓		
Yamaguchi 2007 (74)	✓				✓	✓		
Cardozo 2004 (48)	✓				✓	✓		
Chapple 2004 (50)	✓		✓		✓	✓		
Lee 2002 (65)			✓	✓				
Appell 2001 (46)			✓	✓				
Van Kerrebroeck 2001 (73)	✓		✓					
Dmochowski 2003 (56)	✓		✓					
SCORPIO (37)	✓	✓	✓					
ARIES (39)	✓	✓						
CAPRICORN (42)	✓	✓						
DRAGON (35)	✓	✓	✓					
178-CL-045 (36)	✓	✓						
178-CL-048 (40)	✓	✓	✓					

Study	Placebo	Mirabegron 50 mg	Tolterodine 4 mg	Oxybutynin 5 mg	Solifenacin 5mg	Solifenacin 10mg	Fesoterodine 4mg	Fesoterodine 8mg
Yamaguchi 2011 (75)	✓						✓	✓

Table 50: Overview of included studies evaluating urge incontinence

Study	Placebo	Mirabegron 50 mg	Tolterodine 4 mg	Oxybutynin 5 mg	Solifenacin 5mg	Solifenacin 10mg	Fesoterodine 4mg	Fesoterodine 8mg
Kaplan 2011 (62)	✓		✓					✓
Herschorn 2008 (77)	✓		✓					
Choo 2008 (52)			✓		✓	✓		
Nitti 2007 (67)	✓						✓	✓
Chapple 2007 (49)	✓		✓				✓	✓
Yamaguchi 2007 (74)	✓				✓	✓		
Khullar 2004 (63)	✓		✓					
Chapple 2004 (50)	✓		✓		✓	✓		
Appell 2001 (46)			✓	✓				
Staskin 2007 (72)	✓							
SCORPIO (37)	✓	✓	✓					
ARIES (39)	✓	✓						
CAPRICORN (42)	✓	✓						
DRAGON (35)	✓	✓	✓					
178-CL-045 (36)	✓	✓						
178-CL-048 (40)	✓	✓	✓					
Yamaguchi 2011 (75)	✓						✓	✓

Table 51: Overview of included studies evaluating dry mouth

Study	Placebo	Mirabegron 50 mg	Tolterodine 4 mg	Oxybutynin 5mg	Oxybutynin 10mg	Oxybutynin 15mg	Solifenacin 5mg	Solifenacin 10mg	Fesoterodine 4mg	Fesoterodine 8mg	Trospium 60 mg
Kaplan 2011 (62)	✓		✓							✓	
Herschorn 2010 (58)	✓		✓							✓	
Chu 2009 (53)	✓							✓			
Herschorn 2008 (77)	✓		✓								
Choo 2008 (52)			✓				✓	✓			
Nitti 2007 (67)	✓								✓	✓	
Chapple 2007 (49)	✓		✓						✓	✓	
Yamaguchi 2007 (74)	✓						✓	✓			
Abrams 2006 (45)	✓					✓					
Rackley 2006 (69)	✓		✓								
Corcos 2006 (54)				✓	✓	✓					
Cardozo 2004 (48)	✓						✓	✓			
Khullar 2004 (63)	✓		✓								
Zinner 2004 (78)	✓										✓
Chapple 2004 (50)	✓		✓				✓	✓			
Chapple 2004 (51)	✓		✓				✓	✓			
Homma 2003 (60)	✓		✓		✓						
Lee 2002 (65)			✓		✓						
Jacquetin 2001 (61)	✓		✓								
Malone-Lee 2001 (66)	✓		✓								
Appell 2001 (46)			✓		✓						
Van Kerrebroeck 2001 (73)	✓		✓								
Birns 2000 (47)					✓						
Ho 2010 (59)			✓				✓				
Herschorn 2010 (57)						✓	✓				
Diokno 2003 (55)			✓		✓						

Study	Placebo	Mirabegron 50 mg	Tolterodine 4 mg	Oxybutynin 5mg	Oxybutynin 10mg	Oxybutynin 15mg	Solifenacin 5mg	Solifenacin 10mg	Fesoterodine 4mg	Fesoterodine 8mg	Trospium 60 mg
Dmochowski 2003 (56)	✓		✓								
Staskin 2007 (72)	✓										✓
SCORPIO (37)	✓	✓	✓								
ARIES (39)	✓	✓									
CAPRICORN (42)	✓	✓									
DRAGON (35)	✓	✓	✓								
178-CL-045 (36)	✓	✓									
BLOSSOM (44)	✓		✓								
178-CL-048 (40)	✓	✓	✓								
Lackner 2008 (64)	✓			✓							
Nitti 2010 (68)	✓								✓	✓	
Rogers 2008 (70)	✓		✓								
Rudy 2006 (71)	✓										✓
Yamaguchi 2011 (75)	✓								✓	✓	

Table 52: Overview of included studies evaluating constipation

Study	Placebo	Mirabegron 50 mg	Tolterodine 4 mg	Oxybutynin 5 mg	Oxybutynin 10 mg	Oxybutynin 15 mg	Solifenacin 5 mg	Solifenacin 10 mg	Fesoterodine 4 mg	Fesoterodine 8 mg	Trospium 60 mg
Kaplan 2011 (62)	✓		✓							✓	
Chu 2009 (53)	✓							✓			
Herschorn 2008 (77)	✓		✓								
Choo 2008 (52)			✓				✓	✓			
Nitti 2007 (67)	✓								✓	✓	
Chapple 2007 (49)	✓		✓						✓	✓	
Yamaguchi 2007 (74)	✓						✓	✓			
Abrams 2006 (45)	✓					✓					

Study	Placebo	Mirabegron 50 mg	Tolterodine 4 mg	Oxybutynin 5 mg	Oxybutynin 10 mg	Oxybutynin 15 mg	Solifenacin 5 mg	Solifenacin 10 mg	Fesoterodine 4 mg	Fesoterodine 8 mg	Trospium 60 mg
Rackley 2006 (69)	✓		✓								
Corcos 2006 (54)				✓	✓	✓					
Cardozo 2004 (48)	✓						✓	✓			
Khullar 2004 (63)	✓		✓								
Zinner 2004 (78)	✓										✓
Chapple 2004 (50)	✓		✓				✓	✓			
Chapple 2004 (51)	✓		✓				✓	✓			
Homma 2003 (60)	✓		✓		✓						
Jacquetin 2001 (61)	✓		✓								
Malone-Lee 2001 (66)	✓		✓								
Appell 2001 (46)			✓		✓						
Van Kerrebroeck 2001 (73)	✓		✓								
Ho 2010 (59)			✓				✓				
Herschorn 2010 (57)						✓	✓				
Diokno 2003 (55)			✓		✓						
Dmochowski 2003 (56)	✓		✓								
Staskin 2007 (72)	✓										✓
SCORPIO (37)	✓	✓	✓								
ARIES (39)	✓	✓									
CAPRICORN (42)	✓	✓									
DRAGON (35)	✓	✓	✓								
178-CL-045 (36)	✓	✓									
BLOSSOM (44)	✓		✓								
178-CL-048 (40)	✓	✓	✓								
Lackner 2008 (64)	✓			✓							
Nitti 2010 (68)	✓								✓	✓	

Study	Placebo	Mirabegron 50 mg	Tolterodine 4 mg	Oxybutynin 5 mg	Oxybutynin 10 mg	Oxybutynin 15 mg	Solifenacin 5 mg	Solifenacin 10 mg	Fesoterodine 4 mg	Fesoterodine 8 mg	Trospium 60 mg
Rogers 2008 (70)	✓		✓								
Rudy 2006 (71)	✓										✓
Yamaguchi 2011 (75)	✓								✓	✓	

Table 53: Overview of included studies evaluating blurred vision

Study	Placebo	Mirabegron 50 mg	Tolterodine 4 mg	Oxybutynin 5mg	Oxybutynin 10mg	Oxybutynin 15mg	Solifenacin 5mg	Solifenacin 10mg	Fesoterodine 4mg	Fesoterodine 8mg	Trospium 60 mg
Chu 2009 (53)	✓							✓			
Choo 2008 (52)			✓				✓	✓			
Yamaguchi 2007 (74)	✓						✓	✓			
Corcos 2006 (54)				✓	✓	✓					
Cardozo 2004 (48)	✓						✓	✓			
Khullar 2004 (63)	✓		✓								
Chapple 2004 (50)	✓		✓				✓	✓			
Chapple 2004 (51)	✓		✓				✓	✓			
Homma 2003 (60)	✓		✓		✓						
Appell 2001 (46)			✓		✓						
Van Kerrebroeck 2001 (73)	✓		✓								
Birns 2000 (47)					✓						
Herschorn 2010 (57)						✓	✓				
Staskin 2007 (72)	✓										✓
SCORPIO (37)	✓	✓	✓								
ARIES (39)	✓	✓									
CAPRICORN (42)	✓	✓									
DRAGON (35)	✓	✓	✓								
178-CL-045 (36)	✓	✓									

Study	Placebo	Mirabegron 50 mg	Tolterodine 4 mg	Oxybutynin 5mg	Oxybutynin 10mg	Oxybutynin 15mg	Solifenacin 5mg	Solifenacin 10mg	Fesoterodine 4mg	Fesoterodine 8mg	Trospium 60 mg
BLOSSOM (44)	✓		✓								
178-CL-048 (40)	✓	✓	✓								
Lackner 2008 (64)	✓			✓							
Nitti 2010 (68)	✓								✓	✓	

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

A Bayesian MTC was conducted to estimate the relative efficacy and safety of mirabegron compared with all treatments of interest. An advantage of this technique is that it allows a comparison between treatments even if all the treatments have not been directly compared in RCTs. Indeed, several multicentre RCTs comparing mirabegron versus tolterodine or placebo have been conducted but none versus other antimuscarinics.

The MTC included all treatments specified in the NICE scope; placebo, mirabegron, tolterodine, oxybutynin, solifenacin 5 mg and 10 mg, fesoterodine 4 mg and 8 mg, and trospium, subject to data availability. For oxybutynin and tolterodine, ER and IR formulations are available. The two formulations were assumed to have similar efficacy (confirmed via expert opinion), and were therefore not separated for analyses on efficacy. However, they were separated for analyses on safety.

Analyses were conducted for the general OAB population. The feasibility of conducting an MTC analysis for patient subgroups was also explored, however the lack of data published for relevant subgroups (as identified in the scope) meant that the MTC was not appropriate.

Overview of statistical methods

A strength of the MTC approach is that the estimation of the relative effect between two treatments uses all the information available from the network of evidence, including direct comparisons (where available) and indirect comparisons. A network diagram representing all direct comparisons between treatments included in the analysis was produced for each outcome.

For each population, a fixed effect and a random effect model were used with a non-informative prior distribution allowing for correlation between different arms within multi-arm studies. Random-effects allow for heterogeneity in treatment effects between studies. For each population, a fixed effect and a random effect model were estimated. The model with the best quality of fit, as assessed by the Bayesian deviance information criterion (DIC), was selected (i.e. the model with the lowest DIC). Tolterodine 4 mg was selected as the reference treatment for analyses of efficacy outcomes, since this

treatment was the comparator in the health economic model of mirabegron and it was the most widely used active treatment in reviewed studies, as well as one of the most widely used drugs in practice. For the analyses of AEs, tolterodine ER 4 mg was selected as the reference treatment.

Input data

For continuous data, the mean changes and associated standard errors (SEs) reported in reviewed articles were used as input in the MTC. If the SE was not reported, it was derived from the standard deviation of change, variance or confidence interval around the mean where available. When the mean change was not reported, it was calculated as the difference between mean at 12 weeks and mean at baseline, where available.

For the MTC of safety outcomes, dichotomous data such as the reported number of patients experiencing the specific AEs in arms, the observed proportions of patients experiencing the specific AEs as well as the total number of patients by arms were extracted. If the number of patients experiencing the AEs was not reported in the study, the number of patients with the specific AEs was estimated by using the observed proportion and the total number of patients reported in the study.

Model specifications

A normal likelihood with identity link was assumed for continuous outcomes (mean changes) and binomial likelihood with logit link was associated to the binary data (AEs).

Vague priors were used for all the parameters in the MTC. A non-informative prior of N (0, 10^4) was used for the treatment effect and the study at baseline, in the analysis of efficacy outcomes and safety outcomes, except the analysis of dry mouth. For the analysis of dry mouth events, a non-informative prior of N (0, 100) for the treatment effect and the study at baseline was used.

The parameters in the distributions of random effects for between study correlation have vague prior distributions with Uniform (0, 5) for continuous data and Uniform (0, 2) for binary data.

The effect of treatment compared with mirabegron 50 mg was calculated directly in the model, as the difference between the effect of treatment and the effect of mirabegron 50 mg.

Outputs

Results are presented with summary statistics: estimates for the mean change in number of events for the efficacy outcomes and the odds ratio (OR) estimates for the safety outcomes. Mean values and 95% credible intervals (95% CrI) are reported for differences in changes in symptoms from baseline to 12 weeks between mirabegron and other treatments, and ORs for AEs.

A difference in mean change was considered as statistically significant, when the associated 95% CrI did not include zero. An OR was considered as statistically significant when the associated 95% CI did not include unity.

Assessment of model convergence

The convergence of models was assessed based on three diagnostics tools: Brooks-Gelman-Rubin diagnostic tool in Winbugs and the inspection of the auto-correlation and history plots.

Test of inconsistency

Inconsistency is defined as the conflict in results between direct comparison and indirect comparison in the MTC. It was assessed using the node splitting method developed by Dias (79). This method provides a means of checking for consistency by comparing the direct and indirect evidence on each pairwise comparison (node) and shows how these combine in the MTC analysis.

Implementation of statistical analyses

Analyses were performed using WinBUGS version 1.4 statistical software (MRC Biostatistics Unit, Cambridge, UK). WinBUGS codes provided in the NICE DSU Technical Support Document 2 were used for both fixed effect and random effect models. These models take into account that data might come from multi-arm studies (studies with three or more arms). Winbugs codes used for the MTC analyses of the included outcomes are shown in Section 10.16.

In all MTC analyses, an initial burn-in of 100,000 iterations was discarded and all the results were based on a further sample of 350,000 iterations, except for the analyses of AEs using the random effects model, which were based on a further sample of 500,000 iterations.

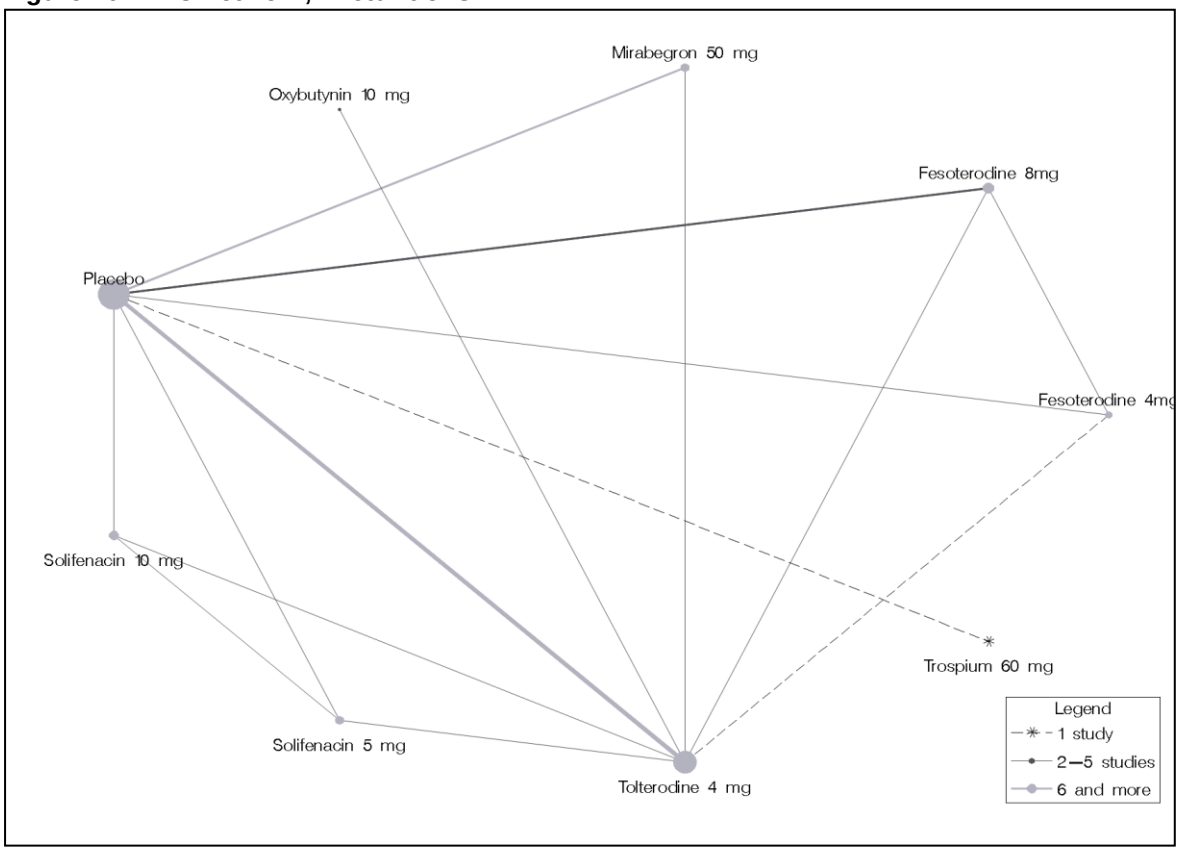
6.7.6 Please present the results of the analysis.

6.7.6.1 General OAB population

Micturitions

Figure 20 shows the network diagram for the change from baseline in the number of micturition episodes/24 hrs. Each line represents one or several direct comparisons between treatments.

Figure 20: MTC network, micturitions

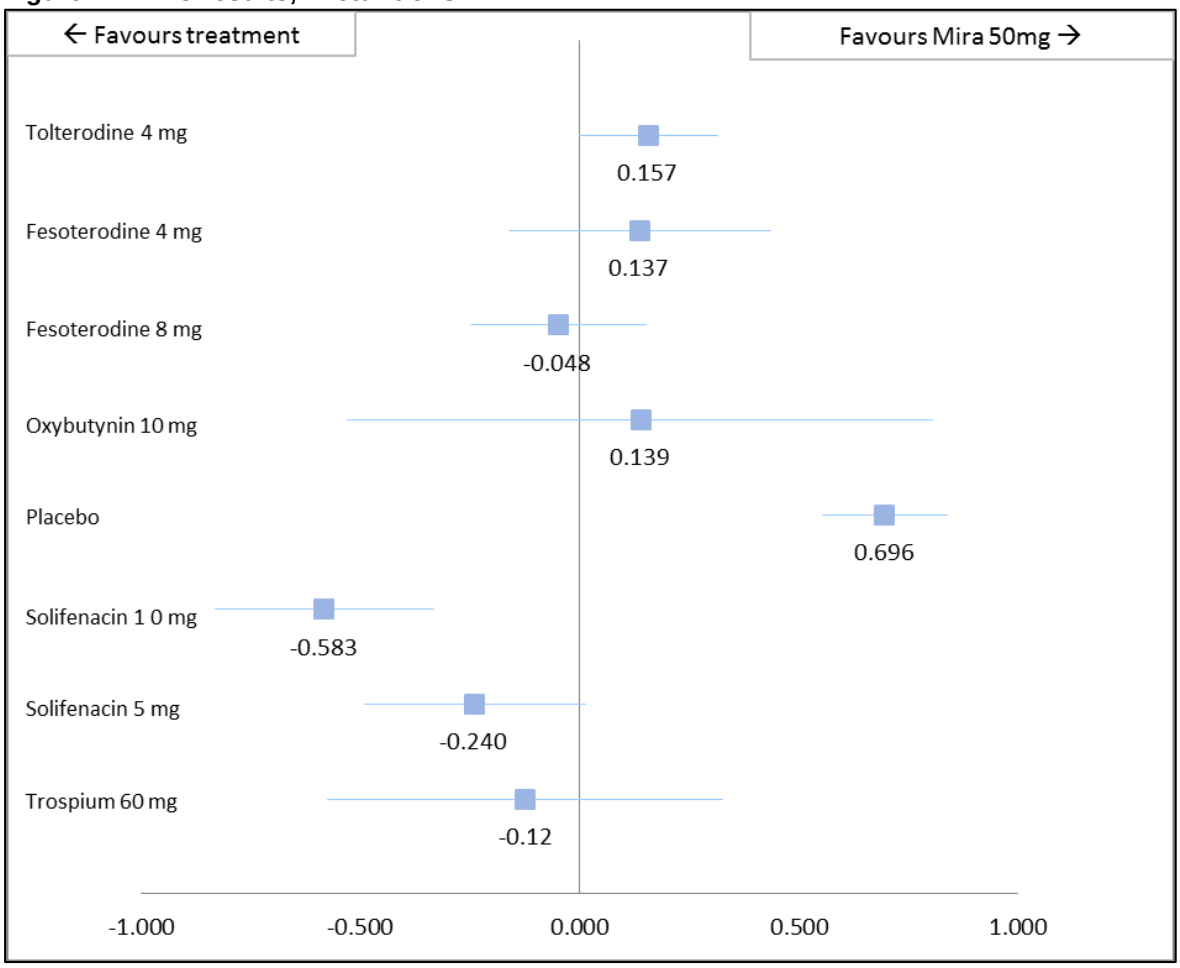


Abbreviations: mg, milligram.

The MTC was conducted using both fixed and random effect models (3 chains: 350,000 iterations after a burn-in of 100,000). Since the random effect model had a higher DIC (due to having a higher effective number of parameters), the fixed effect model was preferred.

The effect of mirabegron 50 mg did not differ significantly from other treatments, except solifenacin 10 mg which is more effective (mean difference vs mirabegron 50 mg of -0.583 [95% CrI -0.832 to -0.333]) and tolterodine 4 mg, which is less effective (mean difference vs mirabegron 50 mg of +0.157 [95% CrI 0 to 0.315]).

Figure 21: MTC results, micturitions

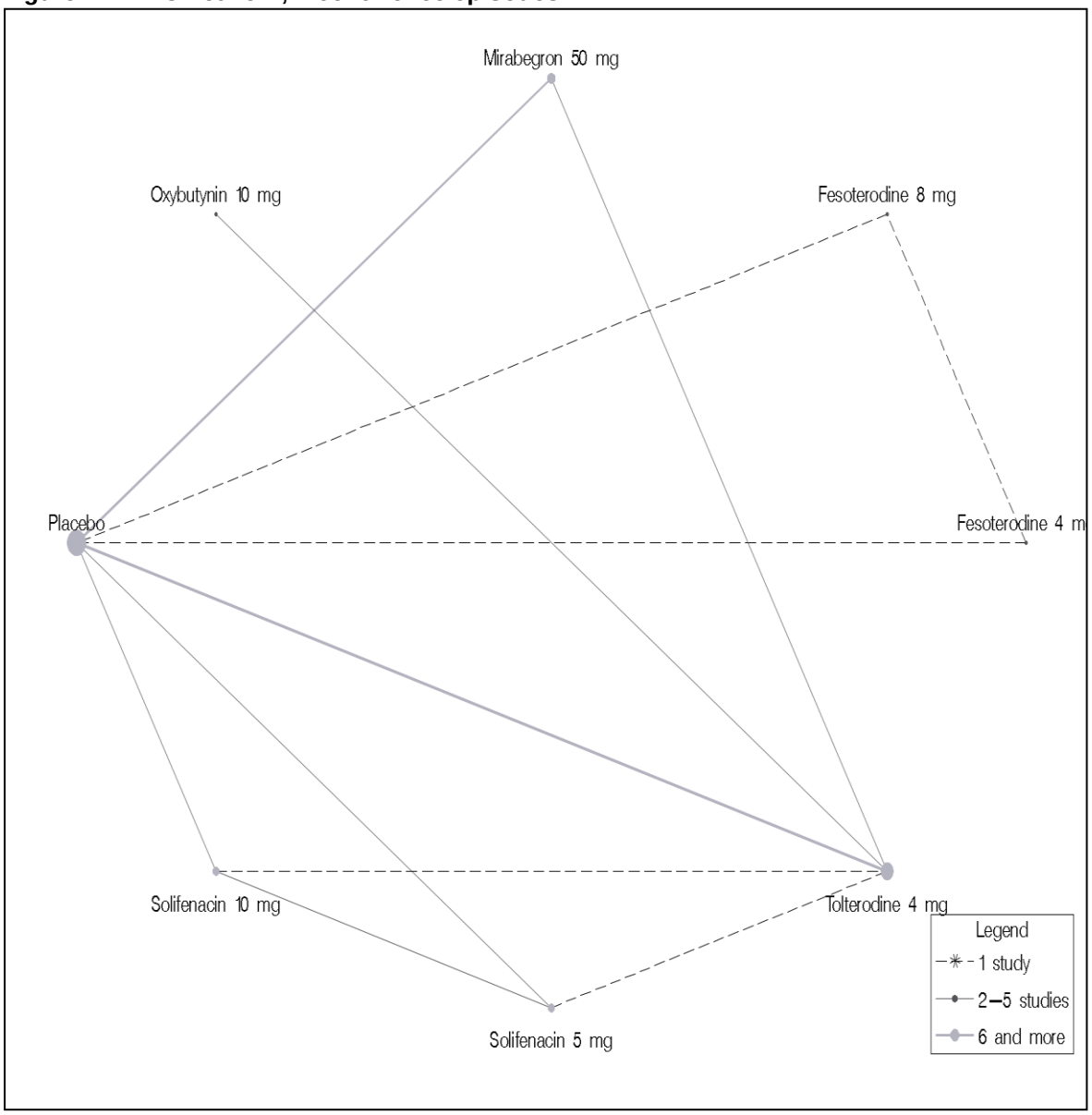


Abbreviations: mg, milligram.

Incontinence episodes

Figure 22 shows the network diagram for the change from baseline in the number of incontinence episodes/24 hrs. Fifteen studies reported data on the change from baseline to end of study in incontinence episodes/24hrs.

Figure 22: MTC network, incontinence episodes

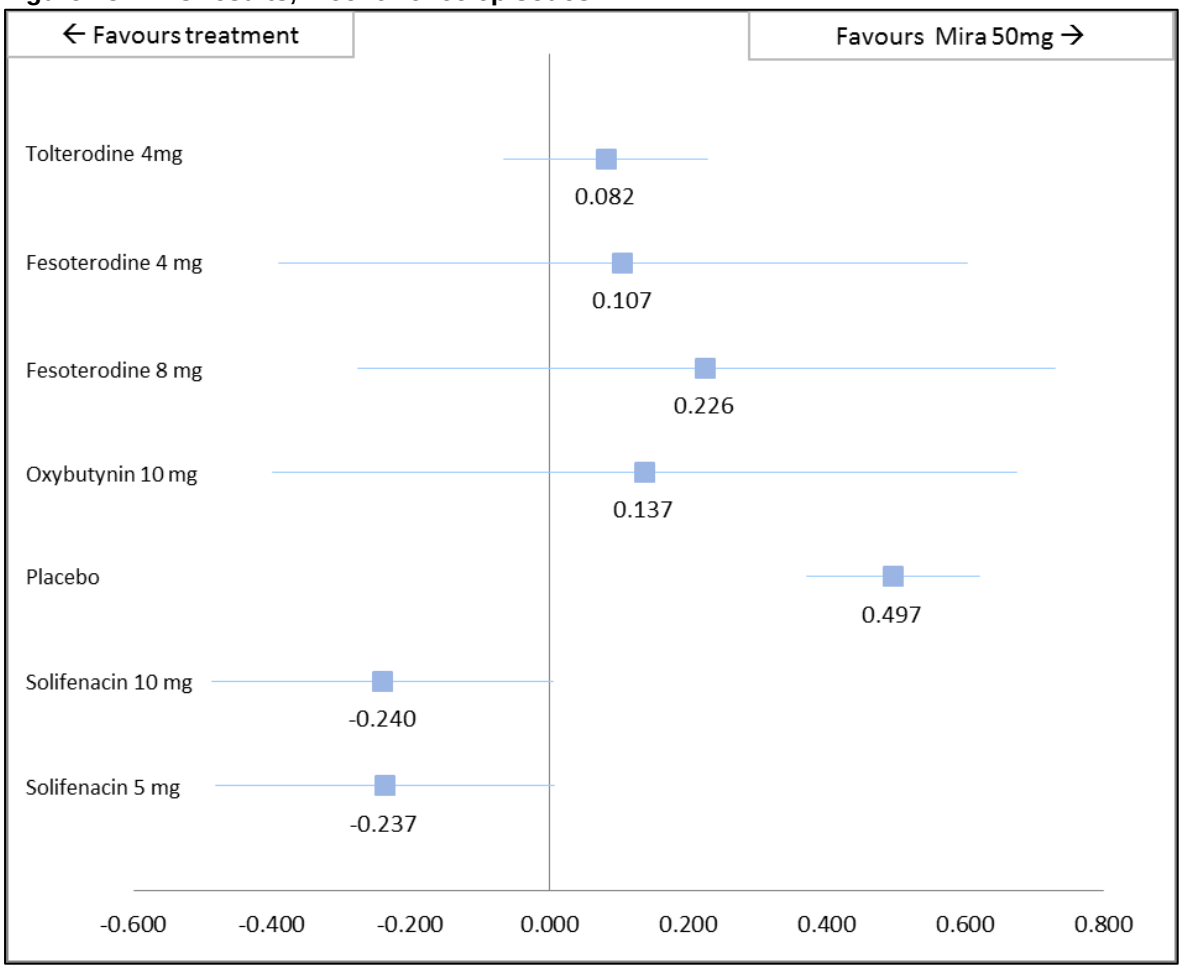


Abbreviations: mg, milligram.

The MTC analyses were conducted using both the fixed and random effect model (3 chains: 350,000 iterations after a burn-in of 100,000). Since the random effects (RE) model had a higher DIC (due to having a higher effective number of parameters) the fixed effects (FE) model was preferred.

Mean changes in daily number of incontinence episodes were greater with mirabegron 50 mg compared with tolterodine 4 mg, oxybutynin 10 mg, fesoterodine 4, and 8 mg, but differences were not statistically significant according to 95% CrI. Solifenacin 10 mg and 5 mg were associated with higher improvement than mirabegron 50 mg, with upper limits of the 95% CrI close to zero.

Figure 23: MTC results, incontinence episodes

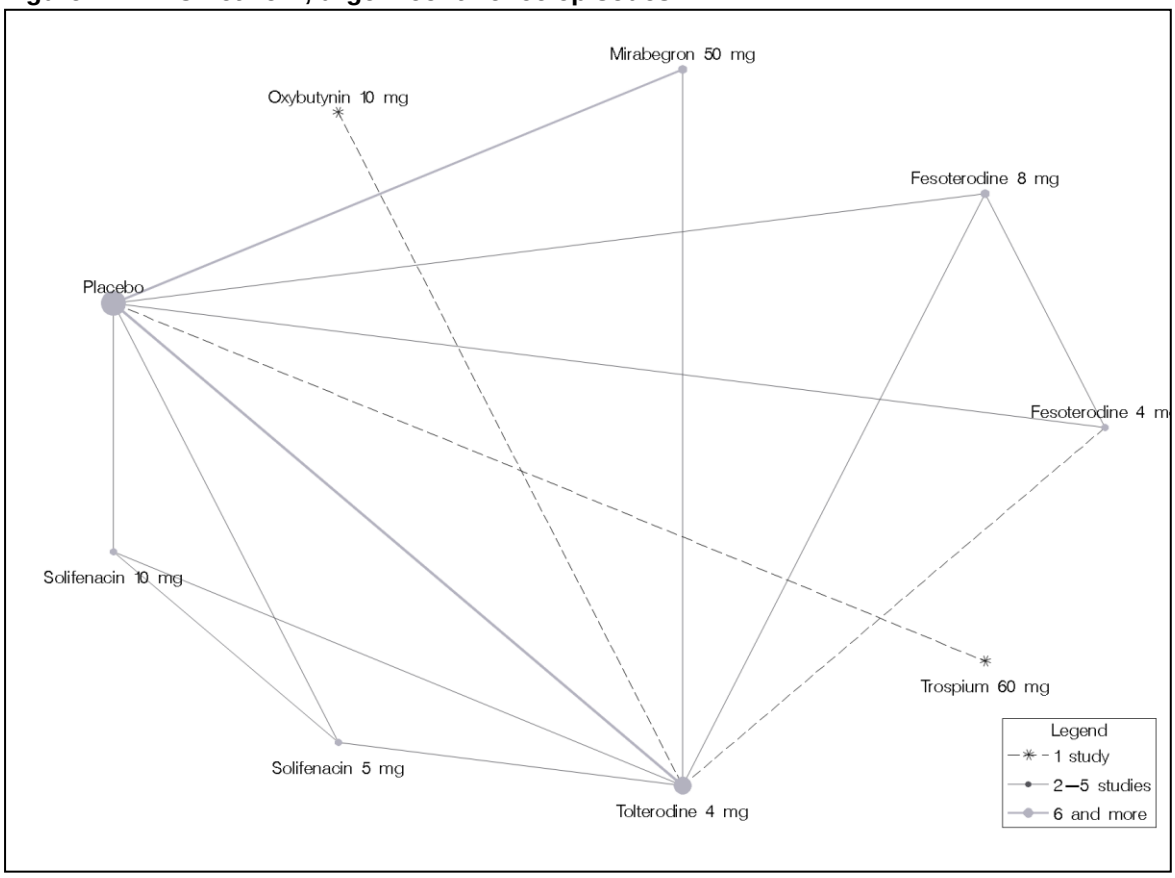


Abbreviations: mg, milligram.

Urge incontinence

Figure 24 shows the network diagram for the change from baseline in the number of urge incontinence episodes/24 hrs. Seventeen studies were included in the assessment of the relative efficacy of OAB treatments on the change from baseline in the urge incontinence episodes.

Figure 24: MTC network, urge incontinence episodes

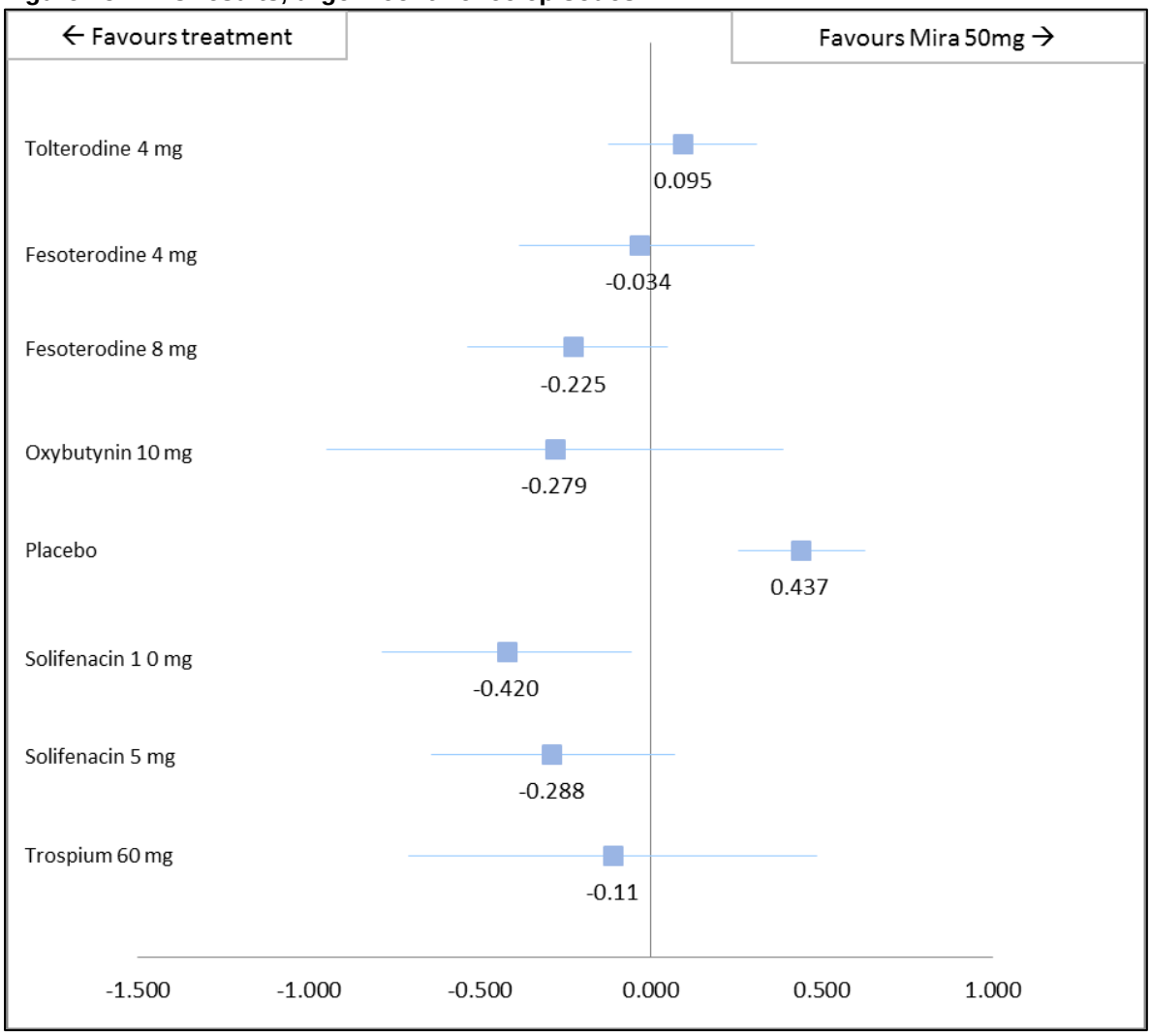


Abbreviations: mg, milligram.

The MTC analyses were conducted using both the fixed and random effect model (3 chains: 350,000 iterations after a burn-in of 100,000). Since the RE model had a higher DIC (due to having a higher effective number of parameters) the FE model was preferred.

The effect of mirabegron 50 mg did not differ significantly from antimuscarinics, according to 95% CrIs, except solifenacin 10 mg, which appeared to be more effective (mean difference vs mirabegron 50 mg of -0.420 [95% CrI -0.786 to -0.056]).

Figure 25: MTC results, urge incontinence episodes

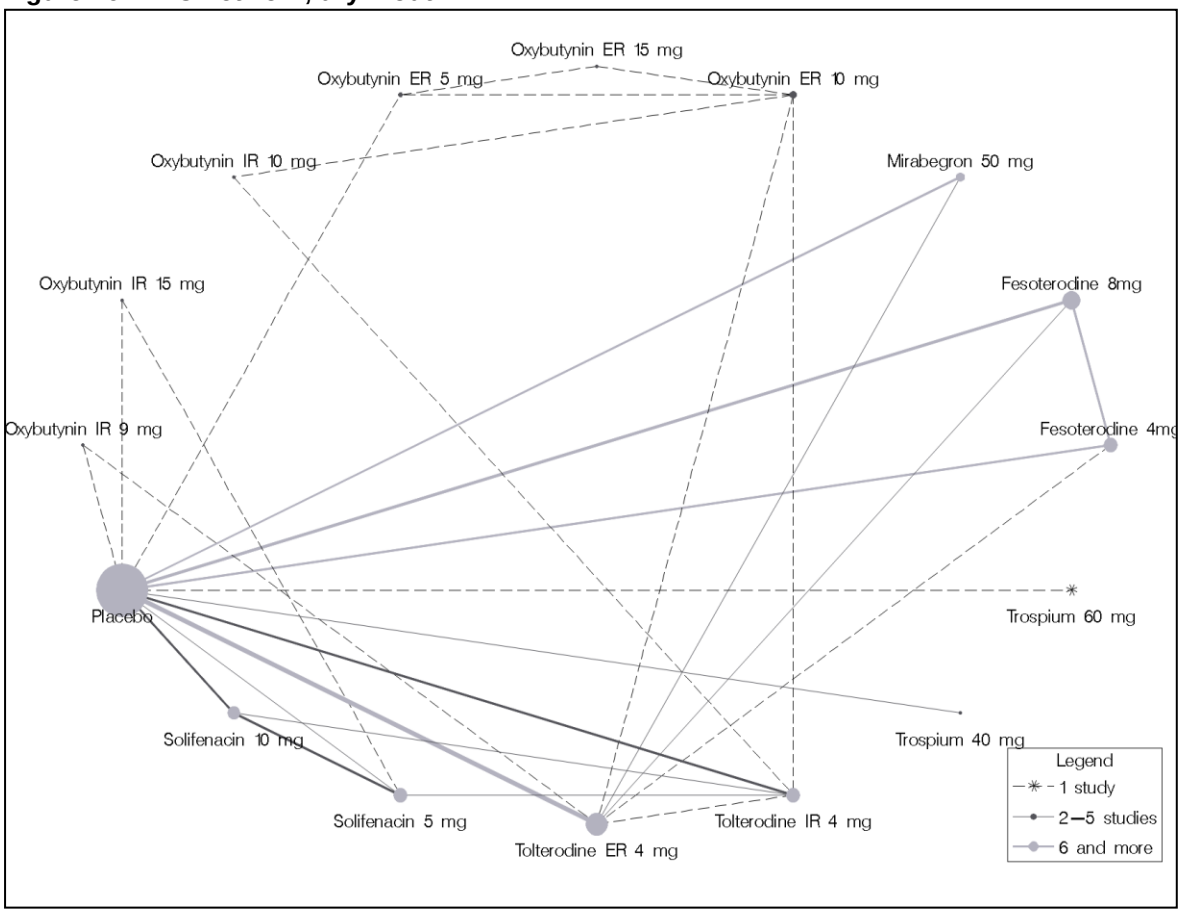


Abbreviations: mg, milligram.

Dry mouth

Figure 26 shows the network diagram for the change from baseline in the number patients with dry mouth. Forty studies were included in the MTC.

Figure 26: MTC network, dry mouth

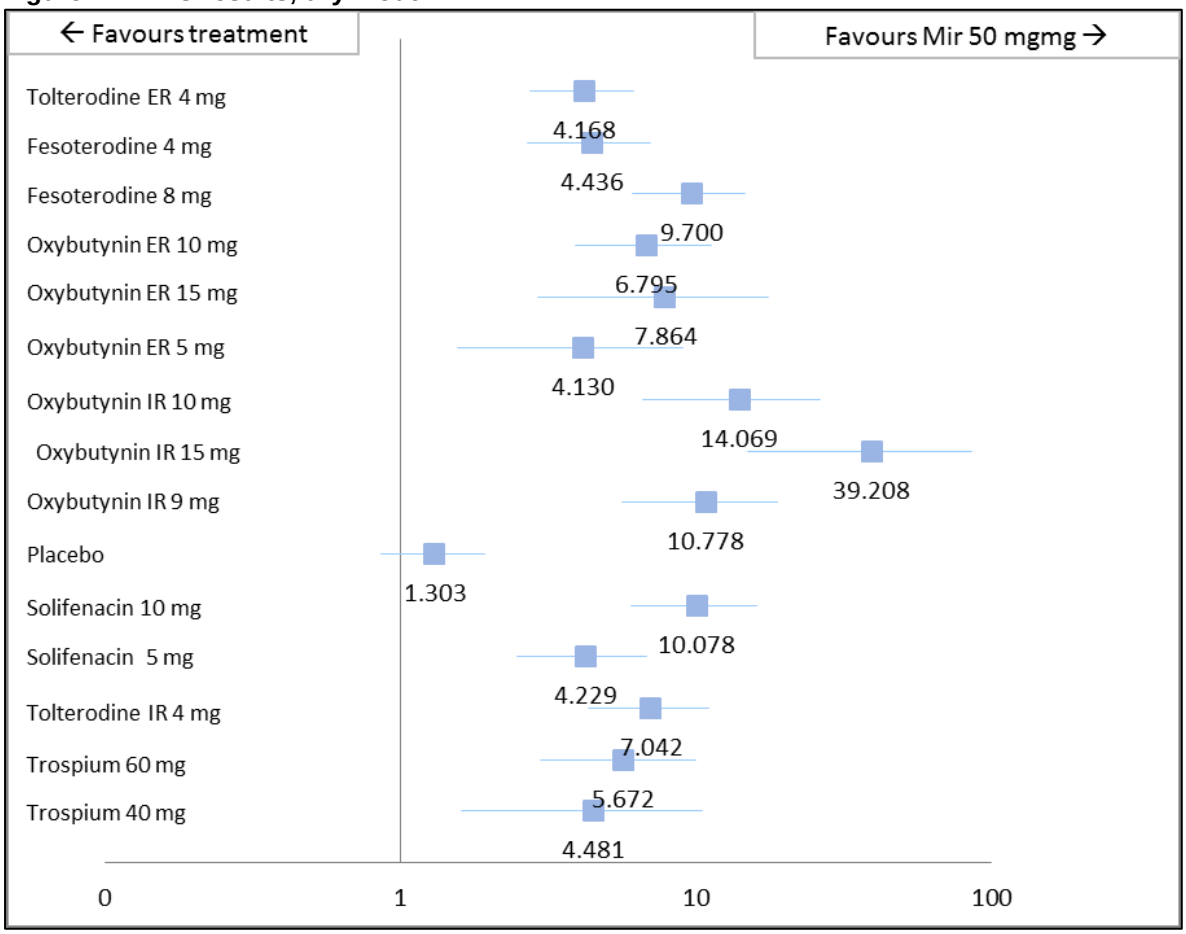


Abbreviations: ER, extended-release; IR, immediate-release; mg, milligram.

The MTC analyses were conducted using both the fixed and random effect model (3 chains: 350,000 iterations after a burn-in of 100,000 for FE model, and 3 chains: 500,000 iterations after a burn-in of 100,000 for RE model). The RE model was preferred, based on DIC.

Mirabegron 50 mg had a probability of dry mouth similar to placebo (with OR 1.303 [95% CrI: 0.859 to 1.916] in favour of mirabegron 50 mg). Moreover, all antimuscarinics were associated with a significantly higher risk of dry mouth compared with mirabegron 50 mg. The odds ratio estimated for the occurrence of dry mouth with tolterodine 4 mg compared with mirabegron 50 mg was estimated at 4.168 [95% CrI: 2.733 to 6.117].

Figure 27: MTC results, dry mouth

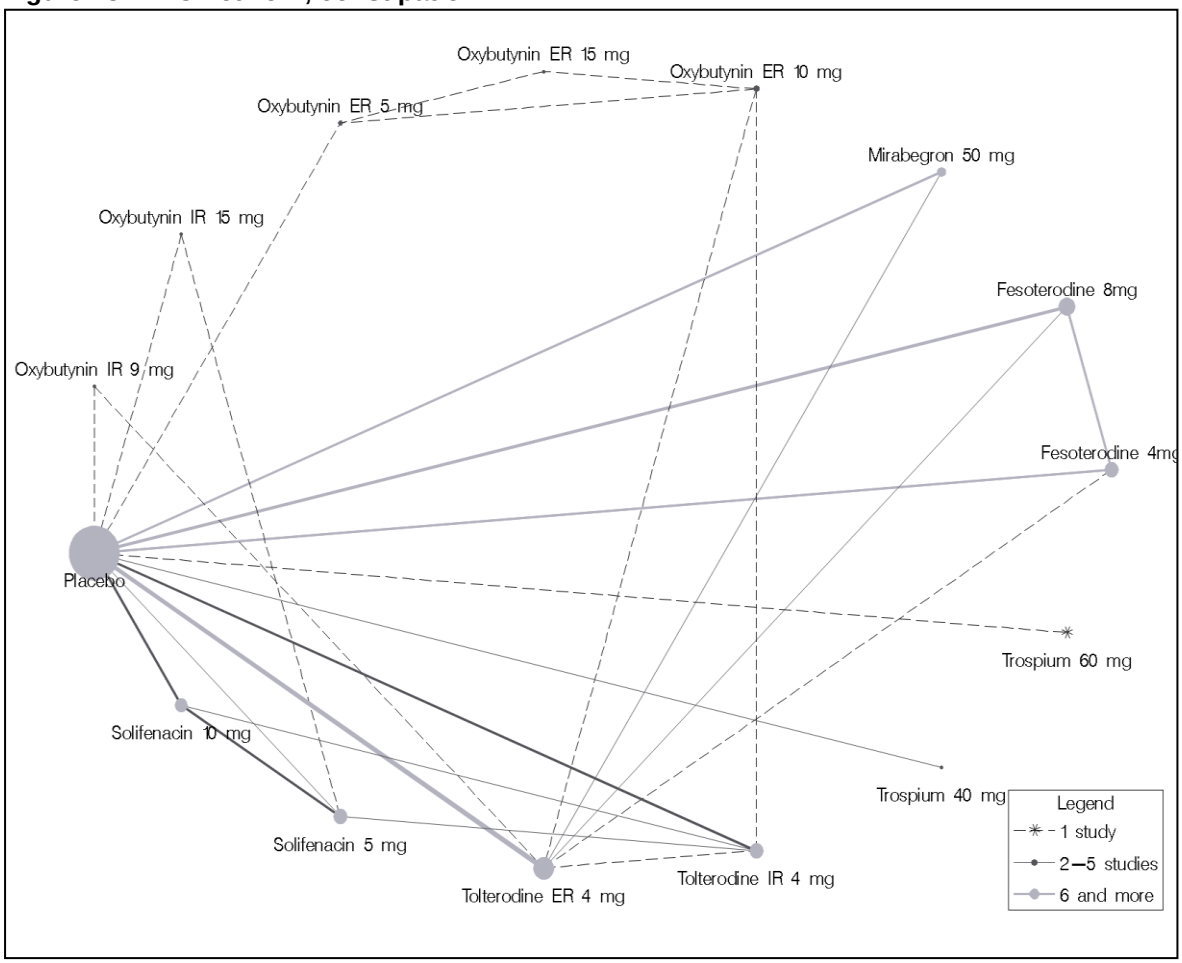


Abbreviations: ER, extended-release; IR, immediate-release; mg, milligram.

Constipation

Figure 28 shows the network diagram for the change from baseline in the number patients with constipation. Thirty seven studies were included in the analysis.

Figure 28: MTC network, constipation

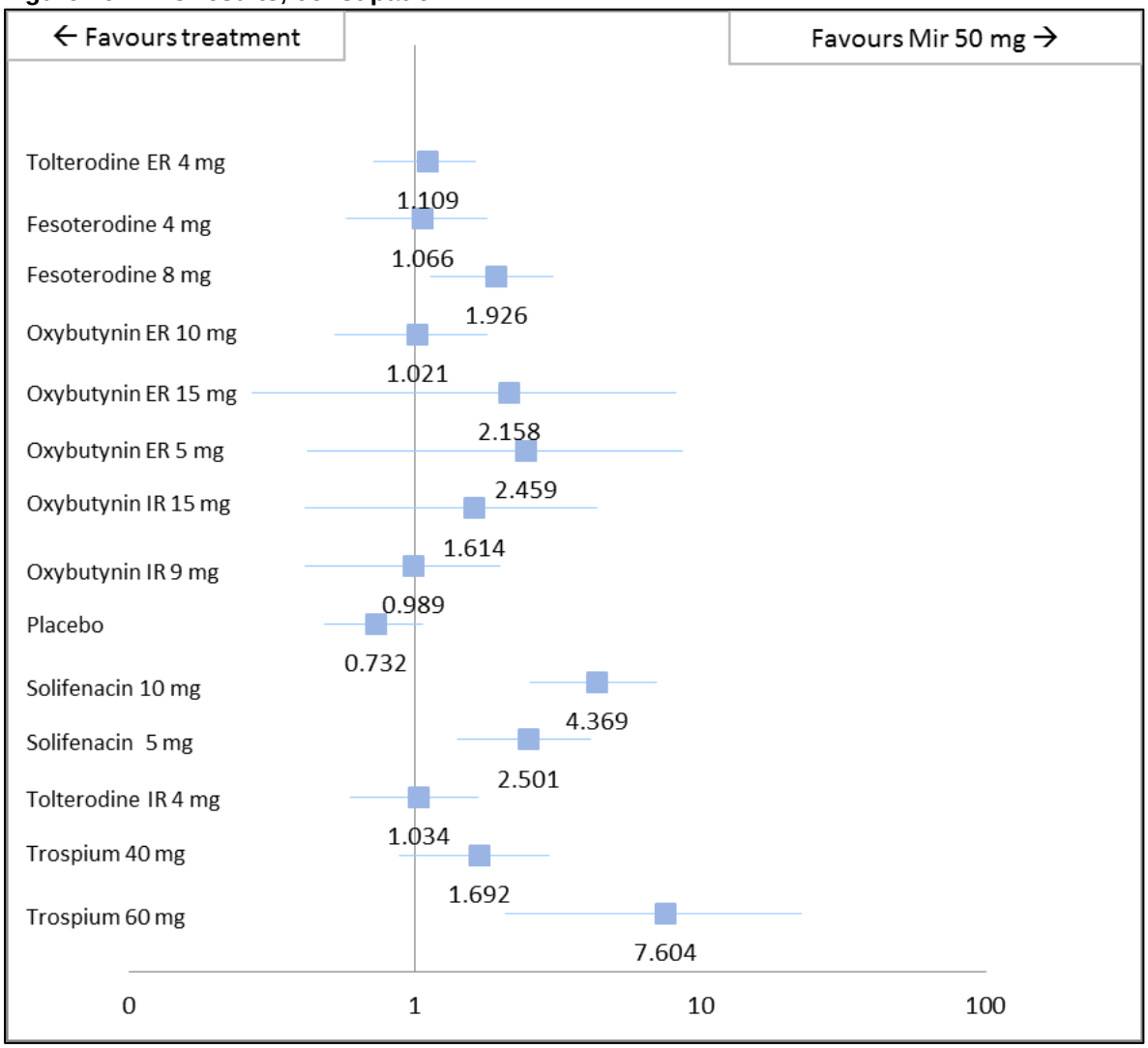


Abbreviations: ER, extended-release; IR, immediate-release; mg, milligram.

The MTC analyses were conducted using both the fixed and random effect model (3 chains: 350,000 iterations after a burn-in of 100,000 for FE model, and 3 chains: 500,000 iterations after a burn-in of 100,000 for RE model). The FE model was preferred based on DIC.

The probability of constipation associated with mirabegron 50 mg is similar to tolterodine ER 4 mg, with an OR estimated at 1.109 [95% CrI 0.716 to 1.647]. Solifenacin 5 mg and 10 as well as fesoterodine 8mg and trospium 60 mg were associated with greater risks of constipation compared with mirabegron 50 mg.

Figure 29: MTC results, constipation

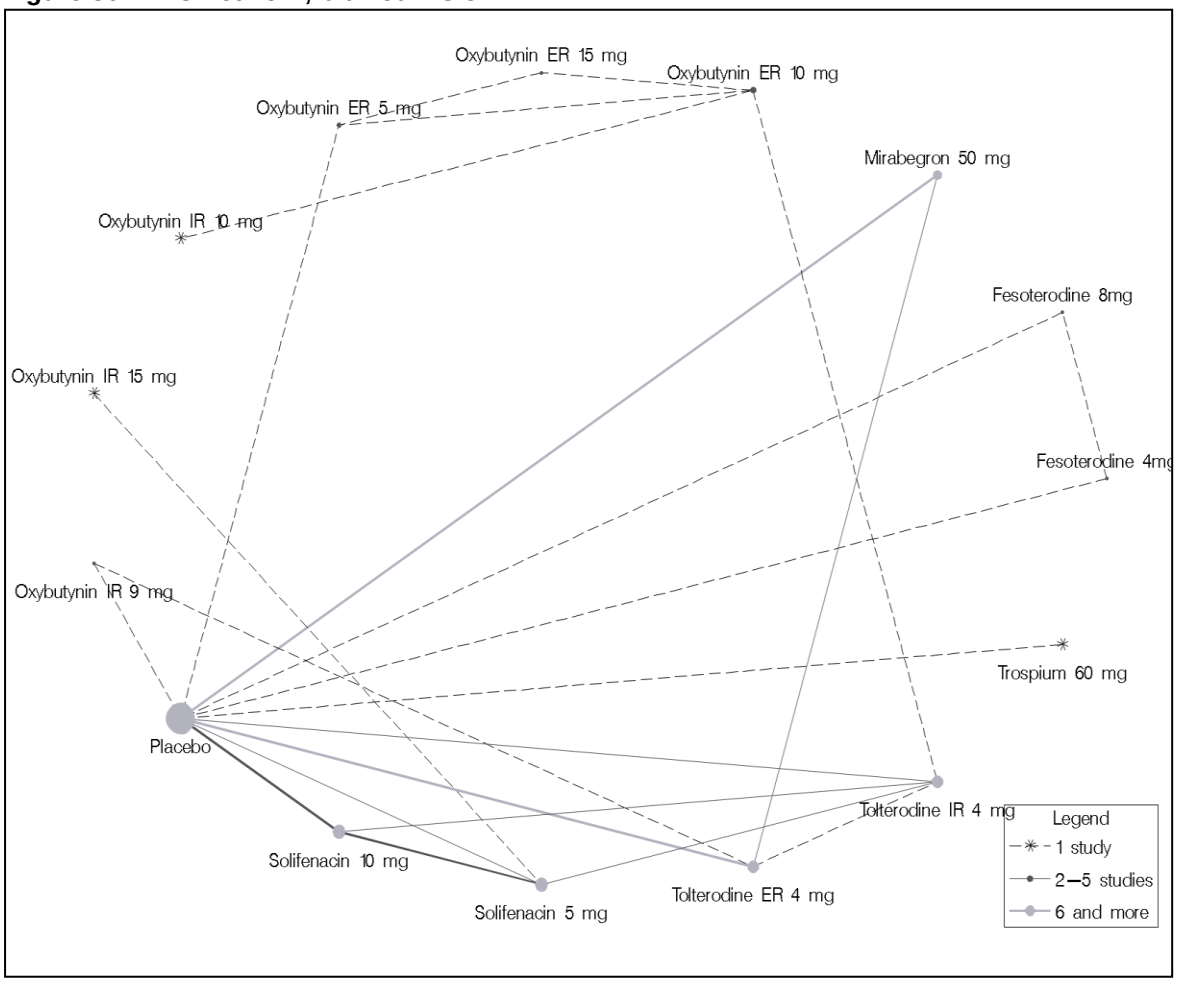


Abbreviations: ER, extended-release; IR, immediate-release; mg, milligram.

Blurred vision

Figure 30 shows the network diagram for the change from baseline in the number patients with constipation. Twenty three studies were included in the analysis.

Figure 30: MTC network, blurred vision

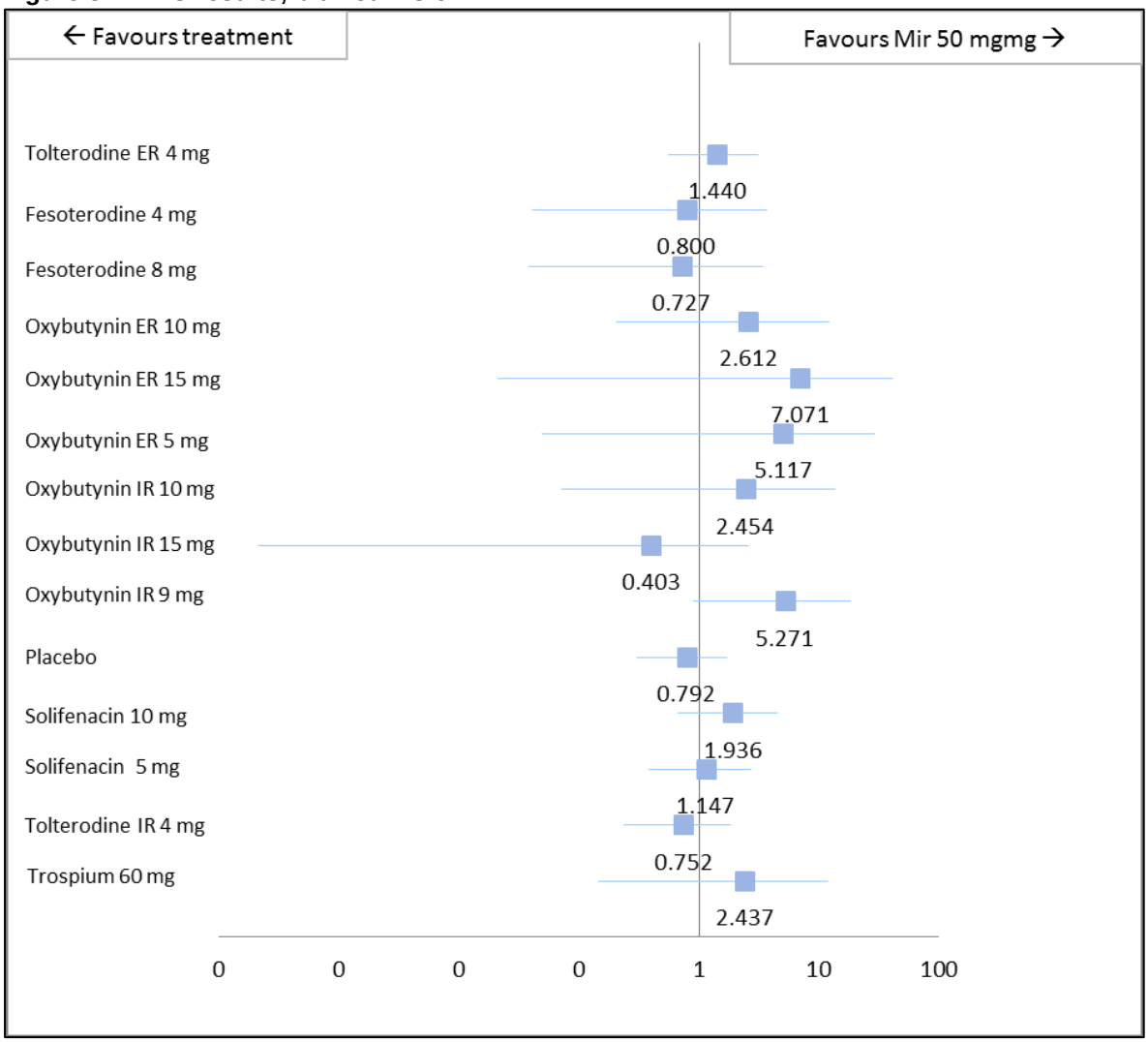


Abbreviations: ER, extended-release; IR, immediate-release; mg, milligram.

The MTC analyses were conducted using both the fixed and random effect model (3 chains: 350,000 iterations after a burn-in of 100,000 for FE model, and 3 chains: 500,000 iterations after a burn-in of 100,000 for RE model). The RE model was preferred.

This event is relatively rare and no clear difference in risk of developing blurred vision was found between treatments, as 95% CrI around ORs were relatively wide.

Figure 31: MTC results, blurred vision



Abbreviations: ER, extended-release; IR, immediate-release; mg, milligram.

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

The heterogeneity has been assessed by determining the deviance information criterion (DIC) for each MTC analyses using both fixed and random effect models. The model with the lower DIC indicates that this is the model with the best fit. The use of a random effect models indicates that heterogeneity between studies is present.

6.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

There was no doubt about the relevance of a trial when performing the MTC analyses.

6.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Whether the hypothesis of consistency between the direct and the indirect treatment effect can be reasonably supported by the data was considered by examining the posterior distribution of the inconsistency parameter (i.e. the difference between the

direct and indirect comparison). The measure of conflict P is reported, estimated as 2.min(prob, 1-prob), where prob designates the probability that the true value of the inconsistency parameter is more than zero. A value of P close to zero suggests the presence of inconsistency.

Potential inconsistencies between direct and indirect evidence from the analysis of the efficacy and safety outcomes have been assessed using the node-splitting method. The results of the assessment of inconsistency are presented in Section 10.17 for each analysed outcome and for each node. These showed evidence of potential inconsistency for the pair (mirabegron, placebo) in the analysis of micturition and incontinence with a Bayesian p-value of 0.042 and 0.005, respectively.

Comparing the direct and indirect evidence of mirabegron studies included in the diagram network, shows that the direct estimate of mean change in micturition or incontinence are lower than their respective indirect estimate (-0.210 and -0.363 respectively).

6.8 Non-RCT evidence

6.8.1 If non-RCT evidence is considered (see Section 6.2.7), please repeat the instructions specified in Sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in Sections 10.6 and 10.7, appendices 6 and 7.

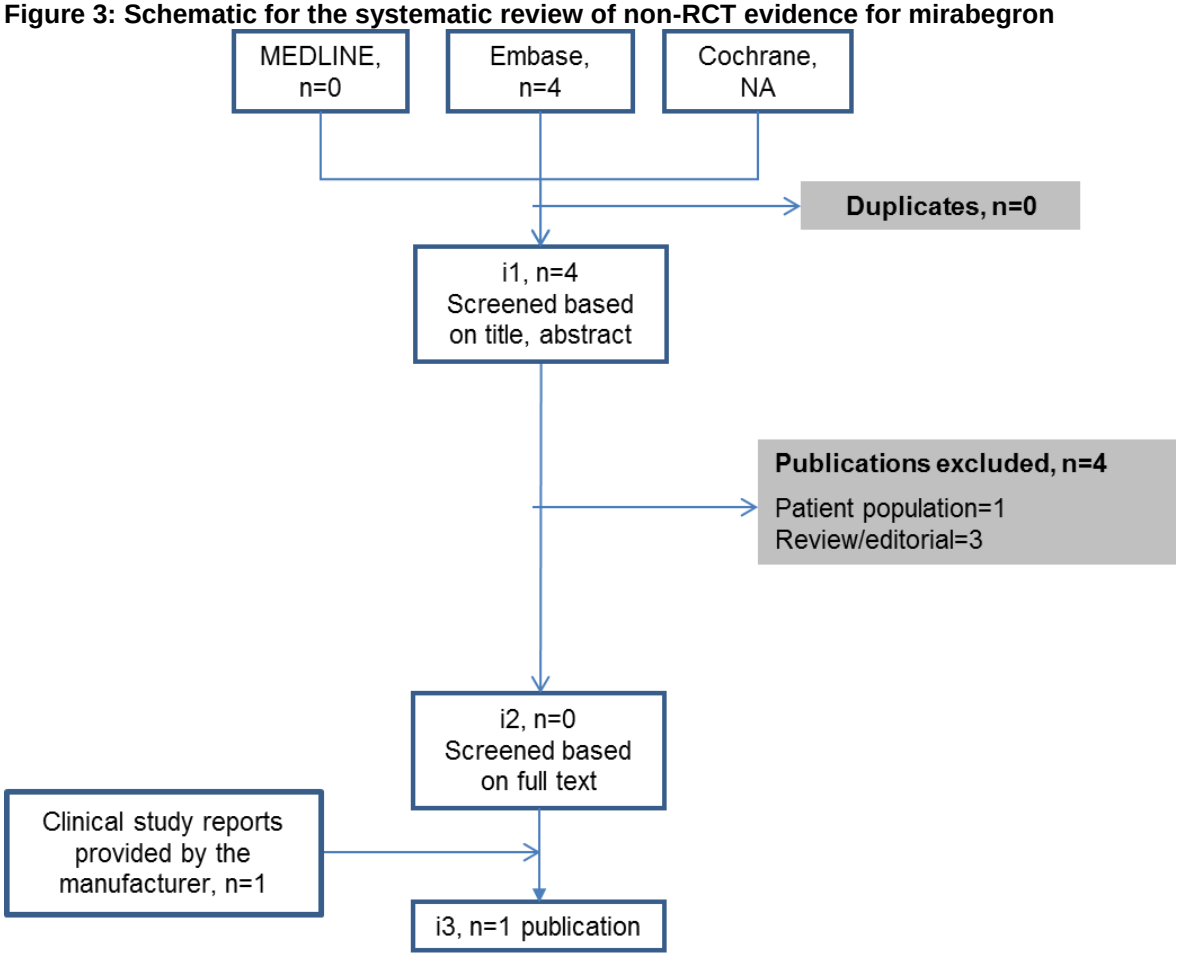
Study selection

The identification of non-RCT evidence is described in Section 6.1. One non-RCT relevant to this submission is outlined in Table 7 in Section 6.2.7. The methodology, critical appraisal and results of relevant non-RCTs are presented below.

Eligibility criteria

Exact details of the search strategy used, eligibility criteria and a complete quality assessment for the trial are provided in Sections 10.6 and 10.7.

Figure 3: Schematic for the systematic review of non-RCT evidence for mirabegron



Following assessment and exclusion of studies based on title, abstract and full text, one record for a non-RCT was identified; study 178-CL-051.

Summary of methodology of relevant non-RCTs

Table 54: Summary of methodology of non-RCT 178-CL-051

Study no. (acronym)	178-CL-051
Study objective	Evaluation of safety and efficacy of long-term (52 weeks) treatment with 50 mg mirabegron in patients with OAB
Location	26 sites in Japan
Design	Phase 3 open-label, uncontrolled study of 204 enrolled patients

Inclusion criteria	**At enrolment**
	• Male or female outpatient aged ≥ 20 years at time of informed consent
	• Symptoms of OAB for ≥ 24 weeks prior to run-in period
	• Capable of walking to the lavatory unaided and measuring urine volume by him/herself
	At randomisation
	• ≥ 8 micturitions per 24 hours and:
	  ○ ≥ 1 urgency episode per 24 hours, and/or
	  ○ ≥ 1 urge incontinence episode per 24 hours

Exclusion criteria	**At enrolment** • No experience of urge incontinence before informed consent • Definite diagnosis of stress incontinence • Symptoms suggesting OAB is transient (e.g. drug-induced or psychogenic) • Complications of UTI • Complications/history of bladder or prostatic tumours • Clinically significant lower urinary tract obstructive disease • Treatment with medication for lower urinary tract obstructive disease within 4 weeks of run-in period • Indwelling catheter or practicing intermittent self-catheterisation • Radiotherapy affecting urinary tract function or thermotherapy for BPH • Surgical therapy potentially affecting urinary tract function within 24 weeks of run-in period • History of acute cerebrovascular disorder, serious cardiovascular disorder or clinically significant orthostatic hypotension within 24 weeks of run-in period • Uncontrolled hypertension (sitting SBP ≥ 180 mmHg or DBP ≥110 mmHg at Visit 1) • Pulse rate ≥110 or < 50 bpm measured at Visit 1 • Clinically significant serious cardiac, hepatic, renal, immunological, pulmonary disease or malignant tumours • Hypersensitivity to β-receptor agonists • Treatment with other investigational medicines within 12 weeks prior to informed consent. • Previous treatment with mirabegron • Pregnancy/ breast feeding **At randomisation** • Polyuria >3000 mL/day • Confirmed PVR ≥ 100 mL or clinically significant lower urinary tract obstructive disease

Study no. (acronym)	178-CL-051
	• Uncontrolled hypertension (sitting SBP ≥ 180 mmHg or DBP ≥110 mmHg at Visit 2) • Pulse rate ≥110 or <50 measured at Visit 2 • Abnormal electrocardiogram • AST/ALT 2.5xULN • Blood creatinine level ≥ 2.0 mg/dL
Duration of study	• 1-week run-in • 52 weeks on treatment
Method of randomisation	N/A: all patients took 50 mg mirabegron
Method of blinding (care provider, patient and outcome assessor)	N/A: open-label study
Interventions, N randomised	• 50 mg mirabegron, N=204 (Dose escalation to 100 mg from Week 8 where necessary.)
Comparators, N randomised	None
Permitted concomitant medications	**Antidepressants** • imipramine (Imidol®, Tofranil®) • amitriptyline (Tryptanol®, etc.) • nortriptyline (Noritren®) • clomipramine (Anafranil®) • dosulepin (Prothiaden®) • maprotiline (Ludiomil®, etc.) • milnacipran (Toledomin®) **Class I antiarrhythmic agents** • pirmenol (Pimenol®) • cibenzoline (Cibenol®) • disopyramide (Rythmodan®, Norpace®, etc.) **Antihistamines** • diphenylpyraline (Hy-stamin®, etc.) • cyproheptadine (Periactin®, etc.) • triprolidine (Venen®, etc.) • promethazine (Hiberna®, Pyrethia®, etc.) • homochlorcyclizine (Homoclomin®, etc.) • alimemazine (Alimezine®) • diphenhydramine (Restamin®, etc.) • clemastine (Tavegyl®, etc.) • chlorpheniramine (Polaramine®, etc.) • mequitazine (Zesulan®, etc.) **Anti-Parkinson drugs** • piroheptine (Trimol®) • mazaticol (Pentona®) • metixene (Methixart®, etc.) • profenamine (Parkin®) **Parasympathetic inhibitors/blockers (including drugs containing narcotics)** • tiquizium (Thiaton®, etc.) • piperidolate (Crapinon®, etc.)

Study no. (acronym)	178-CL-051
	• propantheline (Pro-Banthine®, etc.) • timepidium (Sesden®, etc.) • methylscopolammonium (Daipin®, etc.) • methyloctatropine (Valpin®) • scopolamine butylbromide (Buscopan®, etc.) • pipethanate ethobromide (Panpurol®) • prifinium (Padrin®) • butropium (Butropan®, etc.) • tiemonium (Visceralgine®) • oxapium (Esperan®, etc.) • valethamate (Shinmetane®) • trospium (Spasmex®) • dicyclomine (Resporimin®, etc.) • scopolia extract (Scopolia Extract®, etc.) • atropine (Atropine Sulfate®, etc.) • ipratropium (Atrovent®) • oxitropium (Tersigan®) • tiotropium (Spiriva®) • pridinol (Konlax®, etc.) • mepenzolate (Trancolon®, etc.) **sympathomimetic agents** • amezinium (Amegyl®, etc.) **α- and β-stimulants** • etilefrine (Effortil®, etc.) • methylephedrine (Methy-F®, etc.) • epinephrine (Bosmin®, etc.) • ephedrine (Ephedrine Hydrochloride®, etc.) • norepinephrine (Nor-Adrenalin) **β-stimulants** • isoproterenol (Proternol®, etc.) • methoxyphenamine (Asthma®, etc.) • trimetoquinol (Inolin®, etc.) • salbutamol (Venetlin®, etc.) • terbutaline (Bricanyl®) • tulobuterol (Hokunalin®, etc.) • procaterol (Meptin®, etc.) • fenoterol (Berotec®, etc.) • formoterol (Atock Dry®) • mabuterol (Broncholin®) • salmeterol (Serevent®) • dobutamine (Dobutrex®, etc.) • docarpamine (Tanadopa®) • denopamine (Kalgut®, etc.) • ritodrine (Utemec®, etc.) • isoxsuprine (Duvadilan®, etc.)
Disallowed concomitant medications	**Anticholinergics** • oxybutynin (Pollakisu®, etc.) • flavoxate (Bladderon®, etc.) • propiverine (BUP-4®, etc.) • solifenacin (Vesicare®) • tolterodine (Detrusitol®) • imidafenacin (Uritos®, Staybla®, etc.) **β-2 stimulant** • clenbuterol (Spiropent®)

Study no. (acronym)	178-CL-051
	Therapeutics for prostatic hypertrophy • allylestrenol (Perselin®, etc.) • oxendolone (Prostetin®) • gestonorone (Depostat®) • chlormadinone (Prostal®, etc.) • tamsulosin (Harnal®, etc.) • terazosin (Hytracin®, Vasomet®, etc.) • prazosin (Minipress®, etc.) • silodosin (Urief®) • urapidil (Ebrantil®) • naftopidil (Flivas®, Avishot®) • mixtures (Eviprostat®, Paraprost®, etc.) • pollen extract containing drug (Cernilton®, etc.) **Substrates of CYP2D6 with a narrow therapeutic index** • flecainide (Tambocor®) • propafenone (Pronon®)
Discontinuation of study therapy	• Patient request/withdrawn consent • SAE/AE requiring a change in the protocol • Decision by investigator that termination was necessary • Insufficient efficacy • Patient lost to follow-up
Assessments	Visits at Weeks 8, 16, 28, 40, 52
Primary outcomes (including scoring methods and timings of assessments) Secondary outcomes (including scoring methods and timings of assessments)	**Efficacy endpoints** CFB, based on a 3-day micturition diary, to endpoint in: • micturitions per 24 hours • urgency episodes per 24 hours • incontinence episodes per 24 hours • urge incontinence episodes per 24 hours • nocturia episodes • QoL domain scores on the King's Health questionnaire **Safety endpoints** • Adverse events
Duration of follow-up	No follow up (with the exception of safety reporting) after the week52 final visit
Analysis populations	• FAS • QOL analysis set (patients in the FAS for whom ≥ 1 domain score could be calculated and who had taken the study drug for ≥ 14 days) • SAS
Statistical methods	• Minimum target sample size of 150 patients selected to allow for drop-outs and to ensure ≥ 100 patients received treatment for ≥ 1 year • Handling of missing data: If multiple observations were obtained within the same visit window for a patient, the value obtained closest to the target date was used. If deviations from the scheduled date were the same, the value obtained on the later date was used

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BPH, benign prostatic hyperplasia; bpm, beats per minute; CFB, change from baseline; DBP, diastolic blood pressure; FAS, full analysis set; mg, milligram; mm Hg; millimetres of mercury; N/A, not applicable; OAB, overactive bladder; PVR, post-void residual volume; QoL, quality of life; QTc, corrected QT interval; SAE,

serious adverse event; SAS, safety analysis set; SBP, systolic blood pressure; ULN, upper limit of normal; UTI, urinary tract infection.

Critical appraisal of relevant non-RCTs

A critical appraisal of the non-RCT study included can be found in Section 10.7.

Results of relevant non-RCTs

Of the 231 subjects in study 178-CL-051 who gave informed consent, 204 were enrolled for treatment. Of these, 165 completed treatment and 39 withdrew from the study. Key efficacy results are provided in Table 55 and QoL results in Table 56. A summary of adverse events (AEs) is provided in Table 57.

The efficacy results show that mirabegron 50 mg (with an optional dose increase to 100 mg) improvement was maintained until Week 52 without attenuation. In patients for whom the 50 mg dose was considered to provide insufficient efficacy, and for whom the dose was increased to 100 mg at Week 8, there was an increase in change after dose titration, and change from baseline was comparable with patients maintained at 50 mg. There were no major differences in the incidence of AEs or treatment-related AEs between the subjects maintained at 50 mg and those increased to 100 mg, and most adverse events were of mild severity.

Table 55: Summary of non-RCT 178-CL-051 efficacy results, FAS

Mean±SD (n)	All patients N=202	Patients maintained at 50 mg N=152	Patients increased to 100 mg N=50
Mean number of micturitions			
Week 8	-1.52 ± 2.201 *(196)*	-1.88 ± 2.256 *(146)*	-0.45 ± 1.634 *(50)*
Week 16	-2.08 ± 2.288 *(190)*	-2.16 ± 2.235 *(141)*	-1.86 ± 2.445 *(49)*
Week 28	-2.35 ± 2.460 *(185)*	-2.50 ± 2.454 *(137)*	-1.92 ± 2.454 *(48)*
Week 40	-2.13 ± 2.518 *(170)*	-2.22 ± 2.516 *(126)*	-1.87 ± 2.535 *(44)*
Week 52	-2.04 ± 2.595 *(165)*	-2.19 ± 2.708 *(123)*	-1.60 ± 2.201 *(42)*
Final assessment	-2.01 ± 2.599 *(196)*	-2.16 ± 2.673 *(146)*	-1.57 ± 2.341 *(50)*
Mean number of urgency episodes			
Week 8	-2.28 ± 2.549 (*196*)	-2.66 ± 2.541 *(146)*	-1.18 ± 2.253 *(50)*
Week 16	-2.84 ± 2.619 (*190*)	-3.08 ± 2.565 *(141)*	-2.16 ± 2.682 *(49)*
Week 28	-3.32 ± 2.866 (*185*)	-3.48 ± 2.946 *(137)*	-2.87 ± 2.599 *(48)*
Week 40	-3.25 ± 3.006 (*170*)	-3.28 ± 3.102 *(126)*	-3.14 ± 2.746 *(44)*
Week 52	-3.29 ± 3.030 (*165*)	-3.38 ± 3.092 *(123)*	-3.03 ± 2.863 *(42)*
Final assessment	-3.16 ± 2.935 (*196*)	-3.31 ± 2.948 *(146)*	-2.72 ± 2.884 *(50)*
Mean number of incontinence episodes			
Week 8	-1.02 ± 1.211 *(149)*	-1.18 ± 1.136 *(104)*	-0.66 ± 1.311 *(45)*
Week 16	-1.30 ± 1.454 *(145)*	-1.30 ± 1.150 *(101)*	-1.32 ± 2.001 *(44)*
Week 28	-1.54 ± 1.735 *(141)*	-1.55 ± 1.384 *(97)*	-1.52 ± 2.351 *(44)*
Week 40	-1.53 ± 1.634 *(128)*	-1.41 ± 1.568 *(88)*	-1.77 ± 1.766 *(40)*
Week 52	-1.45 ± 1.594 *(124)*	-1.34 ± 1.428 *(86)*	-1.69 ± 1.918 *(38)*
Final assessment	-1.38 ± 1.656 *(149)*	-1.30 ± 1.400 *(104)*	-1.56 ± 2.143 *(45)*
Mean number of incontinence episodes			

Mean±SD (n)	All patients N=202	Patients maintained at 50 mg N=152	Patients increased to 100 mg N=50
Week 8	-1.04 ± 1.212 *(147)*	-1.23 ± 1.185 *(103)*	-0.58 ± 1.164 *(44)*
Week 16	-1.24 ± 1.317 *(143)*	-1.28 ± 1.132 *(100)*	-1.12 ± 1.681 *(43)*
Week 28	-1.39 ± 1.644 *(139)*	-1.43 ± 1.349 *(96)*	-1.30 ± 2.181 *(43)*
Week 40	-1.40 ± 1.579 *(126)*	-1.33 ± 1.609 *(87)*	-1.56 ± 1.517 (39)
Week 52	-1.37 ± 1.450 *(123)*	-1.31 ± 1.377 *(85)*	-1.48 ± 1.616 *(38)*
Final assessment	-1.33 ± 1.563 *(147)*	-1.32 ± 1.401 *(103)*	-1.33 ± 1.909 *(44)*
Mean number of nocturia episodes			
Week 8	-0.44 ± 0.821 *(165)*	-0.50 ± 0.794 *(122)*	-0.27 ± 0.882 *(43)*
Week 16	-0.53 ± 0.800 *(160)*	-0.50 ± 0.781 *(117)*	-0.60 ± 0.856 *(43)*
Week 28	-0.44 ± 0.844 *(156)*	-0.46 ± 0.816 *(113)*	-0.37 ± 0.920 *(43)*
Week 40	-0.51 ± 0.967 *(144)*	-0.51 ± 0.913 *(105)*	-0.50 ± 1.112 *(39)*
Week 52	-0.54 ± 0.916 *(139)*	-0.52 ± 0.854 *(102)*	-0.59 ± 1.079 *(37)*
Final assessment	-0.48 ± 0.899 *(165)*	-0.49 ± 0.832 *(122)*	-0.47 ± 1.077 *(43)*

Abbreviations: mg, milligram; SD, standard deviation.

Table 56: Summary of non-RCT 178-CL-051 QoL results, QoL

Mean±SD *(n)*	All patients N=202	Patients maintained at 50 mg N=152	Patients increased to 100 mg N=50
General health perception (Domain 1)			
Week 28	-4.5 ± 22.99 *(182)*	-5.7 ± 23.65 *(135)*	-1.1 ± 20.82 *(47)*
Week 52	-7.8 ± 21.37 *(164)*	-8.4 ± 22.87 *(122)*	-6.0 ± 16.39 *(42)*
Final assessment	-6.3 ± 21.86 *(192)*	-6.9 ± 23.36 *(144)*	-4.2 ± 16.58 *(48)*
Incontinence impact (Domain 2)			
Week 28	-27.1 ± 29.49 *(182)*	-29.4 ± 28.23 *(135)*	-20.6 ± 32.27 *(47)*
Week 52	-22.8 ± 27.82 *(164)*	-23.8 ± 27.27 *(122)*	-19.8 ± 29.50 *(42)*
Final assessment	-22.7 ± 28.50 *(192)*	-24.3 ± 27.66 *(144)*	-18.1 ± 30.72 *(48)*
Role limitations (Domain 3)			
Week 28	-23.2 ± 25.06 *(182)*	-25.3 ± 24.84 *(135)*	-17.0 ± 24.94 *(47)*
Week 52	-19.5 ± 27.79 *(164)*	-21.6 ± 26.56 *(122)*	-13.5 ± 30.63 *(42)*
Final assessment	-19.3 ± 27.38 *(192)*	-21.5 ± 26.14 *(144)*	-12.5 ± 30.07 *(48)*
Physical limitations (Domain 4)			
Week 28	-22.1 ± 26.45 *(182)*	-23.7 ± 26.66 *(135)*	-17.4 ± 25.53 *(47)*
Week 52	-17.5 ± 28.29 *(164)*	-18.6 ± 29.24 *(122)*	-14.3 ± 25.39 *(42)*
Final assessment	-17.9 ± 28.00 *(192)*	-19.3 ± 29.08 *(144)*	-13.5 ± 24.23 *(48)*
Social limitations (Domain 5)			
Week 28	-11.6 ± 21.21 *(182)*	-13.1 ± 20.98 *(135)*	-7.3 ± 21.52 *(47)*
Week 52	-9.7 ± 22.82 *(164)*	-10.5 ± 23.94 *(122)*	-7.3 ± 19.26 *(42)*
Final assessment	-9.9 ± 22.90 *(192)*	-10.9 ± 24.01 *(144)*	-7.1 ± 19.10 *(48)*
Personal relationships (Domain 6)			

Mean±SD *(n)*	All patients N=202	Patients maintained at 50 mg N=152	Patients increased to 100 mg N=50
Week 28	-4.9 ± 13.12 *(128)*	-4.7 ± 12.55 *(95)*	-5.6 ± 14.83 *(33)*
Week 52	-4.7 ± 16.52 *(114)*	-3.6 ± 15.96 *(84)*	-7.8 ± 17.90 *(30)*
Final assessment	-4.7 ± 15.99 *(135)*	-4.2 ± 15.32 *(102)*	-6.1 ± 18.07 *(33)*
Emotions (Domain 7)			
Week 28	-19.2 ± 22.68 *(182)*	-19.3 ± 24.24 *(135)*	-18.9 ± 17.63 *(47)*
Week 52	-17.6 ± 24.33 *(164)*	-18.1 ± 26.00 *(122)*	-16.1 ± 18.88 *(42)*
Final assessment	-17.5 ± 24.66 *(192)*	-18.2 ± 26.40 *(144)*	-15.5 ± 18.58 *(48)*
Sleep/energy (Domain 8)			
Week 28	-13.4 ± 18.58 *(182)*	-13.0 ± 18.85 *(135)*	-14.5 ± 17.93 *(47)*
Week 52	-12.3 ± 20.46 *(164)*	-13.3 ± 18.17 *(122)*	-9.5 ± 26.07 *(42)*
Final assessment	-13.0 ± 20.21 *(192)*	-14.1 ± 18.31 *(144)*	-9.7 ± 24.99 *(48)*
Severity measures (Domain 9)			
Week 28	-14.4 ± 16.91 *(182)*	-15.8 ± 16.76 *(135)*	-10.6 ± 16.95 (47)
Week 52	-14.4 ± 16.11 *(164)*	-15.5 ± 16.04 *(122)*	-11.3 ± 16.10 *(42)*
Final assessment	-14.1 ± 16.57 *(192)*	-15.6 ± 16.32 *(144)*	-9.4 ± 16.61 *(48)*

Abbreviations: mg, milligram; SD, standard deviation.

Table 57: Summary of non-RCT 178-CL-051 safety results, SAS

n (%)	All patients N=202	Patients maintained at 50 mg N=152	Patients increased to 100 mg N=50
TEAEs	189 (93.6)	139 (91.4)	50 (100.0)
Mild	175 (86.6)	129 (84.9)	46 (92.0)
Moderate	11 (5.4)	8 (5.3)	3 (6.0)
Severe	2 (1.0)	1 (0.7)	1 (2.0)
Treatment-related TEAEs†	66 (32.7)	51 (33.6)	15 (30.0)
Mild†	59 (29.2)	45 (29.6)	14 (28.0)
Moderate†	0	0	0
Severe†	0	0	0
SAEs	7 (3.5)	4 (2.6)	3 (6.0)
Treatment-related SAEs	0	0	0
TEAEs resulting in permanent discontinuation	15 (7.4)	10 (6.6)	5 (10.0)
Treatment-related TEAEs resulting in permanent discontinuation	5 (2.5)	4 (2.6)	1 (2.0)

Abbreviations: mg, milligram; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
†Mild/moderate/severe categories do not include AEs related to ECGs (where severity was not graded).

6.9 Adverse events

Summary of safety

- The long-term safety study, 178-CL-049 (TAURUS) has shown that 50 mg doses of mirabegron are generally safe and well tolerated.
  - The incidence of treatment-related TEAEs was similar between the mirabegron 50 mg (26.2%) and tolterodine groups (27.6%).
  - The incidence of treatment-related SAEs was 1.2% in the mirabegron 50 mg group and 0.6% in the tolterodine group.
  - The incidence of treatment-related TEAEs leading to study drug discontinuation was 4.3% in the mirabegron 50 mg group and 3.8% in the tolterodine group.
- Dry mouth is a common reason for discontinuation of antimuscarinic therapy for OAB. Mirabegron shows favourable rates of dry mouth:
  - In SCORPIO, rates of dry mouth on mirabegron 50 mg were the same as placebo (1.8%) and much lower than tolterodine (9.5%)
  - In the long-term safety study, TAURUS rates of treatment-related dry mouth were 2.5% on mirabegron and 8.3% on tolterodine.

The identification of clinical evidence is described in Sections 6.1 and 6.2. All studies relevant to this submission are listed in Table 6 in Section 6.2.4. The methodology, critical appraisal and results of relevant studies that are designed primarily to assess safety outcomes are presented in Section 6.9.1. Safety results from other studies, primarily designed to assess efficacy are described in Section 6.9.2.

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.

The systematic review detailed in Section 6.1 identified one study (178-CL-049, TAURUS) designed to primarily assess the safety of mirabegron (41).

Summary of methodology of studies designed to primarily assess safety

Table 58: Summary of methodology of TAURUS, designed to primarily assess safety

Study no. (acronym)	178-CL-049 (TAURUS)
Study objective	Long-term safety and efficacy of mirabegron in patients with symptoms of OAB

Study no. (acronym)	178-CL-049 (TAURUS)
Location	Global; 306 sites (Austria, Australia, Belarus, Belgium, Bulgaria, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Switzerland, Ukraine, UK, US)
Design	Phase III, randomised, double-blind, parallel group, active-controlled study of 2,452 patients
Duration of study	• 2-week single-blind placebo run-in • 12 months on randomised treatment
Method of randomisation	• 1:1:1 • Computer-generated randomisation scheme • Randomisation was stratified by centre
Method of blinding (care provider, patient and outcome assessor)	• Study drugs packaged using double-dummy blinding • During placebo run-in, patients were blinded to study drug. • During double-blind treatment, the investigator, study site personnel, patients, sponsor and sponsor's representatives were blinded to the identity of the randomised drug assignment.
Interventions	• 50 mg mirabegron, N=815 • 100 mg mirabegron, N=824
Comparators	• 4 mg tolterodine ER, N=813
Permitted concomitant medications	• Alpha blockers • 5-alpha reductase inhibitors • CYP3A4 inducers • Loop diuretics These medications were permitted provided patient had been taking them on a long-term basis (i.e. not stopped, started or changed dose within 30 days prior to study entry)
Disallowed concomitant medications	• Anticholinergics • Antispasmodics • CYP2D6 substrates with narrow therapeutic indices • Medications recommended not to be used with tolterodine
Discontinuation of study therapy	• Patient request/withdrawn consent • Patient experienced AEs • Patient experienced lack of efficacy • Patient lost to follow-up • Patient in violation of protocol
Assessments	Visits at screening, baseline and Months 1, 3, 6, 9, 12
Primary outcomes	Incidence and severity of TEAEs

Study no. (acronym)	178-CL-049 (TAURUS)	
Secondary outcomes (including scoring methods and timings of assessments)	CFB to Months 1, 3, 6, 9, 12 and final visit in : • mean number micturitions per 24 hr • mean number incontinence episodes per 24 hr • mean number urgency incontinence episodes per 24 hr • mean volume voided per micturition • mean number of urgency episodes (Grade 3/4) per 24 hr • mean level of urgency • mean number of pads used per 24 hr • mean number of nocturia episodes per 24 hr • symptom bother and HRQoL scores CFB to Month 12 and final visit in: • PPBC	Assessment • 3-day micturition diary • TS VAS, OABq, PPBC
Duration of follow-up	Patients were not contacted after Visit 7 (Month 12)	

Abbreviations: AE, adverse event; CFB, change from baseline; ER, extended-release; hr, hour; HRQoL, health-related quality of life; mg, milligram; OAB. Overactive bladder; OABq, overactive bladder questionnaire; PPBC, patient perception of bladder condition; TEAE, treatment-emergent adverse event; TS VAS, treatment satisfaction visual analogue scale.

Inclusion and exclusion criteria

Inclusion and exclusion criteria for TAURUS are the same as for SCORPIO and have been described previously in Section 6.3.3.

Patient demographics and baseline characteristics

Patient demographics of the SAS dataset are summarised in Table 59. Most of the patients included in the SAS dataset were from Europe (63.4%) or the US (26.6%).

Table 59: Patient demographics of participants across randomised groups, TAURUS, SAS

Baseline characteristics	Randomised groups			Total N=2,444
	Mirabegron 50 mg N=812	Mirabegron 100 mg N=820	Tolterodine ER 4 mg N=812	
Sex, n (%)				
Male	210 (25.9%)	212 (25.9%)	212 (26.1%)	634 (25.9%)
Female	602 (74.1%)	608 (74.1%)	600 (73.9%)	1810 (74.1%)
Age in years, mean (SD)	59.2 (12.56)	60.1 (11.92)	59.6 (12.47)	59.6 (12.32)
Age group in years, n (%)				
<65	523 (64.4%)	504 (61.5%)	509 (62.7%)	1536 (62.8%)
≥ 65	289 (35.6%)	316 (38.5%)	303 (37.3%)	908 (37.2%)
<75	737 (90.8%)	739 (90.1%)	729 (89.8%)	2205 (90.2%)
≥ 75	75 (9.2%)	81 (9.9%)	83 (10.2%)	239 (9.8%)
Race, n (%)				
White	778 (95.8%)	774 (94.4%)	780 (96.1%)	2332 (95.4%)
Black or African American	22 (2.7%)	30 (3.7%)	20 (2.5%)	72 (2.9%)
Asian	8 (1.0%)	8 (1.0%)	5 (0.6%)	21 (0.9%)
Other	4 (0.5%)	8 (1.0%)	7 (0.9%)	19 (0.8%)
Ethnicity, n (%)				
Hispanic/Latino	23 (2.8%)	20 (2.4%)	32 (4.0%)	75 (3.1%)
Non-Hispanic/Non-Latino	789 (97.2%)	800 (97.6%)	778 (96.0%)	2367 (96.9%)
BMI in Kg/m^2	*N=811*	*N=819*	*N=809*	*N=2,439*
Mean (SD)	29.0 (6.29)	28.8 (5.99)	28.5 (5.69)	28.8 (5.99)
BMI category in Kg/m^2, n (%)				
<25	229 (28.2%)	231 (28.2%)	224 (27.7%)	684 (28.0%)
25 to <30	294 (36.3%)	319 (38.9%)	328 (40.5%)	941 (38.6%)
≥ 30	288 (35.5%)	269 (32.8%)	257 (31.8%)	814 (33.4%)
Geographical region, n (%)				
Eastern Europe	260 (32.0%)	270 (32.9%)	258 (31.8%)	788 (32.2%)
Western Europe	257 (31.7%)	242 (29.5%)	262 (32.3%)	761 (31.1%)
Southern hemisphere	34 (4.2%)	39 (4.8%)	37 (4.6%)	110 (4.5%)
Canada	44 (5.4%)	47 (5.7%)	45 (5.5%)	136 (5.6%)
Northeastern US	55 (6.8%)	56 (6.8%)	53 (6.5%)	164 (6.7%)
Midwestern US	29 (3.6%)	33 (4.0%)	33 (4.1%)	95 (3.9%)
Southern US	67 (8.3%)	68 (8.3%)	57 (7.0%)	192 (7.9%)
Western US	66 (8.1%)	65 (7.9%)	67 (8.3%)	198 (8.1%)

Abbreviations: BMI, body mass index; ER, extended-release; Kg, kilogram; m, metre; mg, milligram; SD, standard deviation; US, United States.

Patient characteristics of OAB history are presented in Table 60. With the exception of reason for previous OAB drug discontinuation (ranging from 21.7% to 27.3%), OAB history characteristics were comparable across all treatment groups.

Table 60: OAB history in participants across randomised groups, TAURUS, SAS

Baseline characteristics	Randomised groups		
	Mirabegron 50 mg N=812	Mirabegron 100 mg N=820	Tolterodine ER 4 mg N=812
Type of OAB[†], n (%)			
Urgency incontinence	296 (36.5)	305 (37.2)	317 (39.0)
Frequency	284 (35.0)	287 (35.0)	285 (35.1)
Mixed	232 (28.6)	228 (27.8)	210 (25.9)
Prior OAB surgery, n (%)			
Yes	75 (9.2)	70 (8.5)	68 (8.4)
No	737 (90.8)	750 (91.5)	744 (91.6)
Previous OAB drug[‡], n (%)			
Yes	446 (54.9)	419 (51.1)	447 (55.0)
No	366 (45.1)	401 (48.9)	365 (45.0)
Previous non-drug treatment for OAB[§], n (%)			
Yes	37 (4.6)	24 (2.9)	32 (3.9)
Biofeedback	0	0	0
Exercises	28 (3.4)	20 (2.4)	25 (3.1)
Electrical stimulation	1 (0.1)	0	0
Behavioural	8 (1.0)	4 (0.5)	10 (1.2)
Pessaries	3 (0.4)	1 (0.1)	0
Implants	0	0	0
Other	5 (0.6)	3 (0.4)	4 (0.5)
No	775 (95.4)	796 (97.1)	780 (96.1)
Reason for previous OAB drug discontinuation[¶], n (%)			
Insufficient effect	297 (66.6)	268 (64.0)	283 (63.3)
Poor tolerability	97 (21.7)	108 (25.8)	122 (27.3)
Duration of OAB symptoms (months)			
Mean (SD)	87.4 (96.28)	87.9 (91.52)	83.8 (87.34)
Median	55.9	56.4	55.9
Range	(3 - 653)	(3 - 692)	(3 - 642)

Abbreviations: ER, extended-release; mg, milligram; OAB, overactive bladder; SD, standard deviation.
[†]Types of OAB were defined as follows: urgency incontinence = urge incontinence only, mixed = mixed stress/urge incontinence with urge as a predominant factor, frequency = frequency/urgency without incontinence; [‡]'Yes' included patients who received a marketed drug with an indication for OAB. It did not include patients who only received an OAB drug as an investigational study medication in a previous clinical study; [§]Non-drug treatment which ended ≥ 30 days prior to screening were not included; [¶]Patients could chose >1 reason for discontinuation of previous OAB drug.

OAB-related baseline characteristics are presented in Table 61 and were consistent across treatment groups in the SAS dataset.

Table 61: OAB-related baseline characteristics in participants across randomised groups, TAURUS, SAS

Baseline characteristics	Randomised groups		
	Mirabegron 50 mg N=812	Mirabegron 100 mg N=820	Tolterodine ER 4 mg N=812
Mean number of micturitions per 24 hours			
Mean (SD)	11.12 (2.809)	11.16 (2.917)	10.94 (2.668)
Range	6.3 – 31.7	5.7 – 29.3	4.3 – 26.3
Mean volume voided per micturition (mL)			
Mean (SD)	160.4 (58.80)	164.6 (58.62)	160.8 (56.98)
Range	28 – 346	17 – 350	36 – 354
Mean number of urgency episodes (Grade 3 or 4) per 24 hours			
Mean (SD)	5.66 (3.601)	5.61 (3.722)	5.44 (3.453)
Range	0.0 – 22.7	0.0 – 26.7	0.7 – 20.7
Mean level of urgency			
Mean (SD)	2.45 (0.544)	2.44 (0.525)	2.43 (0.519)
Range	0.3 – 4.0	0.4 – 4.0	0.5 – 4.0
Mean number of nocturia episodes per 24 hours			
Mean (SD)	1.83 (1.361)	1.85 (1.404)	1.77 (1.388)
Range	0.0 – 8.7	0.0 – 9.7	0.0 – 11.3
Mean number of pads used per 24 hours			
Mean (SD)	1.06 (1.872)	0.98 (1.769)	0.98 (1.759)
Range	0.0 – 12.7	0.0 – 12.7	0.0 – 12.7

Abbreviations: ER, extended-release; mg, milligram; mL, millilitre; SD, standard deviation.

Statistical analysis

Planned sample size: Approximately 2,500 patients were planned to be enrolled. This number was not based on a formal sample size calculation, but rather on an estimate of the number of patients who would enrol in this study after prior completion of either SCORPIO or ARIES. Patients who completed the 12-week treatment and safety follow-up periods of these studies (in addition to patients not enrolled in either study but who met the inclusion/exclusion criteria) were eligible.

Populations for analysis: The following population sets (previously defined in Table 16) were analysed; RPAS, RAS, FAS, FAS-I, SAS.

Handling of missing data: For both safety and efficacy data, analysis based on the final visit took into account patients who withdrew before Month 12 and therefore did not have any safety or efficacy measurements available for that month. The final visit analysis used a LOCF approach.

For the subscale analyses of OABq, if <50% of the scale items were missing, the scale was retained with the mean scale score of the items present used to impute a score for the missing items. If >50% of the scale items were missing, no scale score was calculated; the subscale score was considered missing. If a subscale score for calculation of the HRQoL total was missing, the HRQoL total score was not calculated. Missing values were not imputed for all other QoL-related questionnaires.

Laboratory data values below the LLOQ were set to the value of the LLOQ analyses.

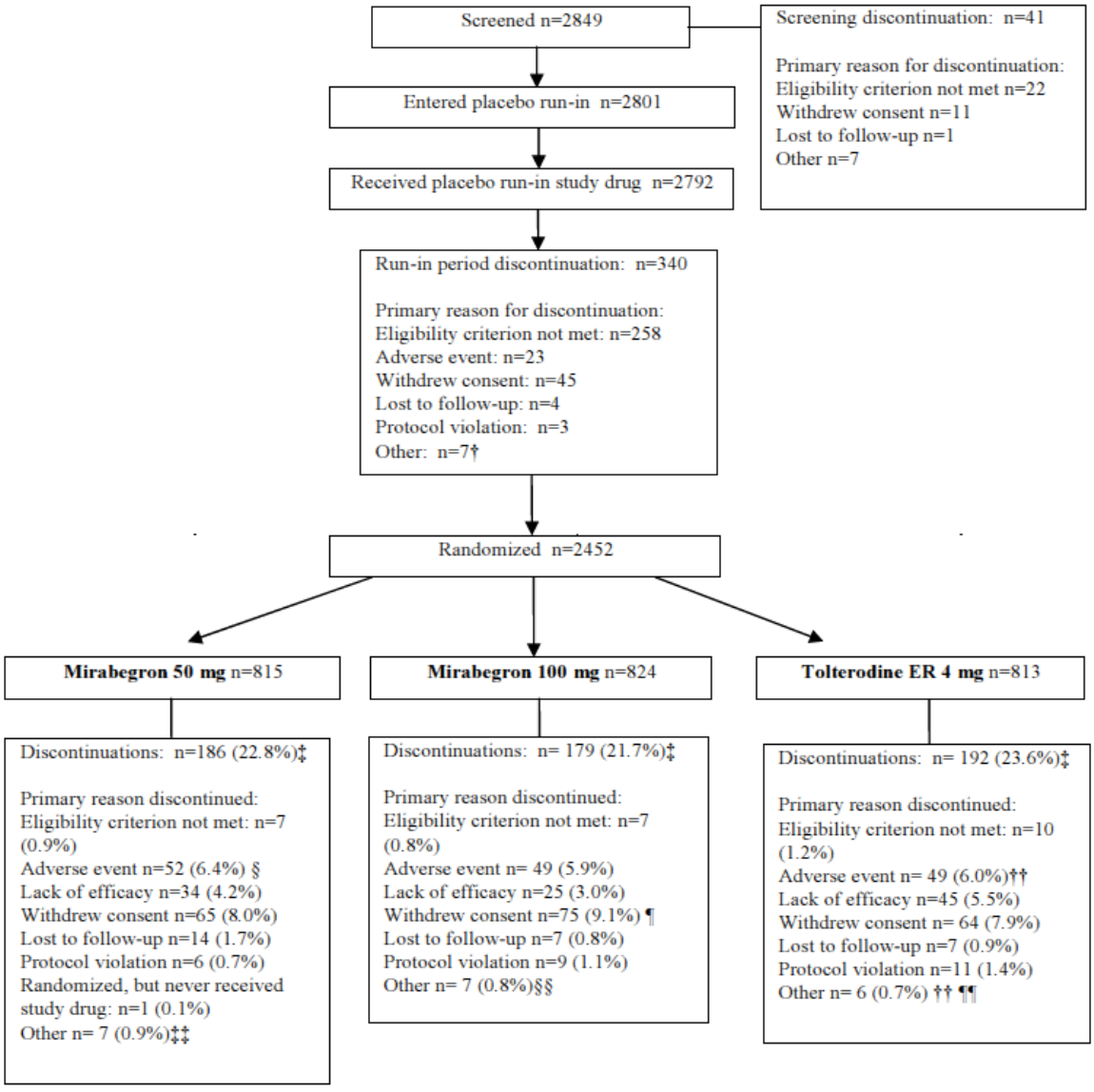
Sub-group analyses

No subgroup analyses were planned or performed post-hoc.

Participant flow

The flow of patients in TAURUS is detailed in Figure 32. A total of 2,452 patients were randomised to the three treatment arms; mirabegron 50 mg N=815, mirabegron 100 mg N=824 and tolterodine ER 4 mg N=813.

Figure 32: Patient flow in TAURUS



Abbreviations: ER, extended-release; mg, milligram.
†Other reasons included unreliable diary, noncompliance with study medication, not randomised per Sponsor's decision, unable to respect study calendar, did not want to continue in study, withdrew due to history of irritated mucous membranes in the mouth and Investigator's decision; ‡Discontinuations are those reported for patients in the RAS; §2 patients discontinued due to a non-TEAE and 2 discontinued due to TEAEs that ended prior to the day study drug was actually permanently discontinued; ¶1 patient experienced several TEAEs that led to permanent discontinuation of study drug; ††4 patients in the tolterodine group are included in Figure 32 as discontinued due to an AE but are not included in Table 64 and Table 68 since the events were not treatment-emergent . 1 patient experienced SAEs of aortic valve incompetence and aortic stenosis that led to permanent discontinuation of study drug. This patient is included in Table 64 and Table 68 but is included as discontinued to "other" reasons in Figure 32; ‡‡Other reasons were noncompliance with study visits, patient did not show up for appointment, lack of efficacy and prohibited medication usage, patient missed visit 6 due to family illness, patient was dissatisfied, not 3 consecutive days in visit 2 diary and patient noncompliant since visit 2; §§Other reasons were patient irritability, site closure, persistent tachycardia, blood pressure cuff errors and study drug dispensing at visit 3 and use, QT prolongation (at baseline, therefore the patient was discontinued), missed scheduled visit and consequently, was noncompliance with visit window; ¶¶Other reasons were SAE of abnormal cardiac catheterisation, blood pressure machine issues, noncompliant with visit windows, unable to come for visit 7 per protocol window, patient stopped medication due to erectile dysfunction in medical history and missed visit 2 questionnaire.

A total of 81.3% of patients in this study had previously been treated in SCORPIO or ARIES (Table 62). There was no meaningful difference between the treatment groups in the current study with regard to prior treatment in either SCORPIO or ARIES.

Table 62: Summary of patients by previous treatment (in SCORPIO or ARIES), TAURUS, SAS

Previous treatment, n (%)	Mirabegron		Tolterodine ER 4 mg N=812	Total N=2,444
	50 mg N=812	100 mg N=820		
Placebo	190 (23.4)	174 (21.2)	180 (22.2)	544 (22.3)
Mirabegron 50 mg	170 (20.9)	180 (22.0)	171 (21.1)	521 (21.3)
Mirabegron 100 mg	183 (22.5)	198 (24.1)	197 (24.3)	578 (23.6)
Tolterodine ER 4 mg	130 (16.0)	107 (13.0)	108 (13.3)	345 (14.1)
Naive	139 (17.1)	161 (19.6)	156 (19.2)	456 (18.7)

Abbreviations: ER, extended-release; mg, milligram.

Analysis sets

Overall, the SAS included 99.7% of patients who were randomised into the study (Table 63).

Table 63: Summary of analysis sets, TAURUS

Analysis set, n (%)	Mirabegron		Tolterodine ER 4 mg	Total
	50 mg	100 mg		
RPAS				2,792
RAS	815 (100.0)	824 (100.0)	813 (100.0)	2,452 (100.0)
FAS	789 (96.8)	802 (97.3)	791 (97.3)	2,382 (97.1)
FAS-I	479 (58.8)	483 (58.6)	488 (60.0)	1,450 (59.1)
SAS	812 (99.6)	820 (99.5)	812 (99.9)	2,444 (99.7)

Abbreviations: ER, extended-release; FAS, full analysis set; FAS-I, full analysis set – incontinence set; mg, milligram; RAS, randomised analysis set; RPAS, run-in period analysis set; SAS, safety analysis set.

Critical appraisal of trial designed to primarily assess safety

A full critical appraisal of TAURUS is available in section 10.3.

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event.

All adverse events (AEs) and serious adverse events (SAEs) listed for TAURUS are treatment-emergent adverse events (TEAEs). All AEs listed were reported after the first dose of double-blind study drug and no more than 30 days after the last dose of double-blind study drug.

TEAEs, common TEAEs and treatment-related TEAEs

An overview of TEAEs is provided in Table 64. The overall incidence of TEAEs was similar across the mirabegron 50 mg (59.7%), mirabegron 100 mg (61.3%) and tolterodine (62.6%) treatment groups. Most TEAEs were mild or moderate in severity in all treatment groups, and the incidence of mild or moderate TEAEs was comparable across all treatment groups. The incidence of severe TEAEs was 6.3% in both mirabegron groups, compared with 4.8% in the tolterodine group.

Table 64: Overview of TEAEs, TAURUS, SAS

AEs Number (%) patients	Mirabegron			Tolterodine ER 4 mg N=812
	50 mg N=812	100 mg N=820	Total N=1,632	
TEAEs	485 (59.7)	503 (61.3)	988 (60.5)	508 (62.6)
Mild	222 (27.3)	240 (29.3)	462 (28.3)	251 (30.9)
Moderate	212 (26.1)	211 (25.7)	423 (25.9)	218 (26.8)
Severe	51 (6.3)	52 (6.3)	103 (6.3)	39 (4.8)
Treatment-related TEAEs	213 (26.2)	192 (23.4)	405 (24.8)	224 (27.6)
Deaths	2 (0.2)	0	2 (0.1)	2 (0.2)
SAEs	42 (5.2)	51 (6.2)	93 (5.7)	44 (5.4)
Treatment-related SAEs	10 (1.2)	4 (0.5)	14 (0.9)	5 (0.6)
TEAEs leading to study drug discontinuation	48 (5.9)	50 (6.1)	98 (6.0)	46 (5.7)
Treatment-related TEAEs leading to study drug discontinuation	35 (4.3)	29 (3.5)	64 (3.9)	31 (3.8)

Abbreviations: ER, extended-release; mg, milligram; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Common TEAEs occurring in at least 2% of patients in any treatment group are detailed in Table 65 with treatment-related TEAEs detailed in Table 66. Hypertension (based on preferred term) was the most frequently reported TEAE across all treatment groups (likely due to the prespecified definition in the protocol and instructions given to site investigators for reporting events of hypertension). With the exception of dry mouth,

which was highest in the tolterodine group, incidence of common TEAEs was generally similar across treatment groups.

Table 65: Common TEAEs occurring in ≥ 2% of patients in any treatment group, TAURUS, SAS

MedDRA (v9.1) preferred term, n (%)	Mirabegron			Tolterodine ER 4 mg N=812
	50 mg N=812	100 mg N=820	Total N=1,632	
Hypertension	75 (9.2)	80 (9.8)	155 (9.5)	78 (9.6)
Urinary tract infection	48 (5.9)	45 (5.5)	93 (5.7)	52 (6.4)
Nasopharyngitis	32 (3.9)	35 (4.3)	67 (4.1)	25 (3.1)
Headache	33 (4.1)	26 (3.2)	59 (3.6)	20 (2.5)
Back pain	23 (2.8)	29 (3.5)	52 (3.2)	13 (1.6)
Constipation	23 (2.8)	25 (3.0)	48 (2.9)	22 (2.7)
Influenza	21 (2.6)	25 (3.0)	46 (2.8)	28 (3.4)
Dry mouth	23 (2.8)	19 (2.3)	42 (2.6)	70 (8.6)
Sinusitis	22 (2.7)	18 (2.2)	40 (2.5)	12 (1.5)
Diarrhoea	15 (1.8)	24 (2.9)	39 (2.4)	16 (2.0)
Arthralgia	17 (2.1)	19 (2.3)	36 (2.2)	16 (2.0)
Dizziness	22 (2.7)	13 (1.6)	35 (2.1)	21 (2.6)
Cystitis	17 (2.1)	11 (1.3)	28 (1.7)	19 (2.3)
Tachycardia	8 (1.0)	19 (2.3)	27 (1.7)	25 (3.1)

Abbreviations: ER, extended-release; mg, milligram.

The most common treatment-related TEAEs included hypertension, dry mouth, constipation and headache (Table 66). Hypertension was the most frequently reported treatment-related TEAE, with similar incidence across all three treatment groups. The highest incidence of treatment-related dry mouth, which is a common side-effect of antimuscarinics and consistent with their pharmacology, occurred in the tolterodine group (8.3%). The incidence of treatment-related dry mouth in the mirabegron 50 mg and 100 mg groups was 2.5% and 2.2%, respectively.

Table 66: Common treatment-related TEAEs occurring in ≥ 2% of patients in any treatment group, TAURUS, SAS

MedDRA (v9.1) preferred term, n (%)	Mirabegron			Tolterodine ER 4 mg N=812
	50 mg N=812	100 mg N=820	Total N=1,632	
Hypertension	43 (5.3)	50 (6.1)	93 (5.7)	42 (5.2)
Dry mouth	20 (2.5)	18 (2.2)	38 (2.3)	67 (8.3)
Constipation	18 (2.2)	17 (2.1)	35 (2.1)	19 (2.3)
Headache	18 (2.2)	14 (1.7)	32 (2.0)	14 (1.7)

Abbreviations: ER, extended-release; mg, milligram.

Treatment-emergent SAEs

The overall incidence of treatment-emergent SAEs was 5.2% in the mirabegron 50 mg group, 6.2% in the mirabegron 100 mg group and 5.4% in the tolterodine group (Table 67). Most of the SAEs reported were not considered to be related to study drug by the investigators.

Table 67: Treatment-emergent SAEs occurring in ≥ 2 patients in any treatment group, TAURUS, SAS

MedDRA (v9.1) SOC, n (%) Preferred term	Mirabegron			Tolterodine ER 4 mg N=812
	50 mg N=812	100 mg N=820	Total N=1,632	
Any SAE	**42 (5.2)**	**51 (6.2)**	**93 (5.7)**	**44 (5.4)**
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.1)	11 (1.3)	12 (0.7)	4 (0.5)
Breast cancer	0	2 (0.2)	2 (0.1)	2 (0.2)
Lung neoplasm malignant	0	2 (0.2)	2 (0.1)	0
Prostate cancer	0	2 (0.2)	2 (0.1)	0
Cardiac disorders	8 (1.0)	2 (0.2)	10 (0.6)	8 (1.0)
Atrial fibrillation	2 (0.2)	0	2 (0.1)	3 (0.4)
Myocardial infarction	1 (0.1)	0	1 (0.1)	2 (0.2)
Angina pectoris	0	0	0	2 (0.2)
Gastrointestinal disorders	3 (0.4)	7 (0.9)	10 (0.6)	2 (0.2)
Injury, poisoning and procedural complications	5 (0.6)	5 (0.6)	10 (0.6)	2 (0.2)
Surgical and medical procedures	2 (0.2)	7 (0.9)	9 (0.6)	4 (0.5)
Infections and infestations	5 (0.6)	3 (0.4)	8 (0.5)	3 (0.4)
Musculoskeletal and connective tissue disorders	3 (0.4)	5 (0.6)	8 (0.5)	2 (0.2)
Osteoarthritis	2 (0.2)	1 (0.1)	3 (0.2)	1 (0.1)
Nervous system disorders	5 (0.6)	2 (0.2)	7 (0.4)	5 (0.6)
Cerebrovascular accident	3 (0.4)	0	3 (0.2)	1 (0.1)
Reproductive system and breast disorders	3 (0.4)	4 (0.5)	7 (0.4)	8 (1.0)
Uterine prolapse	0	2 (0.2)	2 (0.2)	0
Renal and urinary disorders	1 (0.1)	5 (0.6)	6 (0.4)	3 (0.4)
Vascular disorders	4 (0.5)	1 (0.1)	5 (0.3)	2 (0.2)
General disorders and administration site conditions	3 (0.4)	1 (0.1)	4 (0.2)	2 (0.2)
Investigations	1 (0.1)	3 (0.4)	4 (0.2)	0
Liver function test abnormal	0	2 (0.2)	2 (0.1)	0

MedDRA (v9.1) SOC, n (%) Preferred term	Mirabegron			Tolterodine ER 4 mg N=812
	50 mg N=812	100 mg N=820	Total N=1,632	
Respiratory, thoracic and mediastinal disorders	2 (0.2)	1 (0.1)	3 (0.2)	1 (0.1)
Blood and lymphatic system disorders	1 (0.1)	1 (0.1)	2 (0.1)	1 (0.1)
Eye disorders	1 (0.1)	1 (0.1)	2 (0.1)	1 (0.1)
Hepatobiliary disorders	1 (0.1)	1 (0.1)	2 (0.1)	2 (0.2)
Cholelithiasis	0	1 (0.1)	1 (0.1)	2 (0.2)
Skin and subcutaneous tissue disorders	1 (0.1)	1 (0.1)	2 (0.1)	0
Ear and labyrinth disorders	0	1 (0.1)	1 (0.1)	1 (0.1)
Metabolism and nutrition disorders	1 (0.1)	0	1 (0.1)	2 (0.2)
Psychiatric disorders	1 (0.1)	0	1 (0.1)	0

Abbreviations: ER, extended-release; mg, milligram; SAE, serious adverse event; SOC, system organ class.

TEAEs leading to permanent discontinuation of study drug

The overall incidence of TEAEs leading to permanent discontinuation of study drug was comparable across all treatment groups, with 5.9% in the mirabegron 50 mg group, 6.1% in the mirabegron 100 mg group and 5.7% in the tolterodine group (Table 68).

Table 68: TEAEs leading to permanent discontinuation of study drug occurring in ≥ 2 patients in any treatment group, TAURUS, SAS

MedDRA (v9.1) SOC, n (%) Preferred term	Mirabegron			Tolterodine ER 4 mg N=812
	50 mg N=812	100 mg N=820	Total N=1,632	
Any TEAE leading to discontinuation	48 (5.9%)[†]	50 (6.1%)	98 (6.0%)[†]	46 (5.7%)[†]
Gastrointestinal disorders	14 (1.7%)	9 (1.1%)	23 (1.4%)	11 (1.4%)
Constipation	7 (0.9%)	2 (0.2%)	9 (0.6%)	0
Nausea	3 (0.4%)	2 (0.2%)	5 (0.3%)	1 (0.1%)
Dry mouth	3 (0.4%)	1 (0.1%)	4 (0.2%)	4 (0.5%)
Abdominal pain	1 (0.1%)	2 (0.2%)	3 (0.2%)	0
Abdominal pain upper	1 (0.1%)	1 (0.1%)	2 (0.1%)	3 (0.4%)
Gastritis	2 (0.2%)	0	2 (0.1%)	1 (0.1%)
Nervous system disorders	10 (1.2%)	8 (1.0%)	18 (1.1%)	10 (1.2%)
Headache	5 (0.6%)	4 (0.5%)	9 (0.6%)	3 (0.4%)
Dizziness	4 (0.5%)	2 (0.2%)	6 (0.4%)	0
General disorders and administration site conditions	4 (0.5%)	5 (0.6%)	9 (0.6%)	2 (0.2%)
Fatigue	1 (0.1%)	3 (0.4%)	4 (0.2%)	1 (0.1%)

MedDRA (v9.1) SOC, n (%) Preferred term	Mirabegron			Tolterodine ER 4 mg N=812
	50 mg N=812	100 mg N=820	Total N=1,632	
Pain	2 (0.2%)	0	2 (0.1%)	0
Cardiac disorders	4 (0.5%)	4 (0.5%)	8 (0.5%)	7 (0.9%)
Palpitations	0	2 (0.2%)	2 (0.1%)	0
Myocardial infarction	1 (0.1%)	0	1 (0.1%)	2 (0.2%)
Angina pectoris	0	0	0	2 (0.2%)
Atrial fibrillation	0	0	0	2 (0.2%)
Eye disorders	5 (0.6%)	3 (0.4%)	8 (0.5%)	3 (0.4%)
Vision blurred	3 (0.4%)	1 (0.1%)	4 (0.2%)	1 (0.1%)
Dry eye	3 (0.4%)	0	3 (0.2%)	1 (0.1%)
Infections and infestations	6 (0.7%)	2 (0.2%)	8 (0.5%)	3 (0.4%)
Urinary tract infection	3 (0.4%)	0	3 (0.2%)	1 (0.1%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0	7 (0.9%)	7 (0.4%)	1 (0.1%)
Lung neoplasm malignant	0	2 (0.2%)	2 (0.1%)	0
Prostate cancer	0	2 (0.2%)	2 (0.1%)	0
Skin and subcutaneous tissue disorders	2 (0.2%)	5 (0.6%)	7 (0.4%)	1 (0.1%)
Pruritis	0	2 (0.2%)	2 (0.1%)	0
Vascular disorders	4 (0.5%)	3 (0.4%)	7 (0.4%)	4 (0.5%)
Hypertension	4 (0.5%)	2 (0.2%)	6 (0.4%)	3 (0.4%)
Renal and urinary disorders	2 (0.2%)	4 (0.5%)	6 (0.4%)	4 (0.5%)
Dysuria	0	2 (0.2%)	2 (0.1%)	0
Investigations	1 (0.1%)	3 (0.4%)	4 (0.2%)	4 (0.5%)
Liver function test abnormal	0	2 (0.2%)	2 (0.1%)	0
Injury, poisoning and procedural complications	3 (0.4%)	2 (0.2%)	5 (0.3%)	1 (0.1%)
Reproductive system and breast disorders	2 (0.2%)	2 (0.2%)	4 (0.2%)	3 (0.4%)
Psychiatric disorders	1 (0.1%)	2 (0.2%)	3 (0.2%)	1 (0.1%)
Blood and lymphatic system disorders	0	2 (0.2%)	2 (0.1%)	1 (0.1%)
Ear and labyrinth disorders	0	2 (0.2%)	2 (0.1%)	2 (0.2%)
Vertigo	0	2 (0.2%)	2 (0.1%)	1 (0.1%)

MedDRA (v9.1) SOC, n (%) Preferred term	Mirabegron			Tolterodine ER 4 mg N=812
	50 mg N=812	100 mg N=820	Total N=1,632	
Metabolism and nutrition disorders	2 (0.2%)	0	2 (0.1%)	3 (0.4%)
Musculoskeletal and connective tissue disorders	0	2 (0.2%)	2 (0.1%)	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	2 (0.2%)	0	2 (0.1%)	2 (0.2%)
Hepatobiliary disorders	0	1 (0.1%)	1 (0.1%)	0
Immune system disorders	1 (0.1%)	0	1 (0.1%)	1 (0.1%)
Pregnancy, puerperium and perinatal conditions	1 (0.1%)	0	1 (0.1%)	0
Surgical and medical procedures	0	1 (0.1%)	1 (0.1%)	1 (0.1%)

Abbreviations: ER, extended-release; mg, milligram; SOC, system organ class; TEAE, treatment-emergent adverse event.
†Two patients in the mirabegron 50 mg group and four patients in the tolterodine group discontinued the study due to a non-TEAE. Additionally two patients in the mirabegron 50 mg group temporarily interrupted study medication due to an AE but did not permanently discontinue study medication due to the event until several weeks later and so are not included in this table as events leading to discontinuation.

Deaths

A total of five deaths were reported; of which four were considered to be treatment-emergent (two in the mirabegron 50 mg group and two in the tolterodine ER group) (Table 69).

Table 69: Summary of deaths, TAURUS, SAS

Treatment group	Number of deaths	TEAEs leading to death (relationship to study drug)
Mirabegron 50 mg	2	Pneumonia (possible), acute respiratory failure (not related), multi-organ failure (not related), renal vein thrombosis (not related) and staphylococcal sepsis (not related)
		Cardiac failure (not related)
Mirabegron 100 mg	0	N/A
Tolterodine ER 4 mg	2	Coronary artery disease (not related)
		Cerebrovascular accident (not related), pneumonia aspiration (not related)

Abbreviations: ER, extended-release; N/A, not applicable; mg, milligram; TEAE, treatment-emergent adverse event.

An additional death (suicide) occurred in a mirabegron 50 mg-treated patient. This death was considered to be non-treatment-emergent, but possibly related to study medication[d].

TEAEs of interest

TEAEs of interest were based on observations from nonclinical and clinical studies of mirabegron. A summary of TEAEs of interest is provided in Table 70. There was a higher incidence for cardiac arrhythmia AEs of interest in the tolterodine group (6.0%) compared with the mirabegron groups (50 mg; 3.9%, 100 mg; 4.1%). For each of the other AEs of interest, the incidence across treatment groups was similar.

Table 70: Summary of TEAEs of interest, TAURUS, SAS

Category, n (%)	Mirabegron			Tolterodine ER 4 mg N=812
	50 mg N=812	100 mg N=820	Total N=1,632	
QTc prolongation type	3 (0.4%)	2 (0.2%)	5 (0.3%)	3 (0.4%)
Hypertension type	89 (11.0%)	83 (10.1%)	172 (10.5%)	86 (10.6%)
Cardiac arrhythmia	32 (3.9%)	34 (4.1%)	66 (4.0%)	49 (6.0%)
Urinary retention	1 (0.1%)	1 (0.1%)	2 (0.1%)	3 (0.4%)
Acute urinary retention	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
Hypersensitivity	45 (5.5%)	44 (5.4%)	89 (5.5%)	42 (5.2%)
Syncope/seizure	1 (0.1%)	0	1 (0.1%)	1 (0.1%)
Hepatotoxicity	17 (2.1%)	19 (2.3%)	36 (2.2%)	15 (1.8%)

Abbreviations: ER, extended-release; mg, milligram; QTc, corrected QT interval.

6.9.2.1 Safety results from other relevant studies

SCORPIO

The overall incidence of TEAEs was similar across all treatment groups: placebo (43.3%), mirabegron 50 mg (42.8%), mirabegron 100 mg (40.1%) and tolterodine SR (46.7%) (Table 71). Most TEAEs were mild or moderate in severity in all treatment groups, and the incidence of mild, moderate and severe TEAEs was comparable across all treatment groups.

[d] This patient, with reported significant history of depression, personality disorder (borderline) and nervous breakdown, completed suicide through overdose with anxiolytics and antidepressants. The patient's suicide appeared to be motivated by recent pregnancy (confirmed on autopsy) and suspicion of disseminated sclerosis (unconfirmed). Astellas could not exclude a causal association of the event with mirabegron.

Table 71: Overview of TEAEs, SCORPIO, SAS

AEs Number (%) patients	Placebo N=494	Mirabegron			Tolterodine SR 4 mg N=495
		50 mg N=493	100 mg N=496	Total N=989	
TEAEs	214 (43.3)	211 (42.8)	199 (40.1)	410 (41.5)	231 (46.7)
Mild	135 (27.3)	116 (23.5)	102 (20.6)	218 (22.0)	129 (26.1)
Moderate	67 (13.6)	76 (15.4)	80 (16.1)	156 (15.8)	85 (17.2)
Severe	12 (2.4)	19 (3.9)	17 (3.4)	36 (3.6)	17 (3.4)
Treatment-related TEAEs	89 (18.0)	100 (20.3)	102 (20.6)	202 (20.4)	131 (26.5)
SAEs	8 (1.6)	14 (2.8)	12 (2.4)	26 (2.6)	11 (2.2)
Treatment-related SAEs	4 (0.8)	3 (0.6)	2 (0.4)	5 (0.5)	6 (1.2)
TEAEs leading to study drug discontinuation	13 (2.6)	24 (4.9)	16 (3.2)	40 (4.0)	22 (4.4)
Treatment-related TEAEs leading to study drug discontinuation	9 (1.8)	18 (3.7)	13 (2.6)	31 (3.1)	20 (4.0)
Deaths	0	0	0	0	1 (0.2)

Abbreviations: mg, milligram; SAE, serious adverse event; SR, slow-release; TEAE, treatment-emergent adverse event.

Other than dry mouth, which had an incidence of 10.1% in the tolterodine group, the most frequently reported common TEAE (reported in at least 2% of patients in any treatment group) was hypertension. The incidence of dry mouth in both mirabegron groups (50 mg, 2.8%; 100 mg, 2.8%) was similar to the incidence reported in the placebo group (2.6%). The highest incidence of hypertension was reported in the tolterodine group (8.1%); the lowest in the mirabegron 100 mg group (5.4%).

The most common treatment-related TEAEs (Table 72) included hypertension, dry mouth and headache. The highest incidences of treatment-related hypertension and dry mouth were in the tolterodine group. Of the patients who reported headaches, most patients had headaches that were mild or moderate in intensity; severe headaches were reported in one patient in each of the placebo, mirabegron 100 mg and tolterodine groups, and two patients in the mirabegron 50 mg group.

Table 72: Common treatment-related TEAEs in ≥ 2% of patients in any treatment group, SCORPIO, SAS

MedDRA (v9.1) Preferred term, n (%)	Placebo N=494	Mirabegron			Tolterodine SR 4 mg N=495
		50 mg N=493	100 mg N=496	Total N=989	
Hypertension	23 (4.7)	20 (4.1)	23 (4.6)	43 (4.3)	30 (6.1)
Dry mouth	9 (1.8)	9 (1.8)	12 (2.4)	21 (2.1)	47 (9.5)
Headache	6 (1.2)	13 (2.6)	5 (1.0)	18 (1.8)	11 (2.2)

Abbreviations: mg, milligram; SR, slow-release.

The overall incidence of treatment-emergent SAEs was 1.6% in the placebo group, 2.8% in the mirabegron 50 mg group, 2.4% in the mirabegron 100 mg group, and 2.2% in the

tolterodine SR 4 mg group. Most of the SAEs reported were not considered to be related to study drug by the investigators. Most SAEs were unique to a single patient; few SAEs occurred in more than one patient. SAEs of erysipelas, fall, atrial fibrillation, and bunion operation were reported in two patients each. SAEs of atrial fibrillation and bunion operation occurred only in mirabegron-treated patients; erysipelas and fall were each reported in one patient treated with mirabegron 100 mg and one patient treated with tolterodine SR 4 mg.

The overall incidence of TEAEs leading to permanent discontinuation of study drug was 2.6% in the placebo group, 4.9% in the mirabegron 50 mg group, 3.2% in the mirabegron 100 mg group and 4.4% in the tolterodine SR 4 mg group. Most of these TEAEs were considered not related to study drug by the investigator. The highest incidence of an individual TEAE leading to permanent discontinuation was 0.6% (TEAEs of fatigue and urinary retention each occurred in three patients in the tolterodine group; urinary retention was also reported in one patient in the mirabegron 50 mg group). The overall incidence of TEAEs leading to permanent discontinuation of study drug was 1.8% in the placebo group, 3.7% in the mirabegron 50 mg group, 2.6% in the mirabegron 100 mg group and 4.0% in the tolterodine SR 4 mg group.

A summary of treatment-emergent adverse events of special interest (AESIs) including cardiovascular type events (hypertension, Torsades de Pointes/QTc prolongation events, cardiac arrhythmias), urinary retention type events, hypersensitivity type events, syncope/seizure type events and hepatic type events is provided in Table 73.

Table 73: AESIs, SCORPIO, SAS

MedDRA (v9.1) Preferred term, n (%)	Placebo N=494	Mirabegron			Tolterodine SR 4 mg N=495
		50 mg N=493	100 mg N=496	Total N=989	
Hypertension type	46 (9.3)	38 (7.7)	31 (6.3)	69 (7.0)	47 (9.5)
Torsades de Pointes/QTc prolongation type	0	0	0	0	2 (0.4)
Cardiac arrhythmia	5 (1.0)	11 (2.2)	9 (1.8)	20 (2.0)	16 (3.2)
Urinary retention	3 (0.6)	1 (0.2)	1 (0.2)	2 (0.2)	3 (0.6)
Acute urinary retention	1 (0.2)	1 (0.2)	0	1 (0.1)	3 (0.6)
Hypersensitivity	16 (3.2)	22 (4.5)	20 (4.0)	42 (4.2)	20 (4.0)
Syncope/seizure	0	0	0	0	1 (0.2)
Hepatic disorders	7 (1.4)	11 (2.2)	7 (1.4)	18 (1.8)	10 (2.0)

Abbreviations: mg, milligram; SR, slow-release.

ARIES

The overall incidence of TEAEs was similar between the placebo group (50.1%) and the mirabegron 50 mg group (51.6%), and was numerically lower in the mirabegron 100 mg group (46.9%) (Table 74). Most TEAEs were mild or moderate in severity in all treatment groups, and the incidence of mild, moderate and severe TEAEs was comparable across all treatment groups. Only one death was considered treatment-emergent. The incidence of patients with any treatment-emergent SAEs was 2.0% in the placebo group, 2.5% in

the mirabegron 50 mg group and 3.2% in the mirabegron 100 mg group. The incidence of patients who discontinued study drug due to a TEAE was 3.8% in the placebo group, 4.1% in the mirabegron 50 mg group and 4.2% in the mirabegron 100 mg group.

Table 74: Overview of TEAEs, ARIES, SAS

AEs Number (%) patients	Placebo N=453	Mirabegron		
		50 mg N=442	100 mg N=433	Total N=875
TEAEs	227 (50.1)	228 (51.6)	203 (46.9)	431 (49.3)
Mild	117 (25.8)	121 (27.4)	98 (22.6)	219 (25.0)
Moderate	86 (19.0)	86 (19.5)	84 (19.4	170 (19.4)
Severe	24 (5.3)	21 (4.8)	21 (4.8)	42 (4.8)
Treatment-related TEAEs	66 (14.6)	80 (18.1)	70 (16.2)	150 (17.1)
SAEs	9 (2.0)	11 (2.5)	14 (3.2)	25 (2.9)
Treatment-related SAEs	0	3 (0.7)	1 (0.2)	4 (0.5)
TEAEs leading to study drug discontinuation	17 (3.8)	18 (4.1)	18 (4.2)	36 (4.1)
Treatment-related TEAEs leading to study drug discontinuation	10 (2.2)	11 (2.5)	12 (2.8)	23 (2.6)
Deaths	0	0	1 (0.2)	1 (0.1)

Abbreviations: mg, milligram; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Common treatment-related TEAEs included hypertension and headache (Table 75). The highest incidence of treatment-related hypertension was in the placebo group (3.8%); the incidence in the mirabegron 50 mg and 100 mg groups was 3.2% and 2.1%, respectively. The incidence of treatment-related headache was numerically higher in the mirabegron groups (2.5% and 1.6%, mirabegron 50 and 100 mg) than in the placebo group (0.7%). The majority of events of headache were of mild intensity in the mirabegron groups. In the placebo group, 2 events of headache were of moderate intensity and 1 was severe.

Table 75: Common treatment-related TEAEs in ≥ 2% of patients in any treatment group, ARIES, SAS

MedDRA (v9.1) Preferred term, n (%)	Placebo N=453	Mirabegron		
		50 mg N=442	100 mg N=433	Total N=875
Hypertension	17 (3.8)	14 (3.2)	9 (2.1)	23 (2.6)
Headache	3 (0.7)	11 (2.5)	7 (1.6)	18 (2.1)

Abbreviations: mg, milligram.

The overall incidence of treatment-emergent SAEs was 2.0%, 2.5% and 3.2% in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively. Most of the SAEs reported were not considered to be related to study drug by the investigators. Most SAEs were unique to a single patient; few SAEs occurred in more than one patient. SAEs of atrial fibrillation, pneumonia, prostate cancer and chest pain were reported in more than one patient each. Atrial fibrillation, prostate cancer and chest pain occurred

only in mirabegron-treated patients; pneumonia was reported in one placebo-treated patient and one patient treated with mirabegron 50 mg.

The rate of treatment-related TEAEs leading to discontinuation was 2.2%, 2.5% and 2.8% in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively.

A summary of treatment-emergent AESIs including cardiovascular type events (hypertension, Torsades de Pointes/QTc prolongation events, cardiac arrhythmias), urinary retention type events, hypersensitivity type events, syncope/seizure type events and hepatic type events is provided in Table 76.

Table 76: AESIs, ARIES, SAS

MedDRA (v9.1) Preferred term, n (%)	Placebo N=453	Mirabegron		
		50 mg N=442	100 mg N=433	Total N=875
Hypertension type	32 (7.1)	33 (7.5)	27 (6.2)	60 (6.9)
Torsades de Pointes/QTc prolongation type	0	0	0	0
Cardiac arrhythmia	4 (0.9)	9 (2.0)	10 (2.3)	19 (2.2)
Urinary retention	3 (0.7)	0	0	0
Acute urinary retention	2 (0.4)	0	0	0
Hypersensitivity	23 (5.1)	16 (3.6)	24 (5.5)	40 (4.6)
Syncope/seizure	0	0	0	0
Hepatic disorders	5 (1.1)	6 (1.4)	8 (1.8)	14 (1.6)

Abbreviations: mg, milligram.

CAPRICORN

The overall incidence of TEAEs was similar in the mirabegron groups (48.6% and 47.3%, mirabegron 25 and 50 mg, respectively) compared with the placebo group (50.1%) (Table 77). Most TEAEs were mild or moderate in severity in all treatment groups. The incidence of mild and moderate TEAEs was comparable across all treatment groups; the incidence of severe TEAEs was higher in the placebo group (3.7%) than in the mirabegron groups (1.9% and 1.8%, mirabegron 25 and 50 mg). No deaths were reported. The incidence of patients with any treatment-emergent SAEs was 2.8% in the placebo group, 1.6% in the mirabegron 25 mg group and 0.9% in the mirabegron 50 mg group. The incidence of patients who discontinued study drug due to a TEAE was 3.7% in the placebo group, 3.9% in the mirabegron 25 mg group and 2.5% in the mirabegron 50 mg group.

Table 77: Overview of TEAEs, CAPRICORN, SAS

AEs Number (%) patients	Placebo N=433	Mirabegron		
		25 mg N=432	50 mg N=440	Total N=872
TEAEs	217 (50.1)	210 (48.6)	208 (47.3)	418 (47.9)
Mild	113 (26.1)	123 (28.5)	124 (28.2)	247 (28.3)
Moderate	88 (20.3)	79 (18.3)	76 (17.3)	155 (17.8)
Severe	16 (3.7)	8 (1.9)	8 (1.8)	16 (1.8)
Treatment-related TEAEs	77 (17.8)	87 (20.1)	76 (17.3)	163 (18.7)
SAEs	12 (2.8)	7 (1.6)	4 (0.9)	11 (1.3)
Treatment-related SAEs	2 (0.5)	3 (0.7)	1 (0.2)	4 (0.5)
TEAEs leading to study drug discontinuation	16 (3.7)	17 (3.9)	11 (2.5)	28 (3.2)
Treatment-related TEAEs leading to study drug discontinuation	8 (1.8)	11 (2.5)	6 (1.4)	17 (1.9)
Deaths	0	0	0	0

Abbreviations: mg, milligram; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

The most frequently reported TEAE was hypertension. The highest incidence of hypertension was reported in the mirabegron 25 mg group (11.3%); the lowest incidence in the placebo group (8.5%). The incidence of TEAEs of nasopharyngitis, UTI and dizziness was higher in the mirabegron groups than in the placebo group.

Common treatment-related TEAEs included hypertension and headache (Table 78). The incidence of treatment-related hypertension was numerically higher in the mirabegron groups (6.9% and 7.0%, mirabegron 25 and 50 mg groups, respectively) than in the placebo group (5.3%). In the mirabegron groups, the majority of events of hypertension were of mild intensity (51 events); nine events were of moderate intensity and one was severe. The highest incidence of treatment-related headache was in the placebo group (2.1%); the incidence in both the mirabegron 25 mg and 50 mg groups was 0.9%.

Table 78: Common treatment-related TEAEs in ≥ 2% of patients in any treatment group, CAPRICORN, SAS

MedDRA (v9.1) Preferred term, n (%)	Placebo N=433	Mirabegron		
		25 mg N=432	50 mg N=440	Total N=872
Hypertension	23 (5.3)	30 (6.9)	31 (7.0)	61 (7.0)
Headache	9 (2.1)	4 (0.9)	4 (0.9)	8 (0.9)

Abbreviations: mg, milligram.

The overall incidence of patients who experienced one or more treatment-emergent SAEs was 2.8%, 1.6% and 0.9% in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively. Most of the SAEs reported were not considered to be related to study drug by the investigators. Most SAEs were unique to a single patient; few SAEs occurred in more than one patient. SAEs of atrial fibrillation, chest pain and cerebrovascular accident were each reported in more than one patient. Atrial fibrillation was reported in one placebo-treated patient and one patient treated with mirabegron

50 mg. Cerebrovascular accident was reported in 2 placebo-treated patients and none of the mirabegron-treated patients.

The overall incidence of treatment-related SAEs was 0.5%, 0.7% and 0.2% in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively.

The rate of treatment-related TEAEs leading to discontinuation was 1.8%, 2.5% and 1.4% in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively.

A summary of treatment-emergent AESIs including cardiovascular type events (hypertension, QTc prolongation events, cardiac arrhythmias), urinary retention type events, hypersensitivity type events, syncope type events, seizure type events and hepatic type events is provided in Table 79.

Table 79: Summary of AESIs, CAPRICORN, SAS

MedDRA (v9.1) Preferred term, n (%)	Placebo N=433	Mirabegron		
		25 mg N=432	50 mg N=440	Total N=872
QTc prolongation type	0	0	0	0
Hypertension type	37 (8.5)	52 (12.0)	49 (11.1)	101 (11.6)
Cardiac arrhythmia	11 (2.5)	13 (3.0)	13 (3.0)	26 (3.0)
Urinary retention	1 (0.2)	0	0	0
Acute urinary retention	0	0	0	0
Hypersensitivity	15 (3.5)	15 (3.5)	13 (3.0)	28 (3.2)
Syncope/seizure	2 (0.5)	0	0	0
Hepatotoxicity	5 (1.2)	6 (1.4)	4 (0.9)	10 (1.1)

Abbreviations: mg, milligram; QTc, corrected QT interval.

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem

The primary Phase III studies, 178-CL-046 (SCORPIO), 178-CL-047 (ARIES) and 178-CL-074 (CAPRICORN) and the long-term safety study 178-CL-049 (TAURUS) have shown that 50 mg doses of mirabegron once daily for up to 1 year are generally safe and well tolerated with an anticipated tolerability profile based on prior nonclinical and clinical studies.

There is a clinical perception that antimuscarinics may cause urinary retention, particularly in men. The data from TAURUS shows low rates of urinary retention (1 patient in each of the mirabegron groups [0.1%] and 3 patients [0.4%] in the tolterodine group).

UTI has been identified as an adverse drug reaction with mirabegron. In the long-term safety study, TAURUS, the frequency of treatment-emergent UTI was lower in mirabegron 50 mg group (5.9%) compared with tolterodine patients (6.4%). This was similar to the trend observed in SCORPIO where the rates of UTI were 1.4% for both the mirabegron 50 mg and placebo groups (and lower than the tolterodine group, 2.0%). However, in ARIES and CAPRICORN, higher rates were observed in the mirabegron

50 mg groups (2.7% and 4.8%, respectively) than placebo groups (1.8% and 2.3%, respectively).

Mirabegron has been shown to have favourable rates of dry mouth compared with tolterodine. Dry mouth is a common side-effect of the currently available treatments for OAB; the antimuscarinics and is a major cause of discontinuation of antimuscarinic therapy (24).

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Primary evidence for the efficacy of mirabegron in the treatment of patients with symptoms of OAB comes from three randomised, placebo-controlled Phase III studies (178-CL-046 [SCORPIO], 178- CL-047 [ARIES] and 178-CL-074 [CAPRICORN]) conducted primarily in Europe and North America. Evidence for the durability of effect comes from the long-term safety study, 178-CL-049 (TAURUS).

These studies established the clinical efficacy of mirabegron 50 mg. The effect of mirabegron 50 mg, the recommended therapeutic dose, has been consistently shown to be superior to placebo in reducing mean number of incontinence episodes per 24 hours and mean number of micturitions per 24 hours, and change from baseline to final visit in mean volume voided per micturition, change from baseline to Week 4 in mean number of incontinence episodes and micturitions per 24 hours and change from baseline to final visit in measurements of urgency.

Standard and clinically established instruments to assess QoL measures were utilised in these studies to assess the impact of mirabegron on the patient's experience of symptoms and changes in HRQoL. Mirabegron 50 mg led to significant changes in HRQoL measures in parallel with improvements in the objective measures of OAB. These results from QoL endpoints provide strong evidence that patients not only obtained objective improvement but also clinically meaningful benefits from mirabegron 50 mg in the treatment of their disease. The improvement in subjective and objective measures substantially supports the clinical significance of the effect of mirabegron 50 mg.

Efficacy of action for mirabegron was at the first measured time point of Week 4 in the three primary Phase III studies and durability of efficacy was demonstrated in the 52-week clinical safety study, TAURUS.

Mirabegron at the proposed dose of 50 mg once daily is well tolerated in OAB patients. The frequency of AEs was low, generally comparable with placebo, and generally not treatment limiting.

Antimuscarinics are the current standard therapeutic agents used for the treatment of OAB. Typical antimuscarinic side-effects limit their use. AEs associated with antimuscarinic therapy, such as dry mouth were observed with mirabegron at a frequency similar to or lower than placebo and lower than antimuscarinics. The heart rate effect of mirabegron 50 mg is within or below the range observed with other OAB products.

Consistent with its distinct mechanism, mirabegron offers an additional pharmacologic treatment option for patients with OAB. The effect of mirabegron 50 mg has been consistently shown to be superior to placebo for the co-primary, key secondary and QoL endpoints and within range of the effects observed with other OAB products. Mirabegron addresses an unmet medical need for all patients with OAB, including those who are not candidates for antimuscarinic therapy, who are intolerant to antimuscarinic therapy or who have an inadequate response to prior antimuscarinic therapy.

Mirabegron at a proposed therapeutic dose of 50 mg once daily represents a new approach for the treatment of OAB which is generally safe, well tolerated and effective for the treatment of patients with OAB.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

The clinical development programme has involved RCTs with large patient numbers, with adequate randomisation and blinding. The primary and key secondary efficacy outcomes were objective measures (reducing the risk of bias), and are routinely used in OAB clinical studies.

Larger numbers of female patients (reflecting the participation patterns of OAB studies generally) were recruited to the studies than male patients; 1,248 of 4,427 patients (28.2%) in the three primary studies combined FAS dataset (calculated from Table 10). This smaller male sample size has resulted in wide confidence intervals in the male subcategory in the efficacy analyses (Section 6.6.1.5).

Patient reported outcomes were measured using a combination of generic scales such as the EQ-5D and disease-specific scales such as the OAB-q. The EQ-5D, due to its generic nature, may be limited in adequately capturing changes in HRQoL associated with OAB, especially at the mild end of the spectrum, and use of the OAB-q may provide a more sensitive measure of QoL in patients with OAB.

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The population evaluated in the mirabegron development program for OAB is representative of the population that would receive the product after market approval and similar to the population evaluated with other OAB compounds. Inclusion and exclusion criteria in the Phase III studies were broad and allowed inclusion of patients who were antimuscarinic treatment-naïve and patients who received prior OAB antimuscarinic therapy.

The outcomes measured are standard objective endpoints used in assessing the response to treatment in OAB patients. They included both focussed as well as generic subjective assessments. Together they demonstrate significant benefit of mirabegron 50 mg for patients with OAB.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients.

State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Patients recruited into the studies in the clinical development programme are representative of that likely to be seen in clinical practice. In SCORPIO, 35 of the 497 patients (7.0%) randomised to the 50 mg mirabegron group were from the UK. These participants are representative of the population that would receive the product after market approval. The primary Phase III studies (SCORPIO, ARIES and CAPRICORN) consisted of female and male adults with symptoms of OAB (urinary frequency and urgency with or without incontinence) for at least 3 months with frequency of micturition on average ≥ 8 times per 24-hour period during the 3-day micturition diary period and at least 3 episodes of urgency (grade 3 or 4) with or without incontinence during the 3-day micturition diary period preceding the baseline visit.

Adherence and persistence with medication is generally higher in clinical studies than in routine clinical practice. Throughout the mirabegron clinical studies, patients were encouraged to be compliant with the study medication. If patients were observed to be being non-compliant, the study protocol indicated that the investigator should discuss compliance with the patient.

In total, 1,379 of 4,622 patients (29.8%) (calculated from Table 18 to Table 20) randomised in the three primary Phase III studies were randomised to mirabegron 50 mg, the dose indicated in the SPC (Section 10.1). A further 815 of 2,452 patients were randomised to mirabegron 50 mg in the long-term safety study, TAURUS. Of the patients in TAURUS, 687 (84.6%) received 50 mg mirabegron once daily for 6 months and 294 (36.2%) for a year.

7 Cost-effectiveness

Summary of cost-effectiveness

A *de novo* Markov model was developed to analyse the cost-effectiveness of mirabegron 50 mg vs currently available antimuscarinics for the treatment of OAB.

- The model simulated the therapeutic management, the course of disease, and complications in hypothetical cohorts of patients with OAB and was used to predict costs and QALYs over 5 years.
- Base case analysis of the general OAB population compared mirabegron 50 mg with tolterodine ER 4 mg, based on results from SCORPIO. Subgroup analyses for male vs female and previously treated vs treatment-naïve populations were also conducted.
- Secondary analyses compared mirabegron 50 mg with alternative comparators (solifenacin 5 mg and 10 mg, fesoterodine 4 mg, trospium chloride 60 mg MR and oxybutynin 10 mg IR and ER), based on mixed treatment comparison (MTC) results.

Results of the model showed that:

- In the base case analysis of the general OAB population, the ICER for mirabegron vs tolterodine was £4,386 per QALY gained using EQ-5D data.
- In the general OAB population, the ICER for mirabegron vs tolterodine was £3,008 per QALY gained when using OAB-5D data.
- Using data from the MTC, mirabegron was found to be cost-effective when compared with other antimuscarinics resulting in the following ICERs (cost per QALY gained) ; solifenacin 10 mg: £340, fesoterodine 4 mg: £3,607, tolterodine 4 mg: £3,715, oxybutynin 10 mg ER: £3,878, trospium 60 mg MR: £8,881, solifenacin 5mg: £12, 493 and oxybutynin 10 mg IR: £21,796.

7.1 Published cost-effectiveness evaluations

Identification of studies

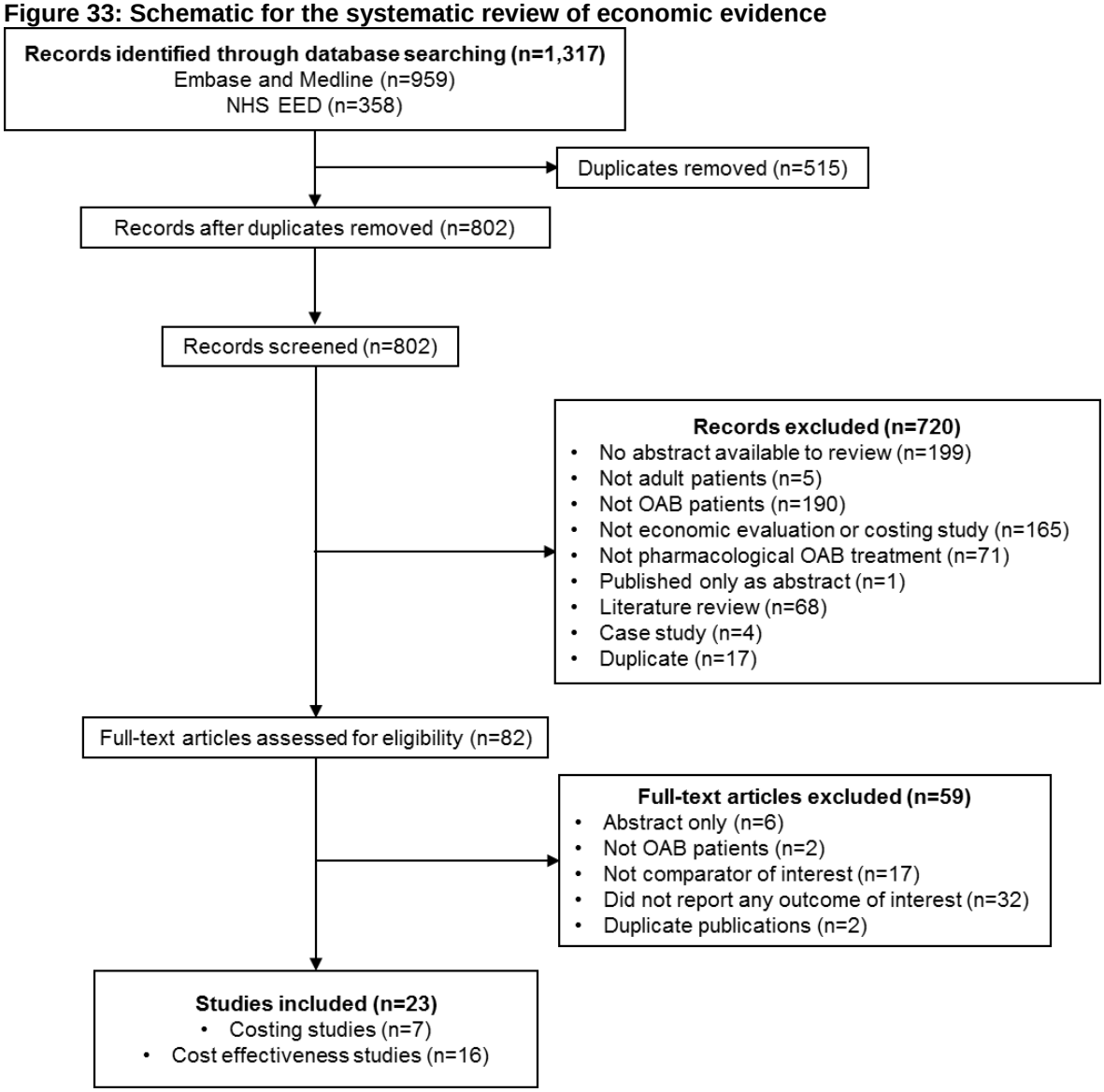
7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in Section 10.10, appendix 10.

A systematic review was conducted to identify cost-effectiveness and costing studies from the published literature for the treatment of overactive bladder (OAB).

The Medline, Embase and NHS EED electronic databases were searched. The search strategy is provided in Section 10.10. A flow diagram of included and excluded records is provided in Figure 33.

In total, 1,317 records were identified through the electronic searches. On removal of duplicates, 820 records were screened on title and abstract. Of these, 82 records were reviewed based on full text, of which 59 were excluded, resulting in 23 records for final inclusion (seven costing studies and 16 cost-effectiveness studies). The costing studies are listed in Section 7.5.3, but have been excluded from further discussion as they were not UK-based studies and therefore not used to inform the model.

Figure 33: Schematic for the systematic review of economic evidence



Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided.

Of the 16 studies identified by the systematic review, six were cost-effectiveness analyses (CEA) (80-85) (one of which was also a cost-consequence analyses [CCA] (80)) which evaluated currently available pharmacological interventions for the treatment of OAB. The remaining 10 studies were cost-utility analyses (CUA) (86-95) that reported a cost per quality adjusted life year (QALY) gained or incremental cost-effectiveness ratio (ICER). Table 80 provides a summary of these economic evaluations. For completeness, quality assessments have been conducted on all 16 of the economic evaluations and are provided in Section 10.11.

In relation to the research question, the form of the economic evaluation was deemed appropriate in all of the studies with each evaluating costs and benefits of comparator treatments over short time horizons ranging from 3 months to 1 year. A majority of these models (thirteen) analyse outcomes over a 1 year time horizon. Ko et al (85) was the only study to use a 3 month time horizon, however no justification for the short time horizon or the impact on the value of the analysis is given. Arikian et al (86) justify the use a of 6 month time horizon on that basis that it was an appropriate duration which reflects the initial phase of care for the treatment of OAB. Guest et al (83) use a 6 month time horizon on the basis that clinical outcomes at 3 months (based on study data) would be maintained for at least another 3 months. Guest et al (83) argues that in the absence of robust data, extrapolating the data further would require a large number of assumptions resulting in substantial uncertainty.

The NICE reference case states that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared. Whilst a lifetime time horizon is typically used in economic evaluations, a shorter time horizon may be justified if there are no differential mortality effects between options as is the case in OAB.

Fourteen of the economic evaluations present an incremental analysis, however many of them only present major outcomes in an aggregated form. Presentation of results in a disaggregated form would increase transparency, interpretation of the outcomes and ultimately the generalisability of the results.

None of the identified studies assess the cost effectiveness of mirabegron; hence a *de novo* evaluation was necessary.

Table 80: Summary list of other cost-effectiveness evaluations

Study	Year	Country	Aim	Model structure, perspective, time horizon	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
Arlandis-Guzman (80)	2011	Spain	Assess the economic value of OAB treatment with fesoterodine relative to ER tolterodine and solifenacin	• Decision tree • Societal, healthcare payer • 1 year	≥ 18 years, ≥ 8 micturitions/24 hrs, OAB symptoms with urinary urgency and ≥ 1 urge urinary incontinence episode/24 hrs	QALYs gained vs baseline after 52 Wks: • Fesoterodine: 0.01014 • Tolterodine: 0.00846 • Solifenacin: 0.00957	Total cost (52 Wks): • Fesoterodine €1,937 • Tolterodine €2,089 • Solifenacin €1,960	Only reported as: • Fesoterodine was cost saving vs tolterodine • Fesoterodine was cost saving vs solifenacin
Arikian (86)	2000	USA	Evaluate the relative treatment costs and cost effectiveness of IR oxybutynin, CR oxybutynin and IR tolterodine	• Decision tree • US payer • 6 months	NR	• QALYs not reported • Cost per success and cost per continent day	Oxybutynin CR/ oxybutynin IR/ tolterodine IR; over 6 months, in US$ **Cost** • Surgery as 2nd line:1402/1395/1650 • Surgery as 3rd line: 893/818/918	Cost per success and cost per continent day were reported. Overall result: increased use of oxybutynin CR first-line would lead to cost savings for payers. Oxybutynin CR/ oxybutynin IR/ tolterodine IR; over 6 months, in US$ **Cost/success** • Surgery as 2nd line: 2682/3022/5176 • Surgery as 3rd line:1708/1774/ 2881 **Cost/continent days** • Surgery as 2nd line:

Study	Year	Country	Aim	Model structure, perspective, time horizon	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
								18.70/21.60/37.20 Surgery as 3rd line: 11.90/12.60/20.70
Cardozo (87)	2010	UK	Assess the cost-effectiveness of solifenacin vs other antimuscarinic strategies commonly used in UK clinical practice.	• Decision tree • UK NHS payer • 1 year	NR	QALYs for urgency/ frequency/ incontinence for the 1000-patient cohort • Fesoterodine 4 mg/8 mg†: 709.6/718.3/ 692.5 • Oxybutynin IR 15 mg: NA/719.6/ 691.7 • Propiverine ER 20 mg: 708.9/718.0/ 688.0 • Solifenacin 5mg/10mg†: 712.3/723.1/ 695.0 • Tolterodine ER 4mg: 709.7/718.1/ 688.0 • Tolterodine IR 2 mg/4 mg†: NA/718.5/688.1	Total cost for 1000 patients, by symptoms (urgency/frequency/incontinence), in £: • Fesoterodine 4 mg or 8 mg: 484,553/462,230/469,062 • Oxybutynin IR 15mg: –/159,896/171,891 • Propiverine ER 20mg: 443,455/420,377/437,683 • Solifenacin 5 mg/10 mg†: 470,840/443,282/456,048 • Tolterodine ER 4mg: 480,090/458,720/476/167 • Tolterodine IR 2 mg/4 mg†: –/472,183/490,554	**ICERs for solifenacin** 5 mg/10 mg† compared with: • Fesoterodine 4 mg/8 mg†: dominant for all symptoms • Oxybutynin IR 15 mg: NA for urgency, £80,009 for frequency and £87,162 for incontinence • Propiverine ER 20mg: £8087 for urgency, £4457 for frequency and £2639 for incontinence • Tolterodine ER 4 mg: dominant for all symptoms • Tolterodine IR 2 mg/4 mg: NA for urgency, dominant frequency and incontinence
Getsios (81)	2004	Canada	Describe a model comparing health-economic	• Markov • Healthcare payer	Community-dwelling Canadian adults with	• QALYs not reported • Cost per incontinent episode avoided	Annual costs per patient • Oxybutynin XL: Can$688 • Tolterodine IR:	• Oxybutynin XL dominated tolterodine

Study	Year	Country	Aim	Model structure, perspective, time horizon	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
			outcomes for the ER formulation of oxybutynin and IR tolterodine in a population of community-dwelling Canadian adults with OAB	• 1 year	OAB		Can$656 Saving of Can$32 per year per patient, increasing to Can$42 when comorbidities and surgery are included.	
Getsios (82)	2004	UK	Evaluate the cost-effectiveness of oxybutynin ER relative to tolterodine IR, for OAB	• Markov • Healthcare payer • 1 year		• QALYs not reported • Difference in QALYs is minimal <0.01 per patient in favour of Oxybutynin	1-year total costs: • Oxybutynin XL 10 mg: £332 • Tolterodine IR 2 mg: £418	• Oxybutynin dominates tolterodine
Guest (83)	2004	Austria, France, UK	Estimate the cost effectiveness of CR oxybutynin compared with IR oxybutynin and tolterodine in the treatment of OAB	• Decision tree • UK NHS payer, France Social Security, Austria Sick Funds, and patient-perspective • 6 months	≥ 18 years, with urge or mixed incontinence with a primary-urge component	• QALYs not reported • Cost in reducing the frequency of incontinence at 6 months • Cost in reducing micturition frequency at 6 months	6-monthly total costs per patient: UK/France/ Austria (in €) • Oxybutynin CR 10 mg: 1078/872/912 • Oxybutynin IR 10 mg: 1097/834/986 Tolterodine 40 mg: 1359/861/1108	• Starting treatment with CR oxybutynin dominant in the UK and Austria, and cost-effective in France.
Hakkaart (88)	2009	UK	Estimate the cost per QALY of solifenacin at two doses (vs	• Markov • Healthcare payer	≥ 18 with symptoms of OAB (including urinary	Mean QALY/patient: Solifenacin 5 mg and 10 mg: 0.711	Total cost/patient, 6 months: • Placebo: £253	• Solifenacin 5 mg vs placebo: £17,602 • Solifenacin 10 mg vs

Study	Year	Country	Aim	Model structure, perspective, time horizon	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
			placebo), over a time horizon of 12-months	• 1 year	frequency, urgency, or urge incontinence) for more than three months	Placebo: 0.697	• Solifenacin 5 mg: £484 • Solifenacin 10 mg: £597	placebo: £24,464
Herschorn (95)	2010	Canada	Estimate the cost effectiveness of solifenacin 5mg/day compared with oxybutynin IR 15mg/day in patients with OAB	• Markov • Canadian healthcare payer • 1 year		• Solifenacin 5 mg: 0.696 • Oxybutynin IR 5mg: 0.686	Total costs for 1 year: • Solifenacin 5 mg: Can$695 • Oxybutynin IR 5 mg: Can$550	**ICER** • Without incontinence pads: solifenacin vs oxybutynin: $14,092 • With incontinence pads: solifenacin dominant
Hughes (84)	2004	UK	Calculate and compare the cost-effectiveness of oxybutynin XL, tolterodine ER, tolterodine IR and oxybutynin IR	• Algorithm based model • UK NHS payer • 1 year	Hypothetical cohort of patients with urge incontinence associated with OAB	• QALYs not reported • Cost per incontinence-free week	<u>Total annual cost</u> • Oxybutynin XL: £76.77 • Oxybutynin IR: £39.61 • Tolterodine IR: £74.21 • Tolterodine ER: £63.91	**ICER (cost/incontinence-free week)** • Oxybutynin IR (vs NR): £5.26 • Oxybutynin XL vs tolterodine IR: £84.82 • Tolterodine IR: dominated • Tolterodine ER vs oxybutynin IR: £7.14
Ko (85)	2006	USA	Compare the cost-effectiveness of various	• Decision tree • USA payer • 3 months	NR	• QALYs not reported • Average cost/patient with continue and	• <u>Average 3-month cost/per patient:</u> • Solifenacin $3373	Solifenacin dominated all other comparators

Study	Year	Country	Aim	Model structure, perspective, time horizon	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
			antimuscarinic agents for the treatment of OAB			successful treatment	• Oxybutynin TD $3603 • Darifenacin $3633 • Oxybutynin ER $3646 • Tolterodine ER $3659 • Trospium $3722 • Tolterodine IR $3750 • Oxybutynin IR $3769	
Kobelt (89)	1998	Sweden	Develop a simulation model to calculate the incremental cost-effectiveness and cost-utility of new treatments for OAB (tolterodine vs no treatment)	• Markov • Perspective: NR • 1 year	NR	Mean cumulative utility with tolterodine is 0.6977 vs 0.6728 with no treatment (for 1 year)	Tolterodine: $59.2/month (dose NR, price based on anticipated sales price in Sweden) Incremental cost per patient and year with tolterodine is SEK5309 ($699) vs no treatment	Tolterodine vs no treatment: SEK213,042 (US$28,032)
Milsom (90)	2009	Denmark, Finland, Norway, Sweden	Compare the cost-effectiveness of solifenacin flexible dosing (5-10 mg) with tolterodine 4 mg SR or placebo for patients with OAB symptoms	• Decision tree • Societal and healthcare payer • 1 year	NR	NR. There were only minor differences in QoL between the three treatment options.	Total yearly costs/patient (Sweden/Norway/Finland/Denmark) in € • Placebo: 712/869/626/806 • Solifenacin flexible: 1142/11091076/1149 • Tolterodine 4 mg SR:	Sweden/Denmark/Norway/Finland **ICER** Total cost • Solifenacin vs placebo: €27,603/€14,318/ €26,817/€20,457 Solifenacin vs tolterodine: Dominance in all country

Study	Year	Country	Aim	Model structure, perspective, time horizon	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
							1216/1205/1122/1277	settings
Nilsson (91)	2012	Sweden	Analyse the cost-effectiveness of newer anticholinergic drugs in relation to oxybutynin IR and no treatment for patients with urgency urinary incontinence	• Decision tree • Healthcare payer • 1 year	NR	• Oxybutynin: 0.9376 • Newer drugs (solifenacin, tolterodine, fesoterodine, darifenacin, oxybutynin patch): 0.9435 • No treatment (no effect): 0.9301 • No treatment (placebo effect): 0.9389	Total cost (1 year): • Oxybutynin €1038 • Newer drugs: €1229 • No treatment (no effect): €1012 • No treatment (placebo effect): €951	• Oxybutynin vs no treatment (no effect): €8,400 • Oxybutynin vs no treatment (placebo effect): Dominated • Newer anticholinergic drugs vs no treatment (no effect): €21,045 • Newer anticholinergic drugs vs no treatment (placebo effect): €65,435 • Newer anticholinergic drugs vs oxybutynin: €37,119
O'Brien (92)	2001	Canada	Examine the cost-effectiveness of tolterodine for patients with urge incontinence who discontinue initial therapy with oxybutynin	• Markov • Societal • 1 year	Adult patients with urge incontinence	QALYs by disease state; normal/mild/moderate/severe: • Switch to no therapy: 0.03/0.17/0.29/0.18 • Switch to tolterodine: 0.07/0.27/0.24/0.11 No therapy: 0.67 per patient; tolterodine: 0.69 per patient	Total cost for 1 year: • No switch: Can$367 • Switch to tolterodine: Can $530	• Switch to tolterodine is cost-effective with an **ICER** of Can$9982
Pradelli	2009	Italy	Investigate the pharmacoecono	• Markov	A patient cohort	QALY/patient	Total cost per year	**ICER (€/QALY)**

Study	Year	Country	Aim	Model structure, perspective, time horizon	Patient population	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (cost/QALY)
(93)			mic performance of treatment with solifenacin, when compared with tolterodine and placebo, in patients with OAB	• Societal, Italian Health Service • 1 year	representative of the Italian patient population with OAB	• Solifenacin:0.810 • Tolterodine 0.800 • Placebo: 0.776 • No treatment: 0.740	• Solifenacin 5 mg: €834 • Tolterodine ER 4 mg: €988 • Placebo: €204 • No treatment: €305	• Solifenacin vs placebo: €18,612 • Solifenacin vs no treatment: €7634 • Tolterodine vs placebo: €33,309 • Tolterodine vs no treatment: €11,457
Speakman (94)	2008	UK	Evaluate the cost-utility of solifenacin, compared with tolterodine in the treatment of OAB	• Markov • UK NHS payer • 1 year	Adults with OAB	• Solifenacin: 0.709 • Tolterodine: 0.705	Total cost (1 year) • Solifenacin 5 mg/day: £509 • Tolterodine: £526	Solifenacin is dominant compared with tolterodine

Abbreviations: CR, controlled-release; ER, extended-release; HS, health state; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; IR, immediate-release; NR, not reported; OAB. overactive bladder; QALY, quality adjusted life year; SR, sustained-release; TD, transdermal; Wk, week; XL, extended-release.
†Where two dosages are quoted, results were given in the publication for the pooled dosage cohorts only.

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996 BMJ 313 (7052): 275–83), or Philips Z, et al. (2004 Health Technology Assessment 8: 36). For a suggested format based on Drummond and Jefferson (1996), please see Section 10.11, appendix 11.

A quality assessment for each cost-effectiveness study is provided in Section 10.11.

7.2 De novo analysis

A Markov model was developed to simulate the therapeutic management, the course of disease, and complications in hypothetical cohorts of OAB patients. The model was used to predict costs and QALYs over 5 years in cohorts initially treated with mirabegron 50 mg or an antimuscarinic.

The base case analysis compared mirabegron 50 mg with tolterodine ER 4 mg, based on results from SCORPIO. Secondary analyses were conducted using alternative comparators (solifenacin 5 mg and 10 mg, fesoterodine 4 mg, trospium chloride 60 mg MR and oxybutynin 10 mg ER and MR)[e], based on results from the mixed treatment comparison (MTC) reported in Section 6.7.

Patients

7.2.1 What patient group(s) is (are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in Sections 1.4 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

Base case analysis was conducted on the OAB population, reflecting the expected licensed indication. Subgroup analyses for male vs female and previously treated vs treatment-naïve populations have also been conducted as outlined in the NICE scope.

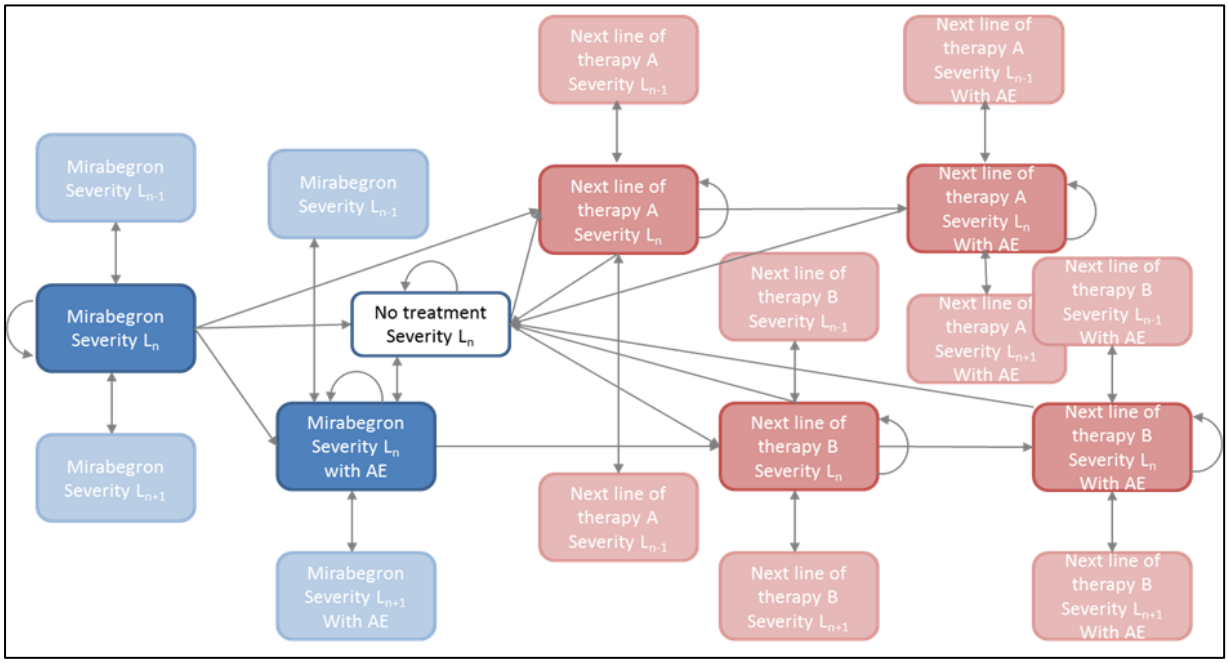
Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

A Markov modelling approach was used. Transitions between the different health states of the model are presented in Figure 34.

[e] Tolterodine IR was not included as a comparator as it is equivalent to tolterodine ER in price, but has more side-effects.

Figure 34: Transition diagram for the general OAB population, prior to botulinum toxin initiation



The model simulates the evolution of two key symptoms in parallel: micturitions and incontinence (primary endpoints within pivotal trials). For both of these symptoms, severity was categorised in to five levels (see Section 7.2.5). Severity levels are numbered from 1 to 5, in order of increasing severity. The modelling of the number of micturitions is described below. Incontinence is modelled in exactly the same way; only the transition probabilities are different.

The simulation starts on initiation of treatment with either mirabegron or an antimuscarinic. At baseline, patients are distributed across five levels of severity of micturition frequency, L1 to L5[f] (denoted $L_{n\pm1}$ in Figure 34). After 1 month on treatment, some patients will improve, and thus transition to lower-severity category, others will stay at the same level of severity, and others may worsen. The probability of changing treatment was driven by adverse events - patients may either stay on treatment, discontinue treatment (i.e. go to “no treatment”), or change treatment (i.e. go to “next line A”). To maintain clarity within the model, only dry mouth and constipation are modelled based on expert opinion that these events are most bothersome to patients and likely to drive treatment discontinuation. The two most frequently reported side-effects causing physicians to switch a patient’s antimuscarinic therapy have been shown to be dry mouth (n=453), and constipation (n=277) within a study of 4,466 OAB patients receiving antimuscarinic therapy (24). Patients with AEs may stay on treatment, in which case they will incur a disutility associated with AEs. They have an increased probability of discontinuation (i.e. going to “no treatment”), and can change treatment. If the

[f] The cut-off points between different levels were based on quintiles for each number in pooled data from the three primary Phase III studies (SCORPIO, ARIES and CAPRICORN), with all visits combined.

treatment switch is primarily due to AEs, the patient will likely receive a new therapy with reduced risk of AE (“next line B”).

At the end of the second month, and subsequent months, patients who stayed on treatment face the same possible events as at the end of first month, which may occur concurrently, i.e. they can

- transition to a different severity level, or stay at same level
- develop AEs, or not
- discontinue treatment, switch to next line A or B, or stay on current treatment.

For patients who discontinued mirabegron or comparator, the following events are possible after 1 month without treatment:

- they can naturally improve, and thus transition to a lower-severity category, but they may also worsen or stay at same level of severity (as the transition probabilities are based on the distribution of patients by severity level, on average the severity is the same as at baseline)
- they can restart previous treatment (e.g. mirabegron), or move to a new treatment (next line A or next line B), or remain without treatment.

For patients who start a new treatment (next line A or next line B), the following events may occur concurrently in one month:

- they can improve, and thus transition to a lower-severity category, worsen or stay at same level of severity
- independently of symptom severity, they can stay on treatment (next line A or B) discontinue treatment (i.e. go to “no treatment”), or move to botulinum toxin[g]
- they can develop AEs (dry mouth or constipation), which increases the probability of discontinuation or move to botulinum toxin.

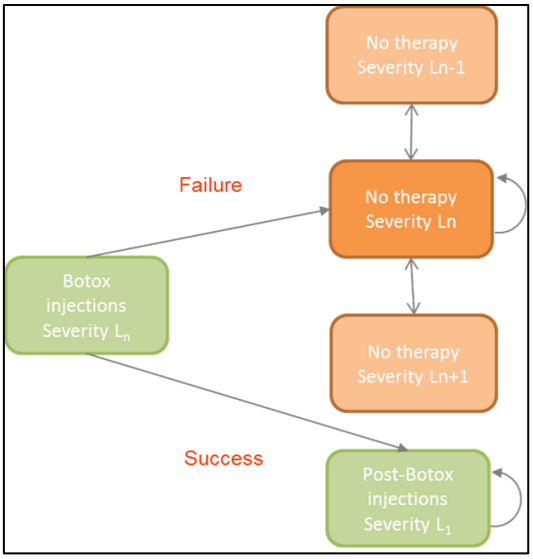
For patients who discontinued next Line A or next Line B, the following events are possible after 1 month without treatment:

- they can spontaneously improve, and thus transition to a lower-severity category, but they may also worsen or stay at same level of severity (as the transition probabilities are based on the distribution of patients by severity level, on average the severity is the same as at baseline)
- they can restart previous treatment (i.e. next line A or B), or move to botulinum toxin, or remain without treatment
- In case of success of botulinum toxin, patients are assumed to move to the lowest level of severity (L1), and stay at that level until the end of simulation (5 years) (Figure 35). In

[g] NICE recommends the use of botulinum toxin for patients who have not responded to conservative treatments (15). Advice from experts suggested that patients are likely to try 2–3 antimuscarinic therapies before botulinum toxin.

case of failure, patients go to “no treatment”, and transitions between different health states occur like for any patient without treatment. The model does not allow for treatment with antimuscarinic or mirabegron among patients after failure of botulinum toxin.

Figure 35: Transition diagram: after botulinum toxin initiation



The model accounts for the fact that probabilities of improvement or worsening of symptoms may differ between the short-term and the long-term. Thus the probability of improvement is greatest in the first month following treatment initiation, it then decreases progressively, and is assumed constant after 3 months (see Section 7.3.2 for further details).

As previously mentioned, the model runs in parallel for two types of symptoms (micturitions and incontinence). Thus, when the model has run, a distribution of patients by levels of micturition and incontinence episode frequency was obtained at monthly intervals, over 5 years. Based on the distributions of patients according to severity different symptoms, average costs and utilities were derived.

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in Section 2.5.

From the literature, several cost-effectiveness publications were identified (Table 80), including several Markov models, all based on a structure developed by Kobelt et al (89). These models consisted of five health states representing different levels of disease severity, which was measured as a composite score based on leakages and micturitions, and an absorbing state for patients discontinuing treatment.

These models had a time-horizon of 1 year. Their limitation is that the treatment pathway after drop-out is not modelled, therefore the difference in costs and outcomes related to treatments used after drop-out is not accurately estimated. In addition, several published cost-effectiveness analyses were based on decision-tree models. These analyses were conducted for time horizons of 6 months to 1 year. These models generally account for treatment discontinuation and switches (due to lack of efficacy, AEs or other reasons), but do not adequately capture the clinical reality of management in the UK.

To that end, it was decided that a new model was required, since existing models did not simultaneously capture the effects of variations of symptom severity over time on HRQoL

and the impact of discontinuations and switches on costs and health outcomes. Capturing discontinuations and switches is particularly important as persistence with antimuscarinics has been reported to be very low among OAB patients.

A Markov model is characterised by a limited number of health states, with transitions from one state to another occurring at fixed time intervals. The Markov model structure is well suited to represent transitions between different levels of symptom severity over time, under the assumption that the probability of transition to a different severity level at a given time is independent of disease severity in previous periods (it can only depend on current level of severity).

Two treatment strategies were compared (Figure 36):

Strategy 1 – mirabegron 50 mg

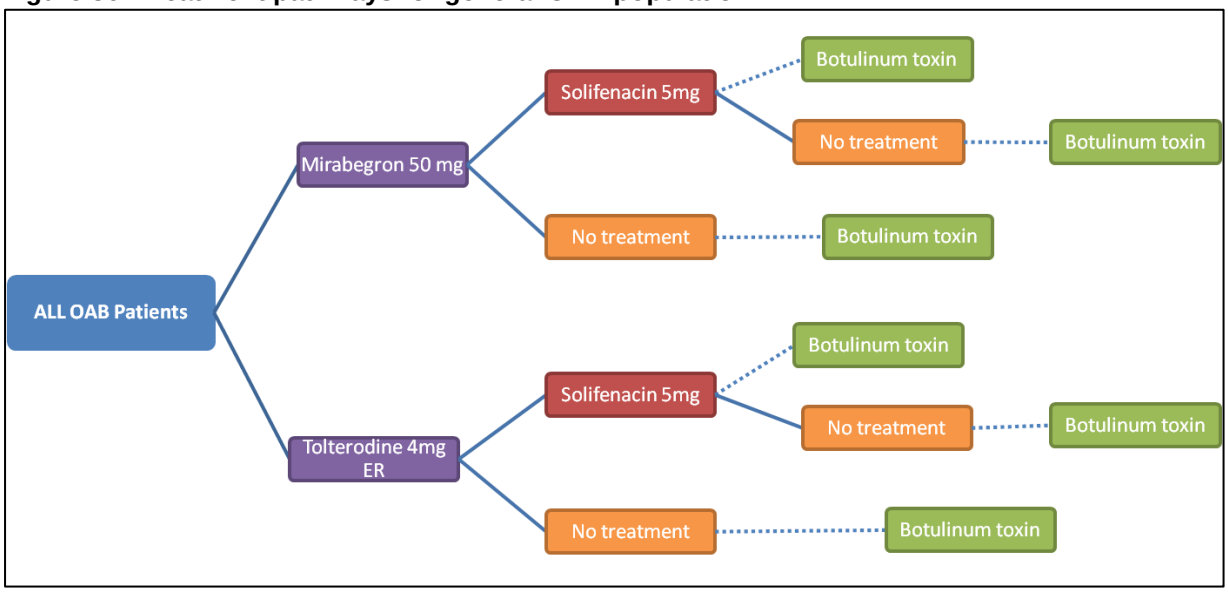
Patients start treatment with mirabegron 50 mg and can continue for up to 5 years[h]. Every month, patients can also switch in case of failure to another OAB treatment: next line of therapy. The next line of therapy is considered to have the cost, efficacy and safety equivalent to solifenacin 5 mg. In case of failure of the next line of therapy, patients can receive botulinum toxin, or remain without treatment.

Strategy 2 – antimuscarinic

Patients start treatment with an antimuscarinic and can continue for up to 5 years. In the same way as for strategy 1, patients can also switch in case of failure to another OAB treatment: next line of therapy. The next line of therapy is considered to have the cost, efficacy and safety equivalent to solifenacin 5 mg. For example if mirabegron is compared with tolterodine, then tolterodine is unlikely to be selected as next line of therapy A2 or B2, but may be a suitable next line in strategy 1 (i.e. as therapy A1 or B1). In case of failure of the next line of therapy, patients can receive botulinum toxin, or remain without treatment.

[h] A time horizaon of 5 years was validated by expert opinion, and based on very few patients remaining on their initial therapy after 5 years of treatment (Table 82).

Figure 36: Treatment pathways for general OAB population



7.2.4 *Please define what the health states in the model are meant to capture.*

Different states were created to represent different levels of OAB severity and stages of therapeutic management.

- OAB severity is described by the level of severity of two key symptoms independently: micturitions and incontinence (chosen to reflect the pivotal trial co-primary endpoints). Each severity level of OAB symptoms is assigned a different quality of life value and a rate of incontinence pad usage. Improvement in symptoms therefore improves quality of life and reduces costly incontinence pad usage.
- The health states are also characterised by a treatment, or absence of treatment; thus patients may either switch from one treatment to another, or discontinue any OAB treatment. Switches and discontinuations have a direct impact on costs, and also affect symptom severity, which is associated with health-related quality of life (HRQoL) and costs.
- Finally, the model health states are characterised by presence or absence of AEs (dry mouth and constipation), which have a direct impact on HRQoL and are associated with increased probability of switch or discontinuation.

7.2.5 *How does the model structure capture the main aspects of the condition for patients and clinicians as identified in Section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to Section 2.1.*

OAB is described by the International Continence Society (ICS) as urgency, with or without urge incontinence, usually with frequency and nocturia (6). Mirabegron is provided to patients as a therapy option for OAB for treatment of these symptoms (see Section 2.1).

The symptoms of frequency of micturitions and incontinence episodes were chosen based on the coprimary outcome measures of the pivotal mirabegron trials. Five severity levels were defined for each based on the mean number of episodes per day – a structural assumption based on the previously accepted and validated markov model developed by

Kobelt et al (89). The cut-off points between different levels were based on quintiles for each number in pooled data from the three primary Phase III studies (SCORPIO, ARIES and CAPRICORN), with all visits combined. A test for correlation between these two symptoms was conducted, and did not show relationship – the symptoms are therefore treated as independant and additive. For micturition severity, Level 1 of eight or less micturitions per day corresponds with the usual threshold used to define OAB. For incontinence severity, Level 1 is defined as the continent level: a patient is considered to be in Level 1 if they experience no incontinence episodes over the previous 3 days. Table 81 summarises the definitions of severity levels for each symptom (micturition and incontinence).

Table 81: Severity levels of symptoms

Symptom	Level 1	Level 2	Level 3	Level 4	Level 5
Mean number of micturitions per day	≤ 8	>8 to ≤10	>10 to ≤ 12	>12 to ≤ 14	>14
Mean number of incontinence episodes per day	0	>0 to ≤1	>1 to ≤ 2	>2 to ≤ 3	>3

Patients may be at different levels for different symptoms. The OAB symptoms profile of a patient can be described in the format [Mx:Iy], where x is the micturition level and y the incontinence level. Thus a classification system for OAB symptoms with 25 different profiles was produced. For example, a patient with the profile [M2:I3] has 8 to 10 micturitions per day and between 1 and 2 incontinence episodes per day.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported.

Table 82: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	5 years Sensitivity analyses were conducted with time horizons from 1, 2, 10 years	Expert opinion and model analyses have suggested that <5% of patients would be expected to continue mirabegron or a comparator medication >5 years (Table 119). Treatment pathways and levels of OAB severity were simulated over 60 cycles of 1 month (i.e. 5 years). Transitions between health states were possible at one-month intervals	Model analyses based on data from SCORPIO (37, 38) and expert opinion
Cycle length	1 month	Visits in SCORPIO occurred at 1-month intervals; therefore transition probabilities were estimated for 1-month intervals	N/A: Assumption
Half-cycle correction	Not used	Assumption that prescriptions are renewed at the beginning of each cycle (i.e. month) and the full cost of medication is incurred even if a patient discontinues treatment half-way through a cycle. Applying a half-cycle correction would lead to an underestimation of drug costs	N/A: Assumption
Were health effects measured in QALYs; if not, what was used?	Yes	As per NICE reference case	NICE methods guide (96)
Discount of 3.5% for utilities and costs	3.5% per annum applied for costs and health benefits. Sensitivity analyses were conducted using differential rates for costs and outcomes, and varying the rates from 0% to 6%.	As per NICE reference case	NICE methods guide (96)
Perspective (NHS/PSS)	Yes	As per NICE reference case	NICE methods guide (96)

Abbreviations: NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence; PSS, Personal Social Services; QALYs, quality adjusted life years.

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in Sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Antimuscarinics are implemented within the model as per their marketing authorisations. Mirabegron is implemented as per its expected marketing authorisation.

The use of botulinum toxin for OAB is outside its marketing authorisation, however it is recommended by NICE for patients who have not responded to conservative treatments (15).

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators.

Treatment continuation rules were not considered necessary in the economic model, given the symptomatic nature of OAB treatments, and the low persistence rates with current treatments.

7.3 Clinical parameters and variables

7.3.1 Please demonstrate how the clinical data were implemented into the model.

For the base case comparison of mirabegron versus tolterodine, data for the following variables were taken from SCORPIO.

- Probabilities of transition between different severity levels, by treatment:
- Probabilities of AEs, by treatment:

For the analysis versus other antimuscarinics, data were derived from the MTC described in Section 6.7.

Other transition probabilities (discontinuation and switch rate) were obtained from the literature and expert opinion.

7.3.1.1 Micturition and incontinence episodes severity levels at baseline

The initial proportions of patients at different severity levels of each type of symptom were obtained from SCORPIO, based on pooled data from the three treatment arms at baseline (described in Section 7.2.5). These proportions, for the general OAB population and the previously treated subgroup, are presented in Table 83.

Table 83: Initial distribution of patients across severity levels, general OAB and previously treated populations

Severity level	General OAB population		Previously treated population	
	Micturition	Incontinence	Micturition	Incontinence
1	6.30%	38.87%	6.25%	29.92%
2	30.69%	18.84%	29.61%	18.65%
3	27.18%	14.64%	26.23%	16.29%
4	19.46%	9.18%	18.65%	10.45%
5	16.37%	18.47%	19.26%	24.69%

Abbreviations: OAB, overactive bladder.

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

7.3.2.1 Logistic regression

Probabilities of transition between severity levels for each symptom were obtained from a multinomial logistic regression model estimated from SCORPIO data. The probability of being at symptom level *j* at month (*t*+1) was expressed as a function of treatment, symptom severity in previous month (*t*), gender and age:

$$Prob(Severity_{t+1} = j \mid x) = \frac{e^{\beta_0^j + \beta_1^j.Treatment \ + \beta_2^j.Severity_{\ t} + \beta_3^j.Sex + \beta_4^j.Age + \beta_5^j.Treatment \ * Severity_{\ t}}}{1 + \sum_{k=1}^{J-1} e^{\beta_0^k + \beta_1^k.Treatment \ + \beta_2^k.Severity_{\ t} + \beta_3^k.Sex + \beta_4^k.Age + \beta_5^k.Treatment \ * Severity_{\ t}}}$$

The log odds of being at a symptom level lower than *j* rather than greater than *j* are as following:

$$Log\left(\frac{Prob(Severity_{t+1} = j \mid x)}{Prob(Severity_{t+1} = 5 \mid x)}\right) = \beta_0^j + \beta_1^j.Treatment + \beta_2^j.Severity_t + \beta_3^j.Sex + \beta_4^j.Age + \beta_5^j.Treatment * Severity_t$$

If the test of the proportional odds assumption is not rejected, an ordinal logistic regression can be used. This assumption is that the effects of any explanatory variables (here treatment, severity in previous month, sex and age) are consistent across different pairs of symptom levels. In other words, that the explanatory variables have the same effect on the odds regardless of the cut-off level:

$$Log\left(\frac{Prob(Severity_{t+1} = j \mid x)}{Prob(Severity_{t+1} = 5 \mid x)}\right) = \beta_0^j + \beta_1 \ .Treatment + \beta_2 \ .Severity_t + \beta_3 \ .Sex + \beta_4 \ .Age + \beta_5 \ .Treatment * Severity_t$$

In the defined model, the null hypothesis of the proportional odds assumption was rejected, so the Ordinal Logistic Regression was not used.

The interaction between the treatment and the severity was also tested and appeared not significant.

Consequently the final equation to compute the transition probabilities was:

$$Prob(Severity_{t+1} = j \mid x) = \frac{e^{\beta_0^j + \beta_1^j . Treatment \ + \beta_2^j . Severity_{\ t} + \beta_3^j . Sex + \beta_4^j . Age}}{1 + \sum_{k=1}^{J-1} e^{\beta_0^k + \beta_1^k . Treatment \ + \beta_2^k . Severity_{\ t} + \beta_3^k . Sex + \beta_4^k . Age}}$$

Detailed results of the regression analyses are provided in Section 10.19.

7.3.2.2 Transition matrices

Using the multinomial logistic regression model described in Section 7.3.2.1, three transition matrices (5x5) were produced for each type of symptom, one for the transition between baseline and the first month, one between the first month and the second month, and finally one between the second month and the third month. Transition matrices are provided in Section 10.20. For patients remaining on treatment beyond 3 months, the transition matrix from 2 to 3 months was reapplied for the cycle from 3 to 4 months and subsequent monthly cycles until discontinuation.

For patients discontinuing treatment, the proportions by level of severity were assumed to be the same as at baseline.

For example, for a patient with micturitions at level 3 at baseline, the probability of improving to level 1 after 1 month is 16.0% on mirabegron (Table 156) and 15.2% on tolterodine 4 mg (Table 157).

Transition matrices for subgroups were obtained using the same method as for the general OAB population. Logistic regression models were estimated based on data from SCORPIO, for the particular subgroup of patients. The resulting transition matrices for the previously treated subgroup are provided in Section 10.21.

Correlation between changes in micturations and incontinence in the utility estimation was tested and has been found to be not significant.

7.3.2.3 Calibration approach

In order to obtain transition probabilities for other treatments, not included in the mirabegron clinical study programme (oxybutynin 10 mg [the same efficacy was assumed for ER and IR], solifenacin 5 mg, solifenacin 10 mg, fesoterodine 4 mg, trospium chloride 60 mg MR), the logistic model was adapted and modified the treatment parameters by calibration following the seven-step approach defined by Vanni et al (97).

The aim of the calibration method was to determine the ß1,…, ß4 estimates in the logistic model for a given treatment by minimizing the distance between the mean change in symptoms from baseline predicted by the model and the mean change determined from a MTC reported in Section 6.7 (shown in Table 84). This calibration procedure was implemented for micturitions and incontinence, and for different treatments. Improvement in urge incontinence was used instead of incontinence improvement for patients treated with trospium 60 mg MR since the mean change in frequency of incontinence episodes was not reported in studies.

Table 84: Difference in the mean change from baseline at 3 months for different antimuscarinics vs mirabegron 50 mg

Treatment	Micturition	Incontinence
Tolterodine ER 4 mg	0.157	0.082
Solifenacin 5 mg	-0.240	-0.237
Solifenacin 10 mg	-0.583	-0.240
Fesoterodine 4 mg	0.137	0.107
Oxybutynin 10 mg	-0.139	0.137
Trospium chloride 60 mg MR	-0.124	-0.112+

Abbreviations: ER, extended-release; mg, milligram; MR, modified-release.
+UUI effect assumed instead of incontinence effect due to lack of comparative evidence.

The distribution of the changes in symptoms predicted by the model was obtained as follows. The modelled cohort was divided in 25 groups of patients according to symptoms severity level at baseline and severity at 3 months (e.g. there are five possible levels at baseline and five levels at 3 months, so 25 groups in total). The proportions of patients in each group were predicted by the model [i]. The mean change in frequency of symptom episodes (micturitions or incontinence) was estimated within each group based on data from the mirabegron 50 mg arm of the SCORPIO study. Thus, it was assumed that the change in frequency of symptoms within each level was independent of treatment. The mean change in frequency of symptoms in the total cohort was calculated as a weighted average of changes in different levels. This is expressed mathematically as following:

$$CS_A = \sum_{i=1}^{5} \sum_{j=1}^{5} p_{ijA}\, CS_{iM}$$

Where:

- is the mean change in frequency of symptoms for treatment A
- 'i' is the symptom level at baseline
- 'j' is the symptom level at 3 months
- is the proportion of patients in severity level i at baseline and severity level j at 3 months among patients treated with drug A
- is the mean change in frequency of symptoms among patients going from level i at baseline to level j at 3 months on mirabegron.

As this calibration problem has only one constraint (the difference in mean changes being equal to zero) and 4 unknowns (the beta coefficients), there was potentially an infinity of solutions. Therefore three solutions, i.e. three series of beta coefficients, were generated for

[i] It is not possible to obtain those proportions from the model programmed in Excel. The Excel model predicts proportions of patients by symptom level at 3 months in a cohort of patients at different levels of severity at baseline. However, it does not provide proportions of patients in a given level at 3 months by symptom level at baseline. A submodel was programmed in Scilab for estimating those proportions.

each symptom by the calibration procedure. These series of beta coefficients were used as parameters in the model to test the robustness of results:

1. First series of Beta coefficients: Initial beta parameters were the coefficients for Mirabegron 50 mg from the logistic regression based on the SCORPIO study
2. Second series of Beta coefficients: Initial parameters were the coefficient for tolterodine ER 4 mg from the logistic regression based on the SCORPIO study (Worst efficacy)
3. Third series of Beta coefficients: Initial parameters were the coefficients for solifenacin 5 mg from a logistic regression based on data from the study 905-CL-015 (used for the indirect comparison) (Best efficacy).

The Scilab software was used to solve this problem of optimisation.

7.3.2.4 Adverse Events

Monthly probabilities of having an AE were derived from SCORPIO. It was assumed that patients may experience two types of AE. To maintain clarity within the model, only dry mouth and constipation are modelled based on expert opinion that these events are most bothersome to patients and likely to drive treatment discontinuation. The two most frequently reported side effects causing physicians to switch a patient's antimuscarinic therapy have been shown to be 'dry mouth' (n=453), and 'constipation' (n=277) within a study of 4,466 OAB patients receiving antimuscarinic therapy (24). These were considered to be bothersome AEs associated with current OAB medications which impact on compliance. The probabilities are presented in Table 85. It was assumed that patients after stopping treatment have a zero probability of having an AE.

Table 85: Probabilities of AEs at 12 weeks, by treatment

Model parameter	Base case value	Sensitivity analysis values	Source
Probability of having a dry mouth AE			
Mirabegron 50 mg	2.8%	2.1% - 3.5%	SCORPIO (37)
Tolterodine 4 mg	10.1%	8.7% - 11.5%	SCORPIO (37)
No treatment	0%		SCORPIO (37)
Probability of having a constipation AE			
Mirabegron 50 mg	1.6%	1% - 2.2%	SCORPIO (37)
Tolterodine 4 mg	2%	1.4% - 2.6%	SCORPIO (37)
No treatment	0%		SCORPIO (37)

Abbreviations: AE, adverse event; mg, milligram.

Similar probabilities were applied for the subgroups of previously treated patients.

For other treatments, log odds ratios of each treatment versus mirabegron 50 mg for each AE were obtained from the MTC reported in Section 6.7.

Table 86: Probabilities of AEs at 12 weeks for other antimuscarinics

Model parameter	Base case value	Sensitivity analysis values	Source
Probability of dry mouth			
Mirabegron 50 mg	2.80%	2.10%-3.50%	Reference / SCORPIO (37)
Tolterodine ER 4 mg	10.70%	8.70%-11.50%	MTC results (Section 6.7)/ Random effect model
Solifenacin 5 mg	10.90%	NA	MTC results (Section 6.7)/ Random effect model
Solifenacin 10 mg	22.50%	NA	MTC results (Section 6.7)/ Random effect model
Fesoterodine 4 mg	11.30%	NA	MTC results (Section 6.7)/ Random effect model

Oxybutynin ER 10 mg	16.40%	NA	MTC results (Section 6.7)/ Random effect model
Oxybutynin IR 10 mg	28.8%	NA	MTC results (Section 6.7) / Random effect model
Trospium 60 mg MR	11.40%	NA	MTC results (Section 6.7)/ Random effect model
Probability of constipation			
Mirabegron 50 mg	1.60%	1.00%-2.20%	Reference / SCORPIO (37)
Tolterodine ER 4 mg	2.00%	1.40%-2.60%	MTC results (Section 6.7)/ Fixed effect model
Solifenacin 5 mg	3.90%	NA	MTC results (Section 6.7)/ Fixed effect model
Solifenacin 10 mg	6.60%	NA	MTC results (Section 6.7)/ Fixed effect model
Fesoterodine 4 mg	1.70%	NA	MTC results (see section 6.7)/ Fixed effect model
Oxybutynin ER 10 mg	1.60%	NA	MTC results (see section 6.7)/ Fixed effect model
Oxybutynin IR 10 mg	1.60%	NA	Assumption (same as Oxybutynin ER 10 mg)

Abbreviations: ER, extended-release; IR, immediate-release; mg, milligram; MR, modified-release; MTC, mixed treatment comparison.

7.3.2.5 Discontinuation

The persistence on OAB medications was studied by Wagg et al (22) based on longitudinal prescriptions database. Data were extracted from the medical records of >1,200,000 registered patients via GP practice software, and anonymised prescription data were collated for all eligible patients with documented OAB (n = 4,833). Data were collected on patients who started treatment between January 2007 and December 2007 and were extracted up to December 2008, to allow each patient a full 12-month potential treatment period. At 12 months, the proportions of patients still on their original treatment were: 35% on solifenacin, 28% on tolterodine ER, 26% on oxybutynin ER, 26% on trospium, 24% on tolterodine IR and 22% on oxybutynin IR.

Furthermore, a 12-week observational study conducted among OAB patients in Spain in 2009 showed that 24% of patients who changed treatment did so because of side effects (98). This estimate was consistent with results of a large survey among OAB patients who used antimuscarinics in the US. Side effects were cited as a reason for discontinuation by 21.1% of 1322 patients who discontinued OAB medications (23).

No real-world data are available on persistence with mirabegron. For the model it was assumed that the discontinuation rate for patients without an AE was similar for mirabegron and the comparator. The specific persistence rate for each treatment was taken from Wagg et al (22). It was also assumed that the discontinuation rate for patients with AEs was similar between treatments. This implies that the overall discontinuation rate would be higher for the treatment with the higher probability of AEs between mirabegron and the comparator. In the base case model, the persistence rate of 28% for tolterodine ER at 12 months was used (22). Therefore, the overall probability of discontinuing was 72%. In addition, since 24% of patients are assumed to discontinue because of AEs, it was estimated that 54.7% of patients without an AE would discontinue by 12 months. Monthly probabilities were calculated using the following formula:

Monthly Proba = 1-((1- "Persistence rate at 12 months")EXP (1/12))

A sensitivity analysis was performed based on the mean duration of treatment within SCORPIO , i.e. 157 days or 5.2 months. This corresponds to a monthly discontinuation rate of 19.1% overall. After subtraction of discontinuations due to AEs, a discontinuation rate of 14.5% was obtained. There are two reasons why this calculation might lead to a higher estimate than above, based on the persistence at 12 months. Firstly, the mean time to discontinuation was only estimated over a period of 12 months, and therefore

underestimates the real average time to discontinuation, since 28% of patients continue treatment beyond 12 months. Secondly, the monthly probability of discontinuation is probably higher in the first months of treatment than after several months of treatment (99).

As no discontinuation rates were found specifically for the patients with AEs such as dry mouth and constipation, it was assumed that 90% of patients with AEs would discontinue treatment. This was tested in a sensitivity analysis with a much lower proportion of 50%.

Table 87: Model inputs: monthly probability of discontinuation of OAB therapy

	Base case	Sensitivity analysis	Sources
Without AEs	6.4%	3% - 14.5%	Base case and upper limit : Wagg, 2012 (22) and Castro-Diaz, 2010 (98) Lower limit : assumption
With AEs	90%	50% - 100%	Expert opinion

Abbreviations: AE, adverse event.

7.3.2.6 Switch to next-line therapy

Treatment patterns among OAB patients before 2004 in the UK were analysed by Odeyemi et al, using the general practice research database (GPRD) (100). Among 5,424 patients who received tolterodine as a first-line therapy, 68.92% discontinued within the study period, and 26.06% of those switched to another medication (most frequently oxybutynin). This probability was used for the base case analysis. However, it should be noted that switch rates were higher among users of other antimuscarinics (33.91% after oxybutynin as first-line and 44.36% after flavoxate, propiverine, trospium or solifenacin as first-line). Furthermore, the probability of switch after discontinuation of second-line therapy (including cases reverting to first-line treatment) appeared to be greater than after first-line, although these rates were not explicitly reported. In addition, probabilities of switch may have increased after 2004, since the number of treatments available for OAB has increased. Therefore, the probability of 26.06% used for the base case analysis might be a relatively low estimate for the UK.

An analysis of health insurance claims data, from a regional managed care plan in the US, showed that 13.3% of all patients switched to another medication, over a period of 12 months, and 13.2% of patients were persistent at 12 months (101). This would suggest that 15.32% of patients discontinuing an antimuscarinic switched to another medication. This proportion was tested in sensitivity analyses. This analysis was also based on data collected before 2004.

Table 88: Model inputs: probability of switch after discontinuation of OAB therapy

	Base case	Sensitivity analysis	Sources
Probability of switch, among all patients discontinuing OAB treatment	26.06%	15.32% - 50%	Base case: Odeyemi, 2006 (100) Sensitivity analyses: D'Souza, 2008 (101)/ Assumption

7.3.2.7 Probability of restarting treatment

No data were found in the literature about the probability of starting treatment again after a period without treatment. It is possible that patients who discontinued because they no longer had symptoms would restart treatment if their symptoms worsened after discontinuation. According to a survey on reasons for discontinuation of OAB medication in

the US, the fact that symptoms had stopped was cited as a reason for discontinuation by 14.5% of those who discontinued (23). An annual probability of 50% was assumed (monthly probability of 5.6%) of starting treatment again among patients who discontinued mirabegron or tolterodine without immediately switching to another drug. Furthermore, it was assumed that a third of these patients would go back to their previous treatment, another third would receive "next line A" and the remaining third would receive "next line B".

Table 89: Model inputs: monthly probabilities of restarting OAB therapy among patients without treatment

	Base case	Sensitivity analysis	Sources
Monthly probability of restarting treatment	5.6%	0% - 20%	Expert opinion
Split between different medications, for general OAB population*			Assumption
- Initial treatment (mirabegron or tolterodine)	33.33%	0% - 50%	
- Next line A	33.33%	0% - 50%	
- Next line B	33.33%	0% - 50%	

Abbreviations: OAB, overactive bladder.
* For the previously treated subgroup, it was assumed that all patients restarting treatment would go back to mirabegron or comparator antimuscarinic.

7.3.2.8 Probability of transition to botulinum toxin

No data were found in the literature about the probability of moving to botulinum toxin, or receiving botulinum toxin following a period without treatment. It was assumed that every year, 1% of patients on next-line therapy (A or B) or having discontinued next-line therapy switched to botulinum toxin in the general OAB population. In the previously treated subgroup, it was assumed that patients starting with mirabegron or tolterodine who failed would not receive further pharmacological therapy. Therefore, their options would be restricted to botulinum toxin and "no treatment". 5% of patients having discontinued mirabegron or tolterodine moved to botulinum toxin therapy annually.

Table 90: Model inputs: Monthly probability of transition to botulinum toxin

	Base case	Sensitivity analysis	Sources
Monthly probability of having botulinum toxin injection in the general OAB population	0.01%	0% - 0.05%	Assumption validated with expert opinion
Monthly probability of having botulinum toxin injection in the previously treated population	0.04%	0% - 0.1%	Assumption validated with expert opinion

Abbreviations: OAB, overactive bladder.

7.3.2.9 Probability of success of botulinum toxin

The probability of improvement of symptoms after botulinum toxin injection was 79%, based on a previously published cost-effectiveness analysis comparing botulinum toxin to antimuscarinics (102). As mentioned above, it was assumed that all patients who improved had symptoms (micturitions and incontinence) at Level 1, from initial botulinum toxin injection to end of the time horizon. Furthermore, for other patients, who did not improve, the transition matrices for patients without treatment were applied.

Table 91: Probabilities of success of botulinum toxin

	Base case	Sensitivity analysis	Source
Probability of success of botulinum toxin	79%	50% - 100%	Wu 2009

injection			(102)

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Transitions between health states were informed by the progression of patients observed over time in SCORPIO. Variations in transition probabilities over the 5-year time horizon of the model has therefore been included. After 3 months, these probabilities are assumed to be constant. Under this assumption, the frequency of micturitions and incontinence episodes are constant after 3 months, consistent with evidence from long-term clinical studies (99).

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the details.

Please provide the following details[j]:

- ***the criteria for selecting the experts***
- ***the number of experts approached***
- ***the number of experts who participated***
- ***declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought***
- ***the background information provided and its consistency with the totality of the evidence provided in the submission***
- ***the method used to collect the opinions***
- ***the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire)***
- ***the questions asked***
- ***whether iteration was used in the collation of opinions and if so, how was it used (for example, the Delphi technique).***

Expert opinion from six key opinion leaders already known to Astellas was collected at an advisory board meeting on 3rd October 2011.

[j] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

The following parameters were assessed and deemed to be appropriate via open discussion amongst the experts following an introductory presentation to the project:

- Monthly probability of initiating botulinum toxin therapy in general OAB population
  - For patients without pharmacological therapy: 0.08% (1% annually)
  - For patients on “next line” (i.e. patients on solifenacin): 0.08% (1% annually)
- Monthly probability of initiating botulinum toxin therapy in previously treated subgroup
  - For patients without pharmacological therapy: 0.43% (5% annually)
  - For patients on “next line” (i.e. patients on solifenacin): 0.43% (5% annually)
- Probability of reinitiating pharmacological therapy, among patients who previously discontinued: 5.61% (50% annually)
- Split between different medications for patients reinitiating treatment
  - Mirabegron or comparator: 1/3
  - Solifenacin: 2/3
- Monthly probability of treatment discontinuation among patients with AEs: 90%
- Number of physician visits when initiating new therapy: 1.5 specialist visits and 1 GP visit.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table.

A table of all variables used in the economic analysis is provided in Section 10.21. Variables include:

- proportion of patients by severity level and transitions between severity levels
- utilities according to symptom severity
- probability of discontinuation, switch after discontinuation, restarting therapy, transition to botulinum toxin
- probability of success of botulinum toxin
- probabilities of AEs (constipation and dry mouth) and associated utility decrements
- medication costs
- resource utilisation and unit costs of healthcare resources
- pad use.

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its

comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

Clinical outcomes were obtained from SCORPIO with a study duration of 12 weeks and extrapolated to the time horizon of 5 years. For patients staying on treatment beyond 3 months, the transition matrix from 2 to 3 months was reapplied for the cycle from 3 to 4 months and subsequent monthly cycles until discontinuation.

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

A list of assumptions within the model is provided in Table 92.

Table 92: List of assumptions used in model

Category	Assumption
Structural assumptions	
Health state utilities	Variations over time are explained by variations in frequency of micturitions and incontinence episodes and by AEs (dry mouth, constipation). There is no impact of treatment or time on health state utilities, other than micturition and incontinence episode frequency, and treatment-related AEs. Model assumes no independent impact of urgency.
AEs	Utility assumed to be reduced from the midpoint of the cycle in which the event occurred up to discontinuation. Thus, AEs would resolve immediately upon discontinuation. It was also assumed that most patients would discontinue treatment at the end of the cycle, i.e. two weeks later on average. However, in reality, a small number of patients could choose to continue treatment despite suffering from AEs.
Numbers of micturitions/ incontinence episodes/24h	Each broken down into 5 levels of severity. Model assumes that the average numbers of micturitions and incontinence episodes within each level are the same for all treatments and are constant over time.
Treatment discontinuations	May be due to AEs or other reasons. The probability of discontinuation for other reasons is independent of symptom severity. Patients with improved symptoms may discontinue treatment if they feel they no longer require treatment; while patients with stable or worsening symptoms may discontinue due to lack of efficacy. In addition, the probability of discontinuation due to other reasons is the same for mirabegron as for the comparator (this implied that the probability of discontinuation on mirabegron was changed when the comparator was changed).
Probability of switch after discontinuation	Independent of the reason for discontinuation and the same for all treatments.
Lines of pharmacological treatment	• For general OAB population, two lines are considered (mirabegron and antimuscarinics). In case of failure of mirabegron or comparator, patients may switch to next line of treatment. There are two treatment options, A and B, according to reason for discontinuation, but it was assumed in base case analysis that the next line of treatment was solifenacin in both situations. The model does not allow for a second switch. Patients will either not be treated or take botulinum toxin in case of failure of second medication. However, patients who have stopped treatment may later reinitiate treatment with one of the previous medications (mirabegron, comparator or solifenacin). • For previously treated subgroup, it was assumed that patients would not receive further pharmacological therapy after stopping mirabegron or comparator antimuscarinic. Therefore, their options would be restricted to

	botulinum toxin and “no treatment”. However, patients who have stopped treatment may later reinitiate treatment with one of the previous medications.
Distribution of patients by disease severity	After treatment discontinuation, distribution is identical to the distribution at baseline.
Treatment-related AEs	Those considered are dry mouth and constipation. It is assumed that there is no significant difference in probabilities of other AEs between mirabegron and antimuscarinics.
After successful treatment with botulinum toxin	• Patients assumed to move to the lowest severity level, and stay at that level until end of simulation. In case of failure, patients go to “no treatment”, and transitions between different health states occur like for any patient without treatment. • Assumption that injections would be repeated at 6-month intervals.
Probability of improvement or worsening of symptoms	The model accounts for the fact that probabilities of improvement or worsening of symptoms may differ between the short-term and the long-term. Thus the probability of improvement is greatest in the first month following treatment initiation, it then decreases progressively, and is assumed constant after 3 months (i.e. probabilities of transition between severity levels are the same in 4th and subsequent months as in 3rd month).
GP/specialist visits	No cost of GP visit is incurred for prescription renewals, as it is assumed that renewals are made during routine visits, occurring independently of treatment.
Number of pads	Linked to number of incontinence episodes/day (i.e. incontinence severity level) and assumed to be independent of treatment for given level of severity.
Number of tablets consumed	• Assumed that patients used 1 tablet/day of mirabegron, tolterodine or solifenacin, for each day of every month until discontinuation. The analyses did not account for drug wastage or partial compliance. • Model does not allow for changes in dosage over time.
Input assumptions	
Treatment discontinuations	• Monthly probability of treatment discontinuation for patients with AEs: 90%
Treatment reinitiation	• Probability of reinitiating pharmacological therapy, among patients who previously discontinued: 5.61% (50% annually) • Split between different medications for patients reinitiating treatment: Mirabegron or comparator = 1/3; Solifenacin: = 2/3
Initiation of botulinum toxin	• Monthly probability of initiating botulinum toxin therapy, in general OAB population: patients without pharmacological therapy = 0.08% (1% annually); patients on “next line” (i.e. patients on solifenacin) = 0.08% (1% annually) • Monthly probability of initiating botulinum toxin therapy, in previously treated subgroup: patients without pharmacological therapy = 0.43% (5% annually); patients on “next line” (i.e. patients on solifenacin): 0.43% (5% annually)
GP/specialist visits	• Visits to specialist and GP occur when a new treatment is started (1.5 specialist and 1 GP visit).

Abbreviations: AE, adverse event; GP, general practitioner; OAB, overactive bladder.

7.4 Measurement and valuation of health effects

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

OAB is usually accompanied by a high frequency of urination and nocturia, with (OAB wet) or without (OAB dry) incontinence. OAB adversely affects many aspects of patients' QoL. OAB has been shown to have significant social, psychological, occupational, domestic, and physical stigmas (28), as well as a strong association with depression (12). As discussed in more detail in Section 2.1, patients with OAB report significantly less sexual satisfaction, higher rates of depressive symptoms and erectile dysfunction, and slightly lower levels of overall health (12). Patients with OAB and nocturia have reported significantly higher symptom bother and decreased HRQoL due to disrupted sleep patterns (13).

OAB patients become anxious in unfamiliar environments: they focus on and may be preoccupied with such concerns as locating the closest bathroom, looking for aisle seating, and estimating the amount of time until their next work break. Embarrassment, frustration, anxiety, annoyance, depression, and fear of odour can have a negative impact on daily activities, such as travel, physical activity, relationships, and sexual function, resulting in social isolation. Such activity may be associated with costly management of absenteeism, presenteeism[k], and depression (29).

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition

The natural history and evolution of OAB with age is uncertain, with some patients experiencing worsening symptoms and some finding that symptoms resolve or become acceptable to live with unmedicated. Patients may experience worsening HRQoL despite treatment if their medication delivers poor efficacy or tolerability.

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in Section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case.

Utility values according to symptom severity were derived from EQ-5D index scores, based on UK time trade-off tariff (103), collected in SCORPIO. A linear regression model was estimated, with adjustment on age, gender, and country (as random effect), accounting for repeated measures by patient:

$$Utility = \beta_0 + \beta_1 ClassMict + \beta_2 ClassInco + \beta_3 Age + \beta_4 Sex + \varepsilon_{patient} + \varepsilon_{country}$$

[k] Presenteeism is defined as productivity loss while at work.

The regression model was estimated from all treatment arms of SCORPIO. It was verified that there was no significant treatment effect, independent of symptom severity. Table 93 shows the resulting parameter estimations for the general OAB population. For example, the coefficient for micturitions at level 1 is 0.06321: this means that the utility of patients with micturitions at level 1 is higher than the utility of patients with micturitions at level 5 by 0.06321, all other things equal. Health utilities values according to symptom severity for the subgroups were obtained using the same method as for the general OAB population.

Table 93: Regression model on EQ-5D utilities

Effect	Level	Estimate	Sensitivity analyses (95% CI)
Intercept		0.7838	
Age		-0.00041	
Micturition severity level	1	0.06321	0.0453 - 0.0811
	2	0.04224	0.0258 - 0.0587
	3	0.02042	0.0045 - 0.0363
	4	0.01039	-0.0316
	5	0	
Incontinence severity level	1	0.05859	0.0422 - 0.0749
	2	0.04367	0.0271 - 0.0602
	3	0.03141	0.0142 - 0.0486
	4	0.01282	-0.0369
	5	0	
Gender	F	-0.04412	
	M	0	

Table 94 describes the EQ-5D utility values for 5 health states: [M1,I1] (Patients in Level 1 for Micturition and Level 1 for Incontinence), …, [M5,I5]. The difference between the best possible health state [M1, I1] and the worst possible health state [M5,I5] was 0.12.

Table 94: Utility values derived from EQ-5D index score for each possible health state

	Micturitions frequency level				
Incontinence frequency level	M1	M2	M3	M4	M5
I1	0.85	0.83	0.81	0.80	0.79
I2	0.83	0.81	0.79	0.78	0.77
I3	0.82	0.80	0.78	0.77	0.76
I4	0.80	0.78	0.76	0.75	0.74
I5	0.79	0.77	0.75	0.74	0.73

In addition, estimated utilities were derived from the OAB-q questionnaires, using the algorithm developed by Yang et al (104). A linear regression model was estimated to predict utilities according per severity level, in the same way as for EQ-5D utilities. This model was used for sensitivity analysis. Estimates of the regression model coefficients are presented in Section 10.19.

Table 95 describes the utility values derived from OAB-q for 5 health states: [M1, I1], …, [M5, I5]. The difference between the best possible health state [M1, I1] and the worst possible health state [M5, I5] was 0.18 (compared with 0.12 for utilities derived from EQ-5D).

Table 95: Utility means derived from OAB-q index score for each possible health state

Incontinence frequency level	Micturitions frequency level				
	M1	M2	M3	M4	M5
I1	0.92	0.88	0.85	0.84	0.82
I2	0.89	0.85	0.83	0.81	0.79
I3	0.87	0.83	0.80	0.78	0.77
I4	0.85	0.81	0.79	0.77	0.75
I5	0.84	0.80	0.78	0.76	0.74

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide details.

As recommended by NICE, the utilities based on EQ-5D were used to estimate utilities for the base case analysis. However, it has been argued that the EQ-5D instrument may be insufficiently sensitive to OAB symptoms. This led to the development of another preference-based disease-specific measure of utility (OAB-5D) by Yang et al (104) derived from the Overactive Bladder Questionnaire (OAB-q). OAB-5D utilities were found to be similar to EQ-5D utilities for the most severe health states, but higher than EQ-5D utilities for less severe health states. A sensitivity analysis was run using these OAB-5D derived utilities.

In SCORPIO, ARIES and CAPRICORN, patients (n=4,394) completed both the EQ-5D and the OAB-q (from which the OAB-5D is derived) every 4 weeks. The data was pooled and utilities based on OAB-5D and EQ-5D were estimated by level of severity for three types of symptoms: micturitions, incontinence and urgency.

Utility scores of EQ-5D and OAB-5D were first described as means and standard deviations, in overall population and by level of symptom (Table 96). The Pearson correlation between EQ-5D and OAB-5D utilities was estimated. For each type of symptom, a linear regression was used to estimate EQ-5D and OAB-5D utilities by symptom level, adjusting for gender, age, and geographical region. The correlation between utility values for one individual at different assessment visits was taken into account by means of a random patient effect. Using a similar method, differences between OAB-5D and EQ-5D utilities were estimated by symptom level, and tested for the null hypothesis of equal mean OAB-5D and EQ-5D utilities.

In addition, linear models, predicting mean OAB-5D and EQ-5D utilities according to severity levels of the three symptoms, with adjustment on gender and age, were created. The purpose of this model was to provide a way to derive utilities from the micturition diary data, which were collected in the clinical studies.

Table 96: Utility scores of EQ-5D and OAB-5D instruments according to levels of symptoms

Clinical symptom†	Symptom levels	Level definition	% patients	Utility mean (±SD)	Utility mean (±SD)
				EQ-5D	OAB-5D
Micturitions	1	< 8	21.2	0.85 (±0.21)	0.90 (±0.08)
	2	8 - <=10	30.7	0.84 (±0.20)	0.87 (±0.09)
	3	10 - <=12	22.7	0.82 (±0.21)	0.85 (±0.09)
	4	12 - <= 14	13.2	0.80 (±0.22)	0.82 (±0.09)
	5	> 14	12.3	0.78 (±0.23)	0.80 (±0.09)

Incontinence episodes	1	0	50.3	0.85 (±0.19)	0.89 (±0.08)
	2	> 0 - <= 1	19.7	0.82 (±0.20)	0.85 (±0.09)
	3	1 - <=2	11.0	0.80 (±0.22)	0.83 (±0.09)
	4	2 - <=3	6.9	0.78 (±0.23)	0.81 (±0.09)
	5	> 3	12.2	0.76 (±0.26)	0.79 (±0.09)
Urgency Grade 3 episodes	1	<1	23.7	0.86 (±0.19)	0.90 (±0.08)
	2	1 - <=3	30.3	0.83 (±0.21)	0.87 (±0.09)
	3	3 - <=5	21.6	0.81 (±0.22)	0.84 (±0.09)
	4	5 - <= 7	11.7	0.81 (±0.22)	0.82 (±0.09)
	5	> 7	12.7	0.78 (±0.24)	0.80 (±0.09)

Abbreviations: EQ-5D, European quality of life – five dimensions; OAB-5D, overactive bladder – five dimensions; SD, standard deviation.
†Clinical symptoms are measured per 24 hours.

Finally, as a test of sensitivity of the instruments, utility changes from baseline to week 12 were estimated according to response in symptoms, defined as 3 possible items: “improvement higher than 1 level of symptoms”, “stable” or “worsening higher than 1 level of symptoms”. A linear model, with the co-variables of gender, age and response as fixed effects, and geographical region as random effect, was created to provide adjusted means (SD) of utility changes from baseline to week 12 by response level.

HRQL studies

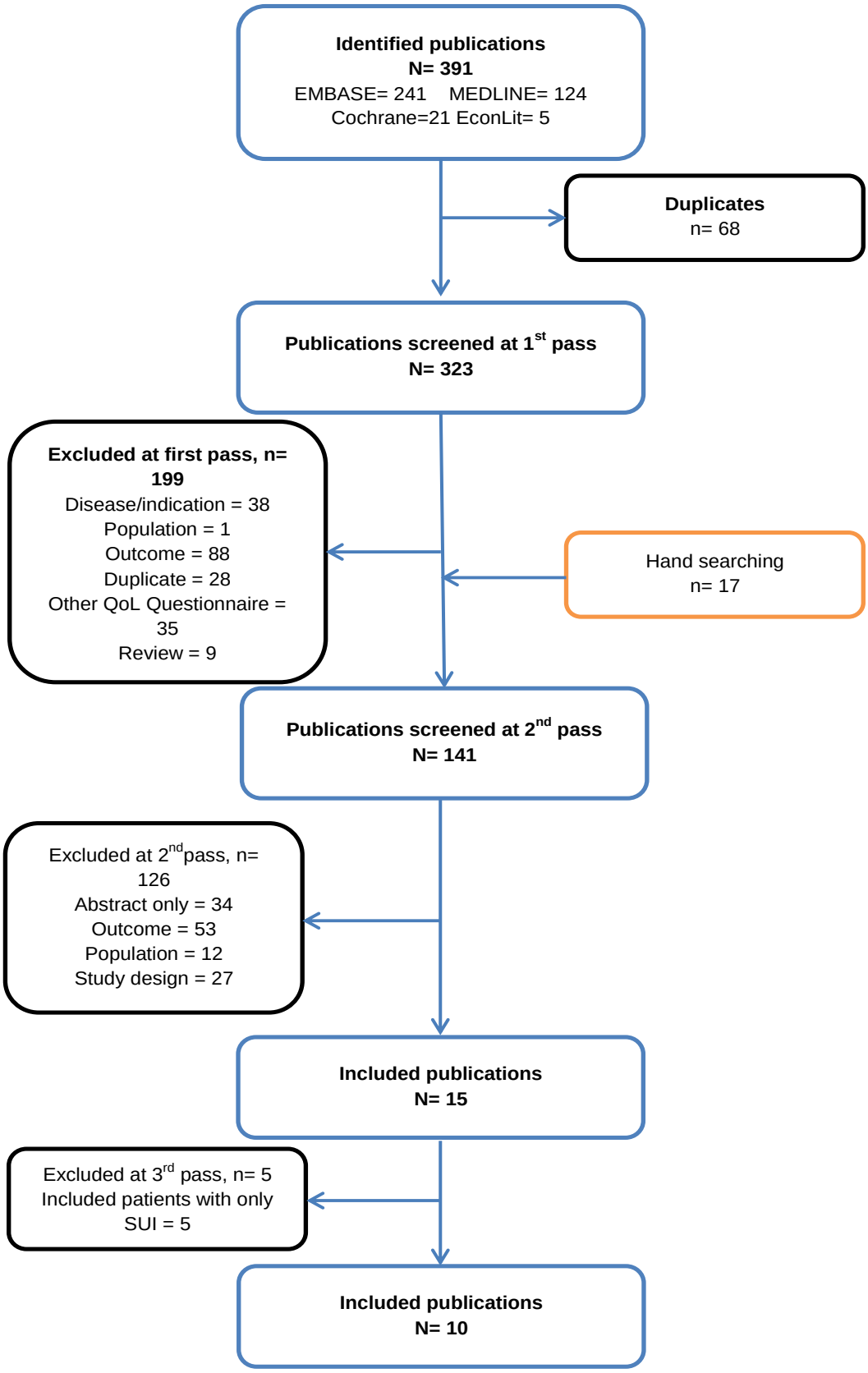
7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

A literature review was conducted to identify references for utility values in OAB. Using Boolean operators, the searches combined terms (including MeSH headings as appropriate) for OAB and QoL. The search strategy is provided in Section 10.12. This was supplemented by hand searching the bibliographies of relevant systematic review articles of the last three years, searching references of included studies, and by searching relevant NICE technology appraisal data.

7.4.6 Provide details of the studies in which HRQL is measured.

A total of 391 publications were identified through the systematic review (Figure 37). After duplicates were excluded and after exclusion at first (based on title/abstract) and second (based on full publication) pass, 15 publications met the inclusion criteria for the QoL SR, including one mapping study. In order to retain the most relevant studies for review, on third pass, a further five publications were excluded as they included patients with only stress urinary incontinence (SUI), which does not fit the specific population outlined in the scope.

Figure 37: Schematic for the systematic review of QoL evidence



An overview of the 10 included studies is provided in Table 97.

Table 97: Included studies from QoL systematic review of EQ-5D health state utility values

Study	Country	Sample size	Population	Elicitation and valuation	Health state description	Follow-up time period (s)for health state; Utilities, mean (SD)	EQ-5D Scale
Coyne 2008 (12)	Multinational	1,434	Men and women aged ≥18 with OAB from EPIC study	EQ-5D questionnaires administered during EPIC study. Health states valued using UK weights.	SG1, Continent OAB; (i) must have urgency but might also have additional storage symptoms, including frequency and/or nocturia, but no UI (ii) no voiding symptoms; and (iii) no post micturition symptoms	One point in time only; 0.9	(-0.0153- 1.0)
					SG2, OAB with UI; (i) must have urgency or UUI but might also have additional storage symptoms, including frequency and nocturia, and any UI, including general UI, UUI, SUI, or MUI; (ii) no voiding symptoms; and (iii) no post micturition symptoms	One point in time only; 0.9	(-0.0153- 1.0)
					SG3, OAB + post micturition; (i) must have urgency or UUI but might also have additional storage symptoms, including frequency, nocturia and/or UI; (ii) must have post-micturition symptom(s); and (iii) no voiding symptoms.	One point in time only; 0.9	(-0.0153- 1.0)
					SG4, OAB + voiding; (i) must have urgency or UUI but might also have additional storage symptoms, including frequency, nocturia, and/or UI; (ii) must have voiding symptom(s); and (iii) no post micturition symptoms.	One point in time only; 0.8	(-0.0153- 1.0)
					SG5, OAB + post micturition + voiding: (i) must have urgency or UUI but might also have additional storage symptoms, including frequency, nocturia, and/or UI; (ii) must have post micturition symptom(s); and (iii)	One point in time only; 0.8	(-0.0153- 1.0)

Study	Country	Sample size	Population	Elicitation and valuation	Health state description	Follow-up time period (s)for health state; Utilities, mean (SD)	EQ-5D Scale
					must have voiding symptom(s).		
					Mean EQ-5D	One point in time only; 0.85	(-0.0153- 1.0)
Currie 2006 (105)	UK	2,193	Study conducted at Cardiff and Vale NHS Trust. Patients identified from academic urology unit inpatient database.	Patients sent postal survey, including the EQ-5D. Source of weights for health states not reported (assumed to be UK weights).	Patients with SUI	One point in time only; 0.57 (0.331)	NR
					Patients with continence problems	One point in time only; 0.764 (0.245)	NR
					Patients with continence problem and SUI	One point in time only; 0.578 (0.333)	NR
					Patients with continence problems other than SUI	One point in time only; 0.625 (0.317)	NR
					Patients with frequency problems and SUI	One point in time only; 0.564 (0.338)	NR
					Patients with frequency problems and incontinence	One point in time only; 0.689 (0.277)	NR
					Patients with frequency problems and continence	One point in time only; 0.746 (0.226)	NR
Haywood 2008 (106)	UK	174	This study uses data from a clinical trial of women with UI	Participants completed baseline EQ-5D questionnaire in clinic setting before randomisation. Follow-up questionnaires mailed at 6 weeks and 5 mo. Source of weights for health states not reported (assumed to be UK weights).	Patients with no incontinent episodes at baseline	Baseline - 0 mo; 0.85 (0.24)	(-0.59-1.0)
					Patients with incontinent episodes a few days a week	Baseline - 0 mo; 0.85 (0.16)	(-0.59-1.0)
					Patients with incontinent episodes about half the week	Baseline - 0 mo; 0.81 (0.20)	(-0.59-1.0)
					Patients with incontinent episodes most days	Baseline - 0 mo; 0.79 (0.23)	(-0.59-1.0)
					Patients with incontinent episodes every day	Baseline - 0 mo; 0.75 (0.32 NS)	(-0.59-1.0)
					From total population- patients that experienced a patient-perceived benefit from physiotherapy	6 weeks; 0.85 (0.23) 5 mo; 0.85 (0.24)	(-0.59-1.0)
					From total population- patients that did not experience a patient-perceived benefit from physiotherapy	6 weeks; 0.73 (0.31) 5 mo; 0.74 (0.38)	(-0.59-1.0)
Tincello 2010 (107)	Multinational	3,739	Women seeking treatment for SUI	Participants identified during the course of a routinely occurring visit and completed the EQ-	Incontinence episode frequencies (≤ 7 per week)	One point in time only; 0.86 (0.18) [Median 0.85]	NR
					Incontinence episode frequencies (7-13 per week)	One point in time only; 0.81 (0.21) [Median 0.80]	NR
					Incontinence episode	One point in time only;	NR

Study	Country	Sample size	Population	Elicitation and valuation	Health state description	Follow-up time period (s)for health state; Utilities, mean (SD)	EQ-5D Scale
				5D. Health states valued using UK weights.	frequencies (≥ 14 per week)	0.74 (0.26) [Median 0.8]	
					Socioeconomic status: In workforce	One point in time only; 0.85 (0.19) [Median 0.85]	NR
					Socioeconomic status: Other	One point in time only; 0.75 (0.25) [Median 0.80]	NR
					Comorbidity affecting HRQoL (No)	One point in time only; 0.86 (0.19) [Median 0.85]	NR
					Comorbidity affecting HRQoL (Yes)	One point in time only; 0.74 (0.25) [Median 0.80]	NR
					Comorbidity affecting UI (No)	One point in time only; 0.82 (0.22) [Median 0.85]	NR
					Comorbidity affecting UI (Yes)	One point in time only; 0.75 (0.25) [Median 0.8]	NR
					Previous surgery (Yes)	One point in time only; 0.76 (0.24) [Median 0.8]	NR
					Previous surgery (No)	One point in time only; 0.79 (0.24) [Median 0.8]	NR
					MUI/UUI	One point in time only; 0.75 (0.25) [Median 0.8]	NR
					Pure SUI	One point in time only; 0.85 (0.2) [Median 0.85]	NR
					Pure UUI	One point in time only; 0.81 (0.18) [Median 0.8]	NR
Verheggen 2012 (108)†	Multinational	Male sub-set of 12,796 (LUTS related to both BPH and OAB) from the EpiLUTS study in US, Sweden and UK	Basis for statistical model was male sub-set from a cross-sectional, population based in which 30,000 men and women reported on occurrence of individual LUTS during previous	SF-12 and disease-specific questionnaires. Relationship between SF-12 and condition-specific measures was estimated. SF-12 converted to EQ-5D using published algorithms. Health states valued using UK weights.	Combination	Baseline - 0 mo; 0.578 3 mo; 0.71 12 mo; 0.716	NR
					Tamsulosin	Baseline - 0 mo; 0.578 3 mo; 0.683 12 mo; 0.693	NR
					Tolterodine	Baseline - 0 mo; 0.578 3 mo; 0.691 12 mo; 0.703	NR
					Placebo	Baseline - 0 mo; 0.578 3 mo; 0.657 12 mo; 0.671	NR

Study	Country	Sample size	Population	Elicitation and valuation	Health state description	Follow-up time period (s)for health state; Utilities, mean (SD)	EQ-5D Scale
			4 weeks				
Sut 2012 (109)	Turkey	109/280 women had OAB (38.9%)	Women who visited outpatient gynaecology and obstetrics unit	Source of weights for health states not reported	Female patients with OAB, aged <60	One point in time only; 0.7 (0.19)	NR
					Female patients with OAB, aged ≥60	One point in time only; 0.6 (0.21)	NR
					Female patients with OAB, BMI <30	One point in time only; 0.68 (0.18)	NR
					Female patients with OAB, BMI ≥30	One point in time only; 0.68 (0.22)	NR
					Presence of any systemic illness (No)	One point in time only; 0.73 (0.17)	NR
					Presence of any systemic illness (Yes)	One point in time only; 0.6 (0.21)	NR
					Menopause (Yes)	One point in time only; 0.64 (0.21)	NR
					Menopause (No)	One point in time only; 0.75 (0.15)	NR
					Female patients with OAB	One point in time only; 0.68 (0.2)	NR
Kobelt 2003 (110)	Sweden	203	Patients with frequent night-time voiding. 30% in control and 27% in nocturia group reported diseases unrelated to the urinary system, with only 3 in the nocturia group reporting >1 disease. Most patients reporting other diseases had mild asthma,	Survey advertised in regional newspapers and by radio. Subjects with frequent night-time voiding invited to contact Department of Urology, Lund University Hospital. Participants completed EQ-5D. Source of weights for health states not reported.	Individuals with nocturia	One point in time only; 0.81 (0.17)	NR

Study	Country	Sample size	Population	Elicitation and valuation	Health state description	Follow-up time period (s)for health state; Utilities, mean (SD)	EQ-5D Scale
			heart disease or diabetes. 44 individuals with nocturia also reported day-time SUI.				
Harvie 2010 (111)	United States	260	260 consecutive new women presenting to a urogynecology practice with symptoms of pelvic organ prolapse or UI. 187 (72%) had UI while 73 (28%) did not. Among women with UI, 77 (41%) had stress/stress-predominant incontinence and 85 (46%) had urge/urge-predominant incontinence	Women completed EQ-5D questionnaire. Source of weights for health states not reported (assumed to be UK weights).	Women with UUI	One point in time only; 0.71 (0.26)	NR
					Women with SUI	One point in time only; 0.78 (0.19)	NR
					Women with no incontinence	One point in time only; 0.80 (0.17)	NR
Patterson 2011 (112)	United States	28	Patients included those scheduled for surgery and those needing testing for clarification of	Patients recruited within large academic centre for urodynamic testing to evaluate a diagnosis of UI. Participants completed the EQ-5D.	UI	One point in time only; Median 0.82 (0.26)	(-0.59-1.0)
					Women with urodynamically	One point in time only;	

Study	Country	Sample size	Population	Elicitation and valuation	Health state description	Follow-up time period (s)for health state; Utilities, mean (SD)	EQ-5D Scale
			their LUTS. 21 had urodynamically proven SUI, 6 had UUI, and 1 had MUI	Health states were valued using US weights.	proven SUI	Median 0.83 (0.23)	

Abbreviations: AFS, autologous fascial slings; BMI, body mass index; BPH, benign prostatic hyperplasia; EPIC, European Prospective Investigation into Cancer and Nutrition; EpiLUTS, epidemiology of lower urinary tract symptoms; EQ-5D, European quality of life - five dimensions; HRQoL, health-related quality of life; LUTs, lower urinary tract symptoms; mo, month(s); MUI, mixed urinary incontinence; N/A, not applicable; NHS, National Health Service; NR, not reported; OAB, overactive bladder; SD, standard deviation, SF-12, short form 12; SG, subgroup; SUI, stress urinary incontinence; TVT, tension-free vaginal tape; TVT-O, transobturator vaginal tape inside-out; UI, urinary incontinence; UUI, urge incontinence.
† Study also reports a mapping algorithm: U (EQ-5D) = 0.8243 + 0.0047DF - 0.039NF - 0.0119URG - 0.0494INCO - 0.0082IPSS, R2 = 0.981.

Table 98: Mapping/regression study

Study	Country	Sample size	Population	Elicitation and valuation	Adjusted odds ratio for EQ-5D health state index scores (grouped)
Monz 2007 (113)	Multinational	Final logistic regression model for EQ-5D health state index included 6,978 patients	Patients seeking treatment for UI. Women experiencing moderate (42%), severe (30%) and very severe (17%) UI symptoms.	For regression analyses, patients grouped into UUI, MUI and SUI, according to answers given on Stress and Urge Incontinence Questionnaire. Severity of UI assessed by the validated Sandvik Index, (slight, moderate, severe, very severe).	**Adjusted odds ratios with 95% CI** UI severity (four severity categories††): 1.31 (1.24-1.39) UI subtype (reference MUI): SUI 0.76 (0.69-0.85), UUI 0.89 (0.77-1.02) Nocturia† (1,2, 3, >4) 1.22 (1.17-1.28) Age (for every ten years): 1.06 (1.02-1.11) BMI† (as continuous variable): 1.03 (1.02-1.04) No. of medical conditions†: 1.63 (1.55-1.70) Full-time employment: 0.99 (0.84-1.17) Not employed: 1.27 (1.08-1.48)

Abbreviations: BMI, body mass index; EQ-5D, EuroQoL 5 dimensions; MUI, mixed urinary incontinence; SUI, stress urinary incontinence; UI, urinary incontinence; UUI, urge Incontinence. †ORs for nocturia, BMI, and no. of medical conditions were not clearly reported (i.e. reference case not reported); †† Severity categories: slight, moderate, severe, and very severe.

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Utility values from the clinical trial appear comparable to values in the published literature in general. The utility values produced using data from SCORPIO are more detailed than those available in the published literature as severity is taken into account. Many of the patient populations reported in the literature contain mixed populations hindering direct comparison with the clinical trial data. Given the general comparability of utility values reported in the literature and the clinical trial and taking into account NICE's preference for patient reported data, utility data from the clinical trial were used in the economic model.

The HRQoL associated with the number of micturitions and incontinence episodes per 24h were each broken down into five levels of severity. The model assumes that the average numbers of micturitions and incontinence episodes within each level are the same for all treatments and are constant over time.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

The treatment-related AEs considered in the model are dry mouth and constipation. These adverse events have been shown to be most bothersome for patients (24), and are therefore most likely to have an impact on quality of life.

Within the 52 week safety study TAURUS, the overall incidence of TEAEs was similar across the mirabegron 50 mg (59.7%), mirabegron 100 mg (61.3%) and tolterodine (62.6%) treatment groups. Most TEAEs were mild or moderate in severity in all treatment groups, and the incidence of mild or moderate TEAEs was comparable across all treatment groups. It was therefore assumed that modelling additional AEs would add unnecessary complication to the health economic model

Patients with AEs may stay on treatment, in which case they will incur an associated disutility. They have an increased probability of discontinuation, and can change treatment. Both dry mouth and constipation have a direct impact on HRQoL and are associated with increased probability of switch or discontinuation. See Section 7.2.2 for further details.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in Sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

A summary of the utility values used in the model are outlined in Section 7.4.3.

The choice of utility values in the model was driven by the NICE reference case where patient reported utility values are preferred. The utility values in the model are tested in sensitivity analysis by varying the coefficients in the regression analysis reported in Section 7.4.3.

Utility decrements for AEs were also derived from SCORPIO. They were derived from a repeated regression model on EQ-5D utility, with AE occurrence since last visit (0/1) as predictor variable, adjusting on gender, age and severity of symptoms (incontinence, urgency, micturition), and random effect on geographical region. Significant difference in utility between patients who reported dry mouth or constipation AE, and those who did not

report such AE was found. The utility decrement of having AE is estimated at -0.0357 according to the described model. It was fealt appropriate to calculate adverse event utilities using this repeated regression model, however it should be noted that utility decrements for AEs derived from the regression model used to calculate health state utilities elicited a near identical figure of -0.03558.

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide details.

No clinical experts were consulted.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Utility values in each month were dependent on symptom levels (micturitions and incontinence) and AEs. A utility decrement was applied for AEs over the full duration of a cycle (month) for patients who stayed on treatment despite experiencing AEs. No utility decrement was applied in cases of immediate discontinuation.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Health effects of urgency and nocturia have been excluded from the model. Urgency is defined as a sudden and compelling need to pass urine, while nocturia is the need to get up at least once during the night to empty the bladder.

Urgency is subjective in nature, and within clinical trials it is measured using varying instruments, and with alternative different severity thresholds, making comparisons difficult and potentially adding considerable uncertainty to the analyses. Therefore it was considered appropriate to exclude urgency from the model.

Nocturia has multiple aetiologies and is multi-factorial in nature and therefore may not just be related to OAB. It has therefore been excluded from the model, consistent with previously published models (86, 87, 89-94).

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQoL is assumed to be dependent on the health state and probability of experiencing AEs, both of which can change over time as detailed in Section 7.3.3.

7.4.15 Have the values in Sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Not applicable.

7.5 Resource identification, measurement and valuation

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to Section 2.

The cost of an outpatient specialist urology follow-up visit was taken from the NHS payment by results (PbR) tariff, 2010-2011.

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

There is little difference between the PbR tariff (£96) and the NHS reference cost (£91). Less specialist outpatient visits are expected for patients treated with mirabegron than the antimuscarinics and therefore use of the PbR tariff provides a conservative estimation of costs for comparators.

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in Section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources.

Seven costing studies (Table 99) were identified through the systematic review detailed in Section 7.1. None of these studies were conducted in the UK and are therefore not relevant to this submission.

Table 99: Costing studies identified through economic systematic review

Reference	Country	Study objective
Altman 2009 (114)	Sweden	National analysis of utilisation and costs associated with the pharmacological treatment for OAB
Jumadilova 2006 (115)	USA	Costs related to comorbidities associated with OAB
Nitz 2005 (116)	USA	To compare post-treatment medical costs for OAB patients when treatment is one of the following: oxybutynin IR, tolterodine ER and oxybutynin ER.
Noe 2002 (117)	USA	To compare the estimated first-line treatment costs of tolterodine ER vs oxybutynin CR in patients with OAB
Perfetto 2005 (118)	USA	To compare 1 year healthcare costs for OAB patients treated with oxybutynin ER vs tolterodine ER in a cost minimisation model
Varadharajan 2005 (119)	USA	To examine the economic impact of oxybutynin IR, tolterodine ER and oxybutynin ER among commercially insured
Zinner 2008 (120)	USA	Resource use and work productivity for patients switching from tolterodine ER to solifenacin

Abbreviations: CR, controlled-release; ER, extended-release; IR, immediate-release; OAB, overactive bladder.

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide details.

Details on collection of expert opinion has previously been described in Section 7.3.5.

The number of botulinum toxin reinjections, following success of first injection was based on expert opinion, which estimated one every 6 months (modelled as 0.17 per month). The number of GP consultations was based on expert opinion, which was estimated to be 1 visit at the start and at every switch.

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to Sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in Section 7.2.2.

It was assumed that patients used one tablet per day of mirabegron, tolterodine or solifenacin, for each day of every month until discontinuation. The analyses do not account for drug wastage or partial compliance.

Table 100: Model inputs: Monthly OAB medication costs

OAB medication	Base case value†	Source‡
Mirabegron 50 mg	£29.40	Astellas £29.00 for 30 tablets
Tolterodine 4 mg ER	£28.01	BNF 63 £25.78 for 28 tablets
Solifenacin 5mg	£28.00	BNF 63 £27.62 for 30 tablets
Solifenacin 10 mg	£36.41	BNF 63 £35.91 for 30 tablets
Trospium chloride 60 mg MR	£25.04	BNF 63 £23.05 for 28 tablets
Fesoterodine 4 or 8 mg	£28.01	BNF 63 £25.78 for 28 tablets
Oxybutynin 10 mg ER	£27.92	BNF 63 £27.54 for 30 tablets
Oxybutynin 10 mg IR	£8.40	BNF 63 £11.60 for 84 tablets of 5 mg

Abbreviations: BNF, British National Formulary; ER, extended-release; IR, immediate-release; mg, milligram; MR, modified-release.
†Considering (365/12) days per month, ‡Costs for OAB medications in BNF 64, September 2012 have remained the same.

Assumptions concerning frequency of GP visits, specialist visits and botulinum toxin reinjections are summarised in Table 101. These assumptions are based on expert opinion. No allowance was made for any resource directly associated with management of AEs, except that AEs may lead to referrals to specialist in case of switch.

Table 101: Model inputs: resource utilisation (physician visits and botulinum toxin reinjections)

Parameter	Base case	Sensitivity analysis values	Sources
Number of GP consultations	1 visit at the start and at every switch	0 - 2	Cardozo 2010 (87) / Assumption
Number of specialist consultations	1.5 visits at the start and at every switch	1 - 3	Cardozo 2010 (87) / Assumption
Number of botulinum toxin reinjections, following success of first injection	0.17 per month (2 per year)	0 – 0.34	Expert opinion (Once every 6 months)

Abbreviations: GP, general practitioner.

Pad utilisation

The numbers of pads used per day by severity level of incontinence were obtained from SCORPIO. The mean number of pads used per day at baseline was calculated by severity level, for all treatments grouped, in the general OAB population for base case analysis. Mean number of pads used per day were then multiplied by 365/12 to get monthly numbers.

Table 102: Model inputs: Pad use per day by level of incontinence

Incontinence severity level	Base case (all patients)	Sensitivity analysis (95% CI)	Sources
1	0.17	0.150 – 0.198	SCORPIO
2	0.75	0.687 – 0.817	
3	1.38	1.282 – 1.486	
4	1.89	1.745 – 2.039	
5	3.34	3.167 – 3.511	

Abbreviations: CI, confidence interval.

Unit costs of other resources used in OAB patients are summarised in Table 103.

Table 103: Model inputs: unit costs of health care resources

Parameter	Base case value	Sources
GP consultation	£36	PSSRU 2011
Specialist visit: Follow-up visit	£96	NHS Payment 2010-2011
Botulinum toxin injection: Initial / Reinjections	£1158/£964	Nottingham Urology Group†
Incontinence pad (per pad)	£0.16	AgeUK incontinence

Abbreviations: GP, general practitioner.

†http://www.nottinghamurologygroup.co.uk/treatments/bladder-botulinum toxin-injections

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in Section 7.2.4.

Not applicable.

7.5.7 Please summarise the costs for each adverse event listed in Section 6.9 (Adverse events). These should include the costs of therapies identified in Section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in Section 7.2.2.

We did not allow for any resource directly associated with management of AEs, except that AEs may lead to referrals to specialist in case of switch.

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

None.

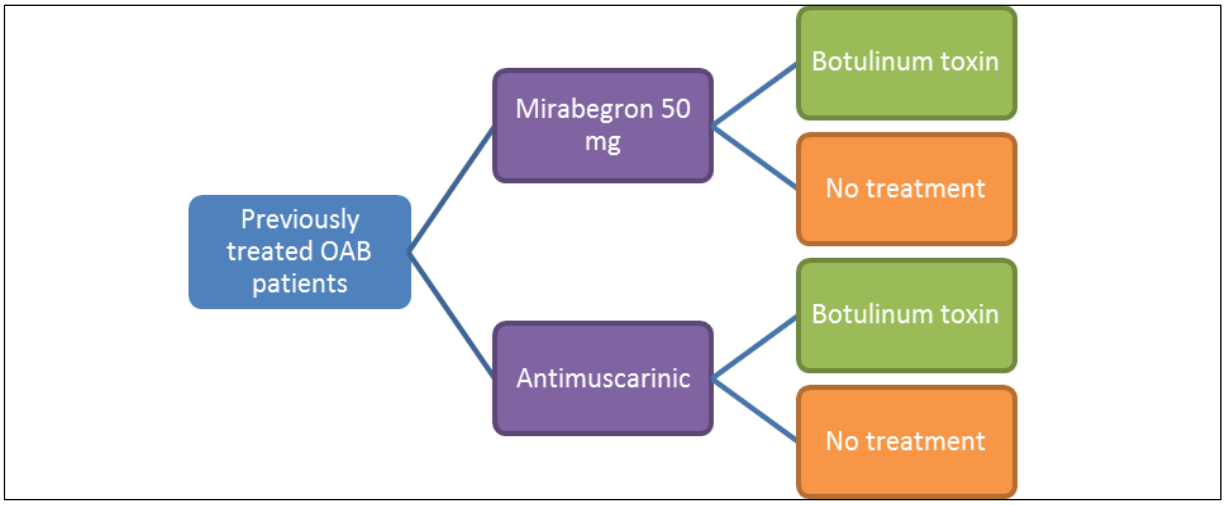
7.6 Sensitivity analysis

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

Sensitivity analyses were conducted to evaluate the impact of structural assumptions on the model outputs.

For previously treated patients, the treatment pathways are simplified as depicted in Figure 38. It was assumed that patients would not receive further pharmacological therapy after stopping mirabegron or comparator antimuscarinic. Therefore, their options would be restricted to botulinum toxin and “no treatment”.

Figure 38: Treatment pathway for previously treated subgroup



A sensitivity analysis was also conducted on the time horizon of the model. The model was computed for additional time horizons of 1, 2 and 10 years.

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in Section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Sensitivity analyses were implemented to evaluate the impact of assumptions used in the model and variability surrounding several model inputs on cost-effectiveness results. Deterministic sensitivity analyses were performed initially, changing one variable or assumption at a time and reporting the results. One-way sensitivity analyses were conducted on all parameters of the model surrounded with uncertainty, namely: proportions of patients by severity level at baseline, transition probabilities between symptom levels (Beta parameters), utilities by symptom levels (Beta coefficients for EQ-5D and Beta coefficients for OAB-5D), probabilities of treatment-related events (discontinuation, switch), probabilities related of botulinum toxin injections, probabilities of AEs and resource use parameters (GP visit, specialist visit, medication cost, incontinence pad utilisation). Outcomes of the model were computed using the limits of confidence intervals around each parameter or other fixed values. A tornado diagram was generated to represent the sensitivity of results to a change in different parameter assumptions (Figure 48).

Structural sensitivity analyses were also performed. The time-horizon was varied from 1 year to 10 years. In addition, studies have shown that OAB is frequently associated with comorbidities such as fractures, skin infections, UTIs and depression and therefore a scenario analysis taking into account OAB-related comorbidities was conducted.

The monthly probabilities of OAB-related comorbidities depend on the incontinence severity level and are shown in Table 104.

Table 104: Monthly probabilities of OAB-related comorbidities depend on the incontinence severity level

Symptom	Continent level 1	Incontinent level 2	Source
Falls with fractures	0.42%	0.90%	Arlandis-Guzman, 2011 (80)
Depression	0.70%	1.72%	
Skin infection	1.78%	1.55%	
UTI	3.17%	5.12%	

Abbreviations: UTI, urinary tract infection.

Patients with comorbidities will incur a disutility associated with the nature of the comorbidity. Table 105 shows the QALY loss associated with each type of comorbidity.

Table 105: QALY loss associated with comorbidities

Symptom	QALY loss associated with comorbidities	Source
Falls with fractures	-0.239	Peasgood, 2009 (121) First year utility loss
Depression	-0.248	NICE CG90 Oct 2009 (122) Moderate depression patients on citalopram, over 12 months Mean QALY for a moderate depressive patients on citalopram:0.602 Mean QALY for a healthy UK person :0.85
Skin infection	-0.017	Assumption: Utility loss of 0.2 over one cycle.
UTI	-0.024	Barry, 1997 (123) Utility loss of 0.2894 for a day with UTI symptoms, over one cycle

Abbreviations: QALY, quality adjusted life year; UTI, urinary tract infection.

Direct costs of OAB-related comorbidities were included and are shown in Table 106.

Table 106: Direct costs of OAB-related comorbidities

Symptom	Value	Source
Falls with fractures/event	£5,048.00	NHS 2011-12 tariff information
Depression over 12 months	£1,522.00	Moderate depression patients on citalopram (NICE CG90, Oct 2009) (122)
Skin infection/event	£96.00	Assumption: unit cost of a specialist visit
UTI/event	£96.00	Assumption: unit cost of a specialist visit

Abbreviations: UTI, urinary tract infection.

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in Section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

A probabilistic sensitivity analysis (PSA) was programmed to assess uncertainty around cost-effectiveness results. This involved assigning statistical distributions to input parameters with a significant impact on the ICER, identified during deterministic sensitivity analyses. Values are drawn at random from statistical distributions for each of these variables, and the ICER was estimated for this new set of parameters. This process was iterated 5,000 times, providing a statistical distribution for the ICER. Using this approach, a credibility interval for the ICER and a cost-effectiveness acceptability curve were obtained.

The types of distribution and associated parameters used for the PSA are shown in Table 107 to Table 111.

Table 107: Specifications of statistical distributions for proportions of patients by severity level at baseline

Input parameters	Severity level	Distribution type	Percentage	N	Source
Micturition	I	Dirichlet	6.30	120	Base case / PSA: SCORPIO, based on pooled data from the 3 treatment arms at baseline DSA: assumption
	II	Dirichlet	30.69	585	
	III	Dirichlet	27.18	518	
	IV	Dirichlet	19.46	371	
	V	Dirichlet	16.37	312	
Incontinence	I	Dirichlet	38.87	741	
	II	Dirichlet	18.84	359	
	III	Dirichlet	14.64	279	
	IV	Dirichlet	9.18	175	
	V	Dirichlet	18.47	352	

Abbreviations: DSA, deterministic sensitivity analysis; PSA, probabilistic sensitivity analysis.

Table 108: Specifications of statistical distributions for coefficients of logistic models for probabilities of transitions between severity levels

Input parameters	Severity level	Distribution type	Mean	SD	Source
Beta coefficients for mirabegron 50 mg					
Micturition	I -> II	Normal	0.6037	0.1938	Base case / PSA: SCORPIO SA: 95% CI assuming normal distribution
	II -> III	Normal	0.3803	0.179	
	III -> IV	Normal	0.1454	0.1699	
	IV -> V	Normal	0.0665	0.1736	
Incontinence	I -> II	Normal	0.3617	0.1818	
	II -> III	Normal	0.4634	0.1832	
	III -> IV	Normal	-0.0251	0.1934	
	IV -> V	Normal	0.204	0.2122	
Beta coefficients for tolterodine ER 4 mg					
Micturition	I -> II	Normal	0.3667	0.1908	Base case / PSA: SCORPIO SA: 95% CI assuming normal distribution
	II -> III	Normal	0.1826	0.1753	
	III -> IV	Normal	-0.0609	0.1662	
	IV -> V	Normal	0.055	0.1678	
Incontinence	I -> II	Normal	0.1431	0.1765	
	II -> III	Normal	0.1768	0.1787	
	III -> IV	Normal	-0.3271	0.1907	
	IV -> V	Normal	-0.0298	0.2085	
Beta coefficients for solifenacin 5 mg					
Micturition	I -> II	Normal	0.998	0.1908	MTC based on SCORPIO and calibration method (7-step approach defined by Vanni et al. 2011) (97) Initial betas for the calibration were those for mirabegron
	II -> III	Normal	0.493	0.1753	
	III -> IV	Normal	0.038	0.1662	
	IV -> V	Normal	-0.073	0.1678	
Incontinence	I -> II	Normal	1.140	0.1765	
	II -> III	Normal	0.734	0.1787	
	III -> IV	Normal	0.035	0.1907	

Input parameters	Severity level	Distribution type	Mean	SD	Source
	IV -> V	Normal	0.114	0.2085	50 mg

Abbreviations: CI, confidence interval; ER, extended-release; mg, milligram; PSA, probabilistic sensitivity analysis; SA, sensitivity analysis; SD, standard deviation.

Table 109: Specifications of statistical distributions for coefficients of linear models for health state utilities

Input parameters	Severity level	Distribution type	Mean	SD	Source
Micturition	I -> II	Normal	0.06321	0.00914	Base case: SCORPIO SA: CI assuming normal distribution
	II -> III	Normal	0.04224	0.00839	
	III -> IV	Normal	0.02042	0.00810	
	IV -> V	Normal	0.01039	0.00806	
Incontinence	I -> II	Normal	0.05859	0.00834	
	II -> III	Normal	0.04367	0.00844	
	III -> IV	Normal	0.03141	0.00879	
	IV -> V	Normal	0.01282	0.00941	

Abbreviations: CI, confidence interval; SA, sensitivity analysis; SD, standard deviation.

Table 110: Specifications of statistical distributions for resource utilisation parameters

Input parameters	Distribution type	Mean	SD	Source
GP visits (per month)	Lognormal	1	0.5	Base case: Cardozo 2010 (87) SA: Assumption
Specialist visit (per month)	Lognormal	1.5	0.5	Base case: Cardozo 2010 (87) SA: Assumption

Abbreviations: GP, general practitioner; SA, sensitivity analysis; SD, standard deviation.

Table 111: Specifications of statistical distributions for parameters related to discontinuation, switch, AEs and transition to botulinum toxin

Input parameters	Distribution type	Mean	SD	Alpha	Beta	Source
Switch / discontinuation						
Monthly probability of discontinuation with AE	Beta	0.900	0.138	3.384	0.376	Base case/SA: Assumption
Monthly probability of discontinuation without AE Mirabegron	Beta	0.064	0.025	6.002	88.329	Mean: Wagg, 2012 (22) Castro-Diaz, 2010 (98) SD: assumption
Monthly probability of discontinuation without AE Tolterodine	Beta	0.064	0.025	6.002	88.329	
Monthly probability of switch after discontinuation	Beta	0.261	0.070	9.987	28.336	Base case: Odeyemi, 2006 (100) SA: D'Souza, 2008 (101)/ Assumption
Probability of restarting treatment at 1 month	Beta	0.056	0.065	0.648	10.891	Base case/SA: Assumption
AEs						
Probability of having a dry mouth AE on mirabegron 50 mg	Beta	0.028	0.004	47.600	1652.400	Base case/PSA: SCORPIO DSA: 95% CI
Probability of having a dry mouth AE on tolterodine ER 4 mg /	Beta	0.101	0.009	113.118	1006.858	Base case/PSA: SCORPIO DSA: 95% CI

Input parameters	Distribution type	Mean	SD	Alpha	Beta	Source
next line of therapy						
Botulinum toxin injection						
Probability of having botulinum toxin injections at 1 month	Beta	0.001	0.0015	0.310	370.457	Base case and SA: Assumption

Abbreviations: AE, adverse event; CI, confidence interval; DSA, deterministic sensitivity analysis; PSA, probabilistic sensitivity analysis; SA, sensitivity analysis; SD, standard deviation.

7.7 Results

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see Section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over).

Predicted proportions of patients by severity level at 3 months are compared with estimated proportions from SCORPIO in Table 112, for micturitions and incontinence episodes, and for both treatments. Predicted and observed proportions are not identical, which is partly related to the fact that patients were less likely to discontinue in the trial than in the model, since the model aims to reflect persistence in real practice. However, predicted proportions are all within the limits of the 95% confidence intervals around proportions estimated from the trial.

Table 112: Summary of model results compared with clinical data

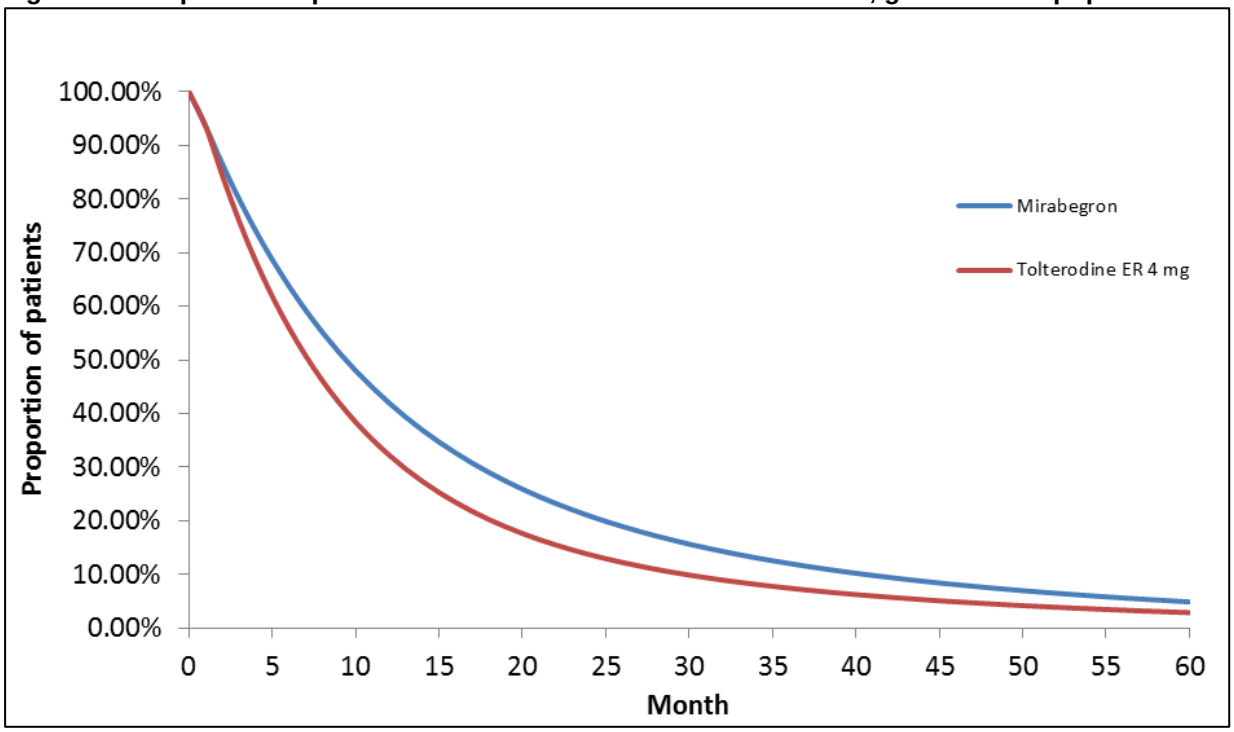
Outcome	Clinical trial result	Model result
Micturition (mirabegron) severity level 1	33.40%	31.70%
Micturition (mirabegron) severity level 2	31.40%	30.20%
Micturition (mirabegron) severity level 3	18.80%	19.90%
Micturition (mirabegron) severity level 4	9.20%	9.10%
Micturition (mirabegron) severity level 5	7.30%	9.10%
Micturition (tolterodine) severity level 1	32.40%	29.60%
Micturition (tolterodine) severity level 2	29.70%	29.40%
Micturition (tolterodine) severity level 3	18.50%	19.30%
Micturition (tolterodine) severity level 4	9.40%	10.80%
Micturition (tolterodine) severity level 5	10.10%	11.00%
Incontinence (mirabegron) severity level 1	62.70%	61.90%
Incontinence (mirabegron) severity level 2	19.00%	19.30%
Incontinence (mirabegron) severity level 3	7.60%	6.90%
Incontinence (mirabegron) severity level 4	4.40%	4.70%
Incontinence (mirabegron) severity level 5	6.40%	7.20%
Incontinence (tolterodine) severity level 1	63.70%	61.40%
Incontinence (tolterodine) severity level 2	17.10%	17.60%
Incontinence (tolterodine) severity level 3	5.90%	6.50%
Incontinence (tolterodine) severity level 4	4.60%	4.90%
Incontinence (tolterodine) severity level 5	8.70%	9.60%

7.7.1.1 Switch/discontinuations

The predicted proportions of patients who switched or discontinued mirabegron or tolterodine over time are presented in Figure 39. The model estimated that 57.82% of patients would switch or discontinue compared with 67.50% on tolterodine at 1 year. At 1 year, 42.00% of

patients remain on mirabegron and 32.28% on tolterodine (including patients who discontinued and restarted mirabegron or tolterodine as they cannot be isolated in the model). At 5 years, 4.90% of patients were still on treatment with mirabegron, compared with 2.88% on tolterodine.

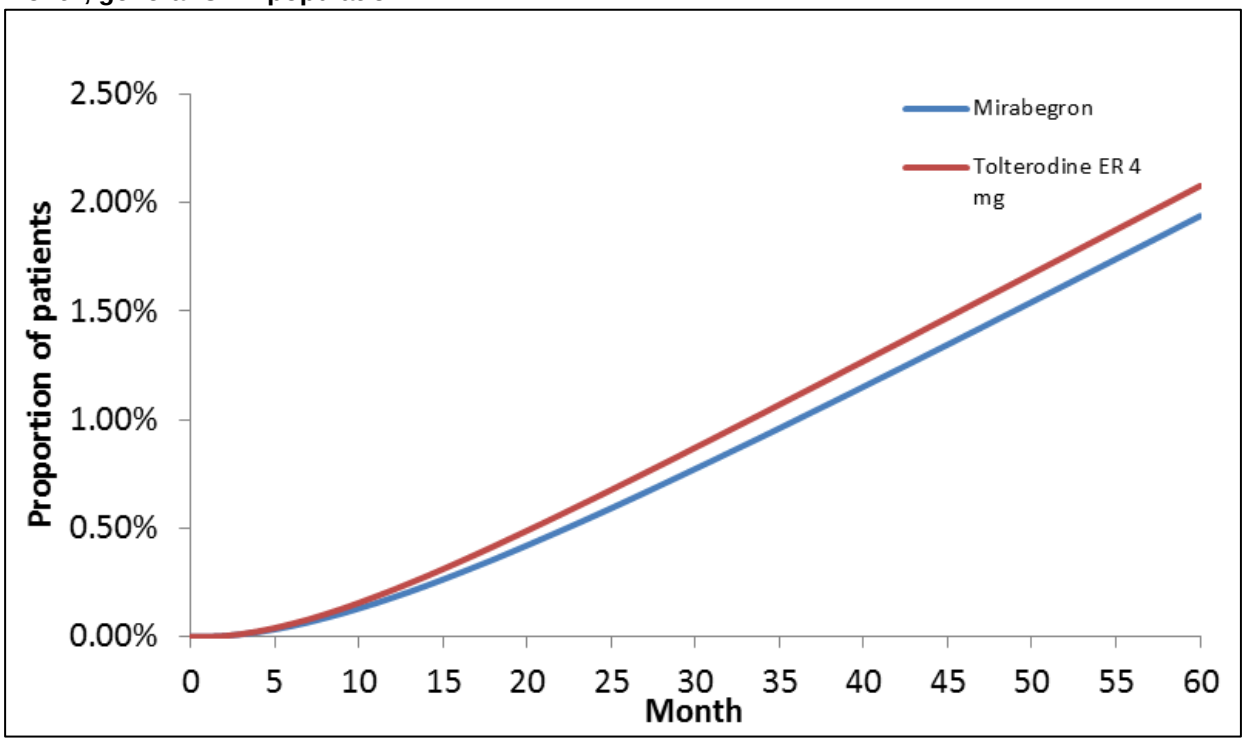
Figure 39. Proportion of patients who are under treatment of interest, general OAB population



7.7.1.2 Patients on botulinum toxin

The predicted proportions of patients receiving initial botulinum toxin injection or continuing botulinum toxin (receiving repeated botulinum toxin injection or between injections, i.e. those patients for whom botulinum toxin is successful) by treatment over time are presented in Figure 40. The model predicted that 1.94% of patients receiving mirabegron would be treated with botulinum toxin at 5 years, compared with 2.08% of patients receiving tolterodine.

Figure 40. Proportion of patients with botulinum toxin injection or between injections by month, general OAB population



7.7.1.3 Adverse events

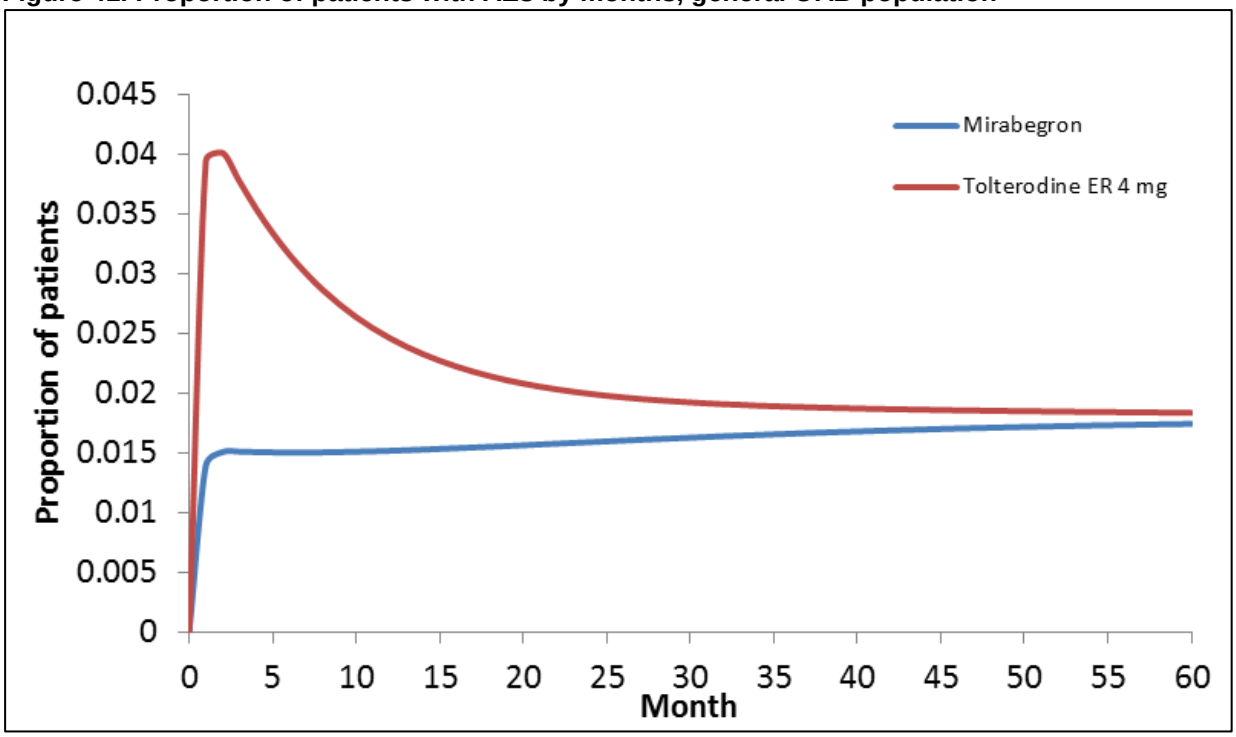
Two types of AEs were considered in the model: dry mouth and constipation.

The model includes specific health states for patients with AEs, but different AEs are not separated into different health states, as this would increase the complexity of the model, and it would be a problem to represent patients with several side-effects. Therefore, the probability of discontinuation associated with AEs in any given health state was an aggregate probability calculated from probabilities of discontinuation associated with different side-effects. Similarly the utility decrement of AEs was an average decrement, weighted according to treatment-specific probabilities of different side-effects (dry mouth and constipation).

Proportions of patients with AEs (model predictions)

The predicted proportions of patients with AE by treatment over time are presented in Figure 41. The proportion of patients experiencing AEs is highest in the first month for patients on tolterodine; it decreases progressively after 1 month as an increasing proportion of patients are without medication. For patients on mirabegron, the proportion of patients with AEs is stable after 1 month: some patients discontinue treatment and are therefore no longer at risk of AEs, but others switch to solifenacin 5 mg, which has a greater risk of AEs than mirabegron.

Figure 41. Proportion of patients with AEs by months, general OAB population



Further information on the predicted proportion of patients by severity level at baseline and every 6 months are presented in Section 10.16. The model predicted that patients treated with mirabegron were more likely to be in severity levels 1 and 2 (i.e. less severe levels) at 12 months, for all symptoms, most notably for micturitions.

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Health states in the model describe the 5 severity levels for micturition and 5 severity levels for incontinence for each of the treatment groups. Therefore there are a large number of health states (25 severity groups) for each treatment line. In order to clearly represent the proportion of the cohort in any health state over time, these severity groups have been disaggregated and presented graphically (Figure 42 to Figure 45).

Figure 42: Markov trace of mirabegron treatment arm by micturition severity level

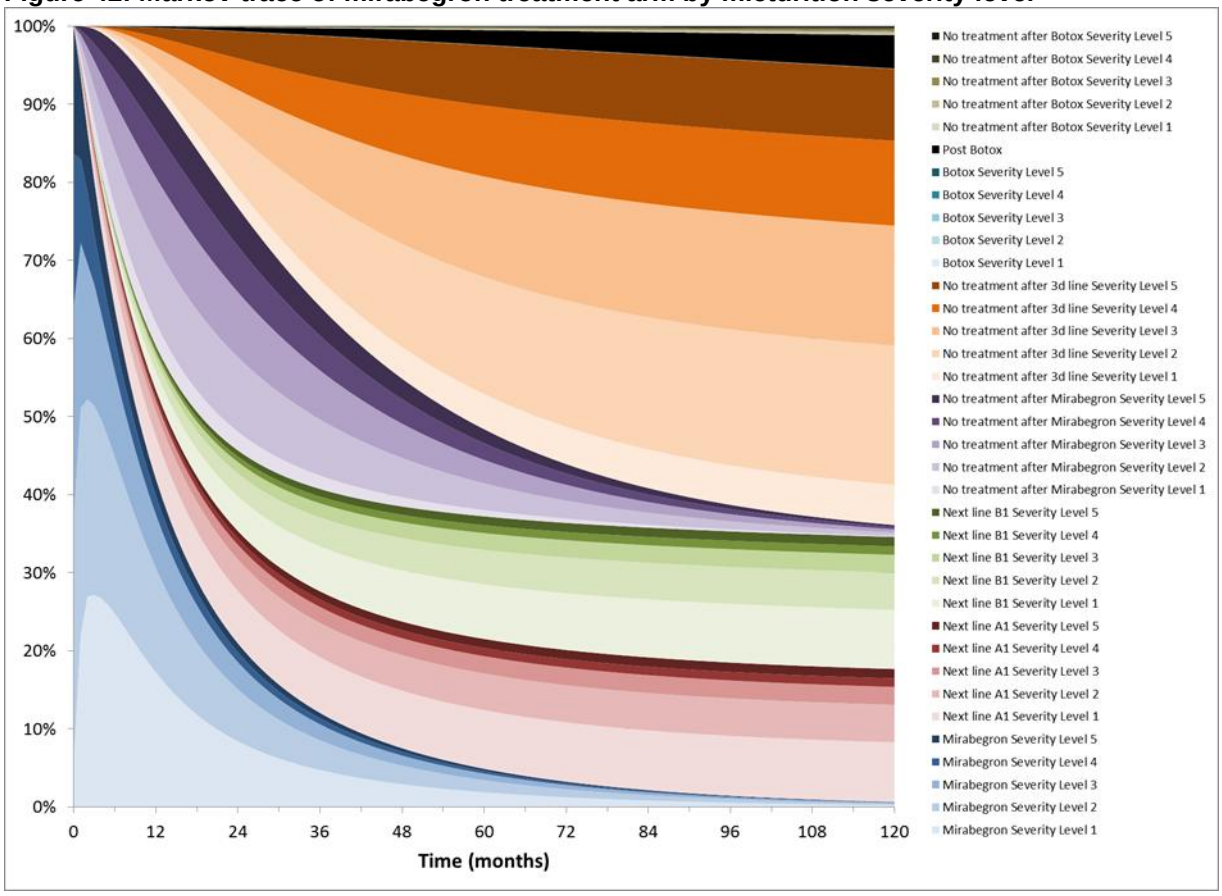


Figure 43: Markov trace of mirabegron treatment arm by incontinence severity level

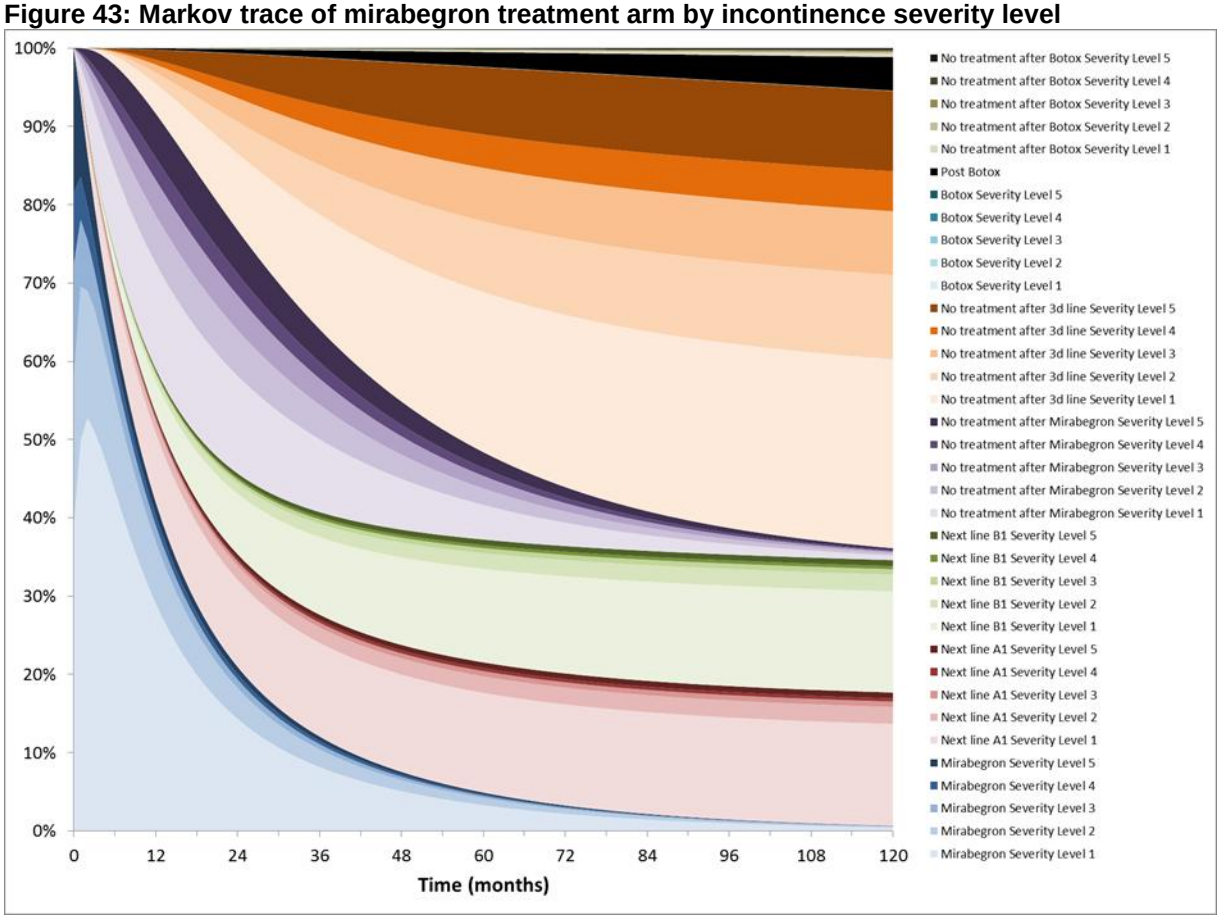


Figure 44: Markov trace of tolterodine treatment arm by micturition severity level

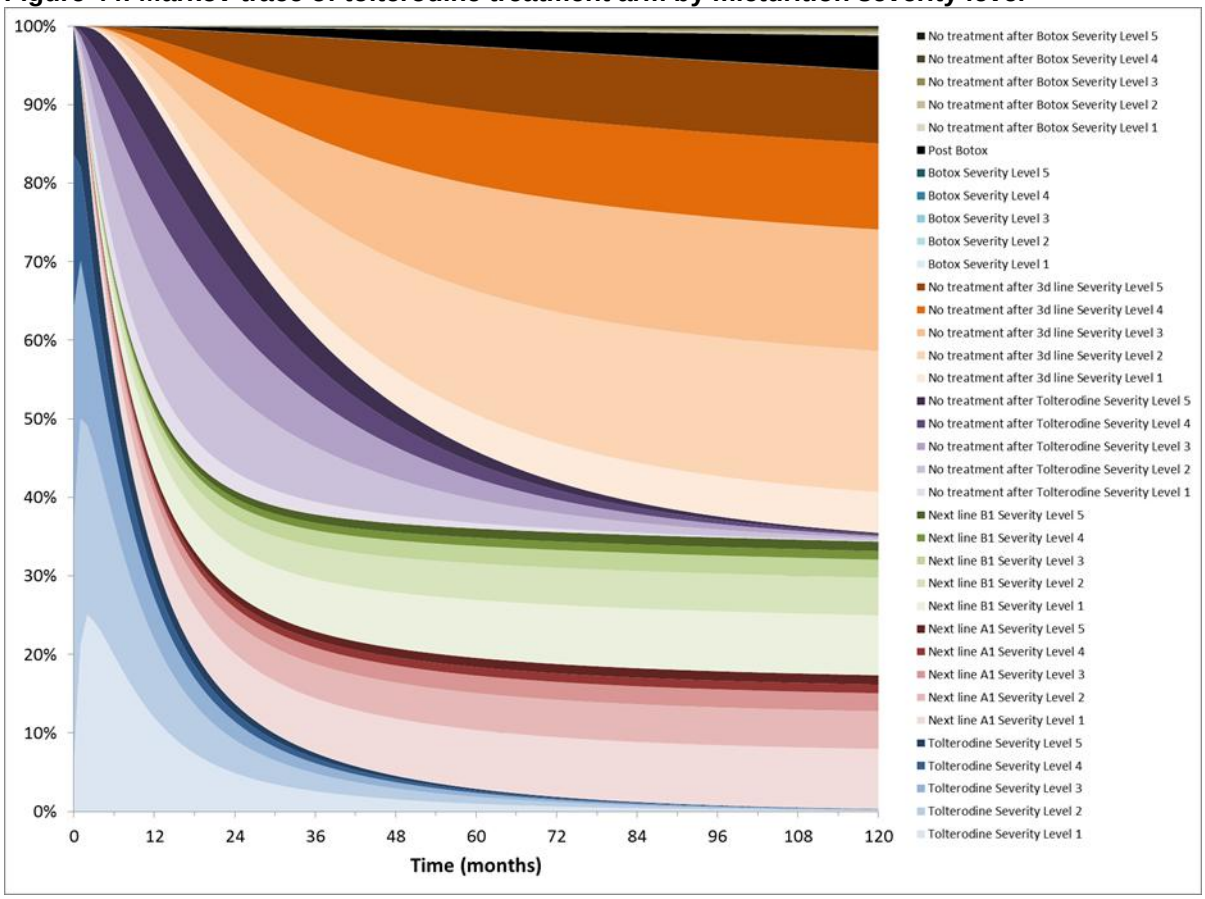
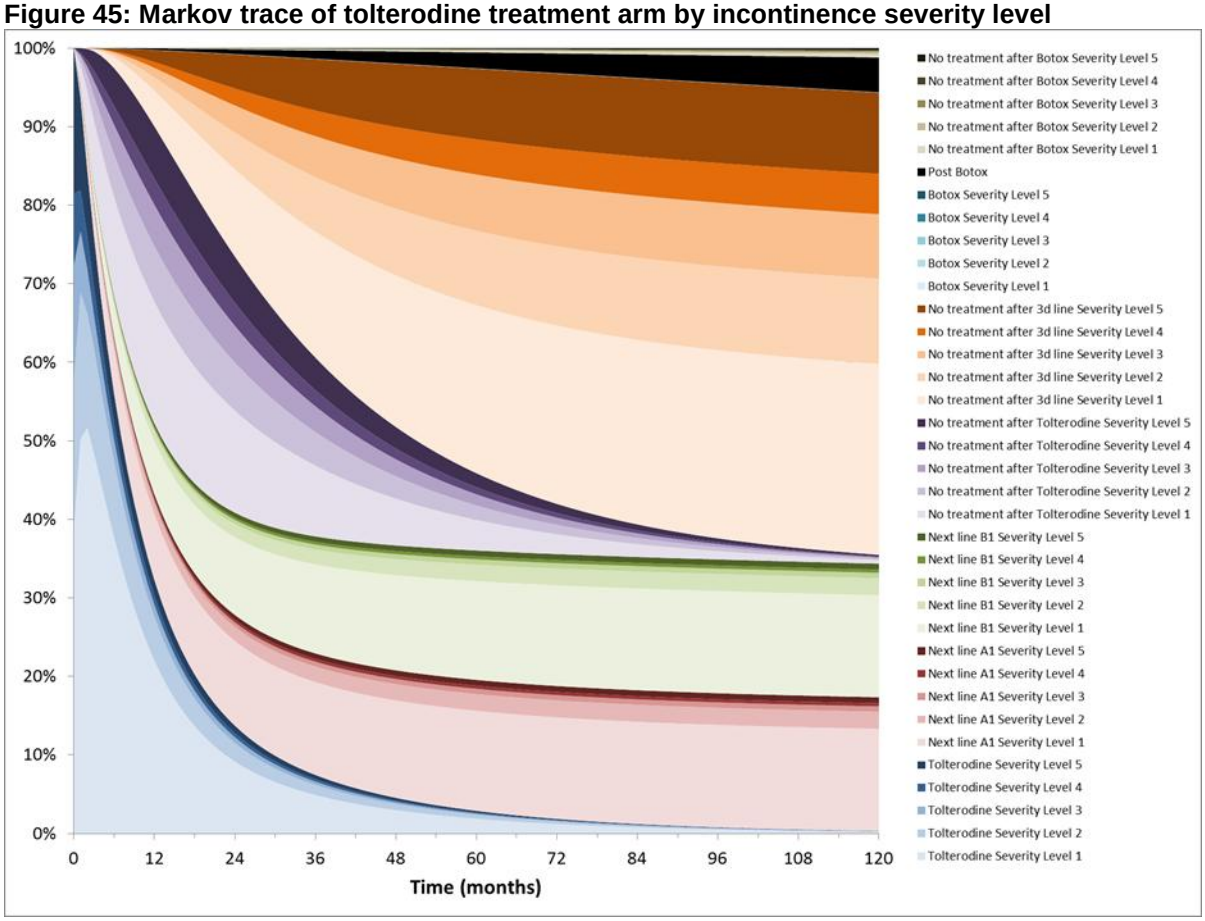


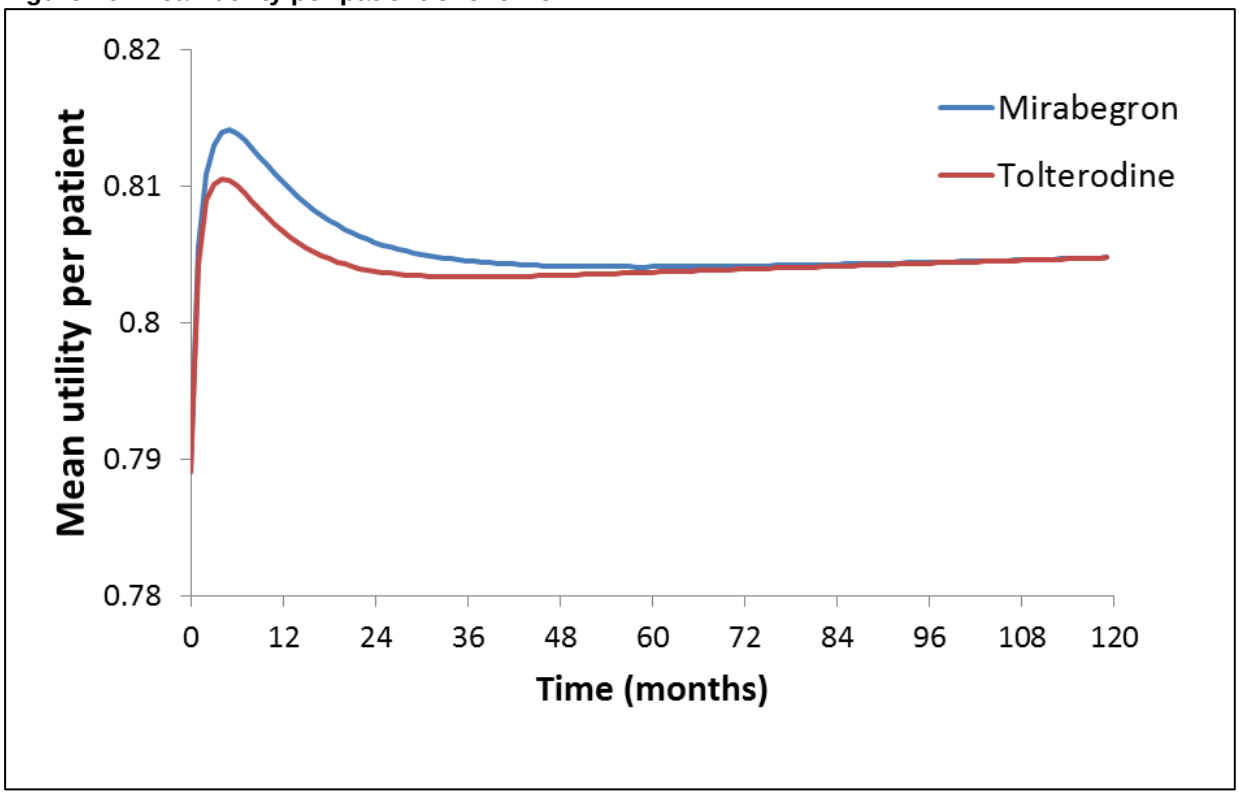
Figure 45: Markov trace of tolterodine treatment arm by incontinence severity level



7.7.3 *Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.*

QALYs accrue over time according to the number of patients in each health state as described in Section 7.7.2. The mean utility per patient is therefore dependent upon the baseline utility of patients with OAB, the number of micturitions and incontinence episodes per month, and the AEs associated with each treatment arm. Figure 46 summarises how QALYs accrue over time by presenting a plot of the mean utility per patient.

Figure 46: Mean utility per patient over time



7.7.4 *Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.*

As described in Section 7.7.2, the model comprises a large number of health states, namely 25 severity groups with and without AEs for each treatment group; therefore it is impractical to provide a summary of all outcomes for each health state. A summary of the disaggregated QALYs by symptom is therefore presented in Table 113, and a summary of disaggregated costs by resource use is presented in Table 114. It should be noted that neither the intervention nor the comparator extend life, therefore the number of life years (Lys) is equal for each health state. A summary of the model outputs, including total costs, total LYs and total QALYs is presented in Table 115.

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost.

Table 113: Summary of QALY gain by health state

Health state	QALY mirabegron	QALY tolterodine	Increment	Absolute increment	% absolute increment
Baseline	3.4005	3.4010	-0.0005	0.0005	3.82%
Micturition severity level 1	0.0735	0.0679	0.0055	0.0055	46.91%
Micturition severity level 2	0.0591	0.0584	0.0007	0.0007	5.88%
Micturition severity level 3	0.0198	0.0200	-0.0002	0.0002	1.95%
Micturition severity level 4	0.0060	0.0065	-0.0004	0.0004	3.73%
Micturition severity level 5	0.0000	0.0000	0.0000	0.0000	0.05%
Incontinence severity level 1	0.1527	0.1497	0.0030	0.0030	25.36%
Incontinence severity level 2	0.0350	0.0341	0.0010	0.0010	8.31%
Incontinence severity level 3	0.0137	0.0140	-0.0003	0.0003	2.72%
Incontinence severity level 4	0.0035	0.0036	-0.0001	0.0001	1.27%
Incontinence severity level 5	0.0000	0.0000	0.0000	0.0000	0.00%
Total	**3.7638**	**3.7552**	**0.0086**	**0.0118**	**100.00%**

Abbreviations: QALY, quality adjusted life year.
Note: figures may not sum due to rounding.

Table 114: Summary of predicted resource use by category of cost

Item	Cost mirabegron	Cost tolterodine	Increment	Absolute increment	% absolute increment
Drug cost	£451.43	£343.70	£107.72	£107.72	46.6%
Other OAB medication	£364.92	£393.42	-£28.50	£28.50	12.3%
Primary care visit	£101.38	£105.83	-£4.45	£4.45	1.9%
Specialist (urology) follow-up visit	£405.53	£423.31	-£17.78	£17.78	7.7%
Initial botulinum toxin injection	£25.50	£27.42	-£1.92	£1.92	0.8%
Repeat botulinum toxin injection	£68.16	£75.36	-£7.19	£7.19	3.1%
Incontinence pads	£228.70	£238.71	-£10.00	£10.00	4.3%
Total	**£1,645.62**	**£1,607.75**	**£37.88**	**£231.10**	**100%**

Abbreviations: OAB, overactive bladder.

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Base case results for the general OAB population using EQ-5D utilities are presented in Table 115. Compared with tolterodine, mirabegron is cost-effective with an ICER of £4,386/QALY gained.

Table 115: Base case results, general OAB population, mirabegron vs tolterodine based on SCORPIO data

Treatment	Total			Incremental			ICER (£) versus tolterodine
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Tolterodine 4 mg	£1,607.75	4.666	3.755	-	-	-	-
Mirabegron 50 mg	£1,645.62	4.666	3.764	£37.88	0	0.00864	£4,386

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; mg, milligram; QALY, quality adjusted life year.

When analysis using the MTC results was performed, mirabegron is cost-effective in all cases. The results of this analysis are presented in Table 116.

Table 116: Base case results, general OAB population, mirabegron vs antimuscarinics, based on MTC results

Treatment	Total			Incremental			ICER (£) versus mirabegron
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Solifenacin 10 mg	£1,647.60	4.666	3.762	£3.53	0	0.0104	£340
Fesoterodine 4 mg	£1,601.40	4.666	3.758	£38.09	0	0.0106	£3,607
Tolterodine 4 mg	£1,601.64	4.666	3.759	£37.85	0	0.0102	£3,715
Oxybutynin 10mg ER	£1,587.06	4.666	3.755	£42.12	0	0.0109	£3,878
Trospium chloride 60 mg MR	£1,551.86	4.666	3.759	£83.89	0	0.0094	£8,881
Solifenacin 5 mg	£1,592.94	4.666	3.768	£58.19	0	0.0047	£12,493
Oxybutynin 10 mg IR	£1,421.00	4.666	3.7516	£208.18	0	0.0146	£14,234

Abbreviations: ER, extended-release; ICER, incremental cost-effectiveness ratio; IR, immediate-release; LYG, life year gained; mg, milligram; MR, modified-release; QALY, quality adjusted life year.

To further explore the cost-effectiveness of mirabegron a full incremental analysis versus comparators is presented below (Table 117).

Table 117: Base case results, general OAB population, mirabegron vs antimuscarinics, incremental analysis using persistence with solifenacine or tolterodine

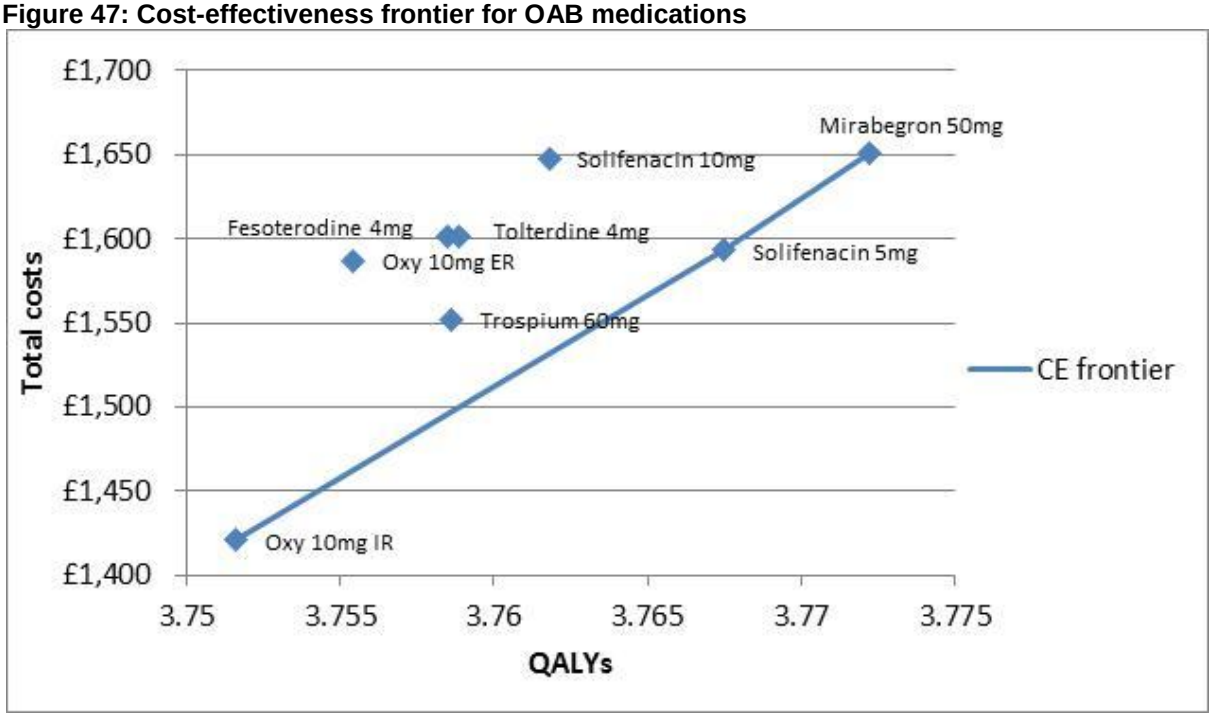
Intervention	Total cost	Total QALYs	Cost	QALYs	ICER (£/QALY) next best
Oxybutynin 10 mg IR	1421.00	3.7516	-	-	-
Trospium chloride 60 mg MR	1551.86	3.7586	Weakly dominated		
Oxybutinin 10mg ER	1587.06	3.7554	Dominated		
Solifenacin 5 mg	1592.94	3.7675	171.94	0.0159	10,813.84
Fesoterodine 4 mg	1601.40	3.7585	Dominated		
Tolterodine 4 mg	1601.64	3.7589	Dominated		
Solifenacin 10 mg	1647.60	3.7618	Dominated		
Mirabegron 50 mg	1651.14	3.7722	58.20	0.0047	12,382.98

Abbreviations: ER, extended-release; ICER, incremental cost-effectiveness ratio; IR, immediate-release; MR, modified-release; QALY, quality adjusted life year.

These results have been interpreted in graphical format (Figure 47). The cost-effectiveness frontier joins the treatments that may be cost-effective (depending on the cost-effectiveness

threshold) – i.e. those that are not dominated by any other treatment by either strict[l] or extended[m] dominance. Treatments that lie above or to the left of the frontier are dominated by those that lie on the frontier and are therefore not cost-effective, regardless of willingness to pay. Figure 47 demonstrates that while mirabegron is more costly than comparators, it delivers more QALYs. Given that all options on the cost-effectiveness frontier are within a willingness to pay threshold of <£20,000 per QALY gained, mirabegron is an efficient use of resources.

Figure 47: Cost-effectiveness frontier for OAB medications



Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

For sensitivity analyses, health state utilities based on EQ-5D were used.

Detailed results of the deterministic sensitivity analyses are shown on the tornado chart (Figure 48) for the general OAB population. The model is mostly sensitive to changes in the:

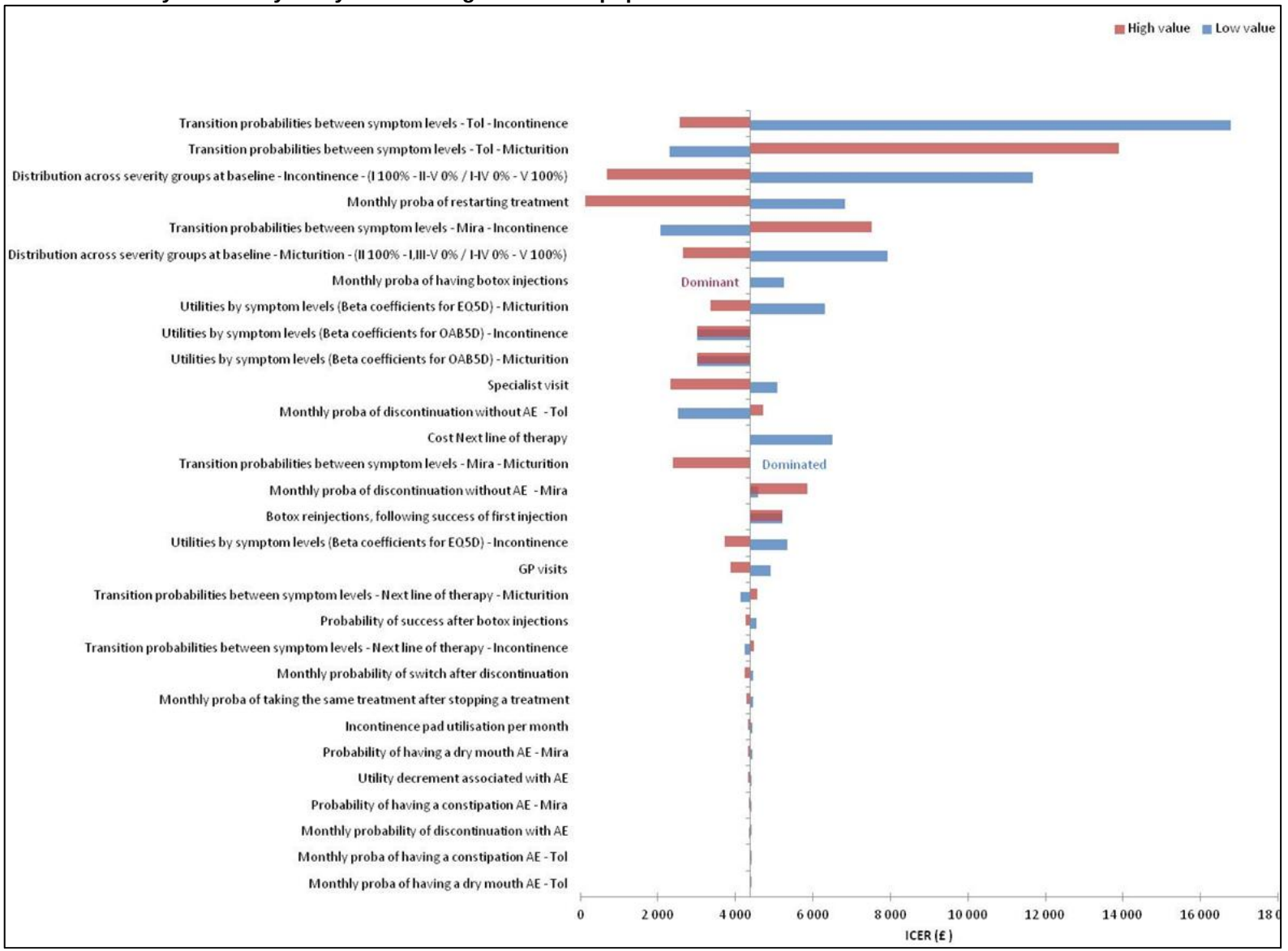
- distribution of patients by micturition severity level at baseline,
- distribution of patients by incontinence severity level at baseline,
- transition probabilities between symptom levels of incontinence for mirabegron and tolterodine,
- monthly probability of restarting treatment,

[l] Strict dominance means that the 'dominant' treatment is both more effective and less costly than its comparator.
[m] Extended dominance means that one treatment is more effective *and* has lower cost-effectiveness ratios than the 'dominated' treatment.

- number of specialist visits when starting new medication,
- monthly probability of discontinuation without AE and
- probability of having botulinum toxin injections.

In all scenarios, except two, mirabegron remained cost-effective or was dominant compared with tolterodine from the healthcare payer perspective.

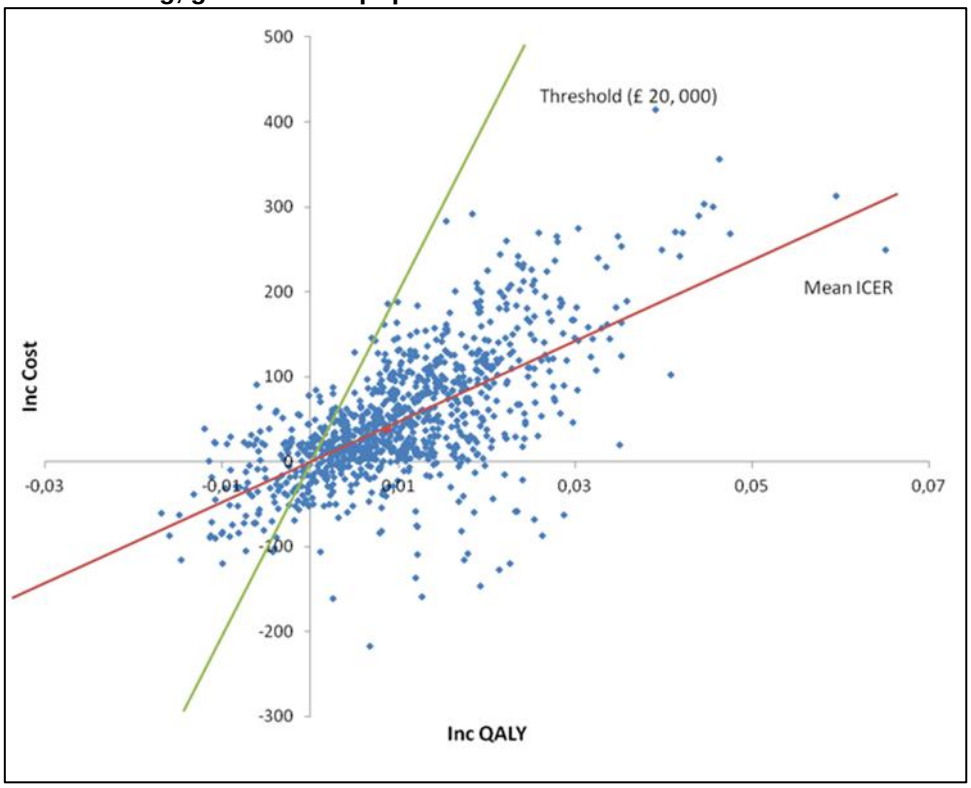
Figure 48: Results of one-way sensitivity analyses for the general OAB population



7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The results of the PSA for the general OAB population are illustrated by the cost-effectiveness plane (Figure 49) and the cost-effectiveness acceptability curve (CEAC) (Figure 50). Figure 49 shows the cost-effectiveness pairs obtained from 1000 simulations, with varying model inputs.

Figure 49: Representation of the results of PSA on the cost-effectiveness plane, mirabegron 50 mg vs tolterodine 4 mg, general OAB population



On average, patients treated with mirabegron are expected to gain an additional 0.01 QALYs at a cost of £49.86 (Table 118). The mean ICER is therefore £4,886, which is substantially lower than the cost-effectiveness of £20,000 per QALY gained.

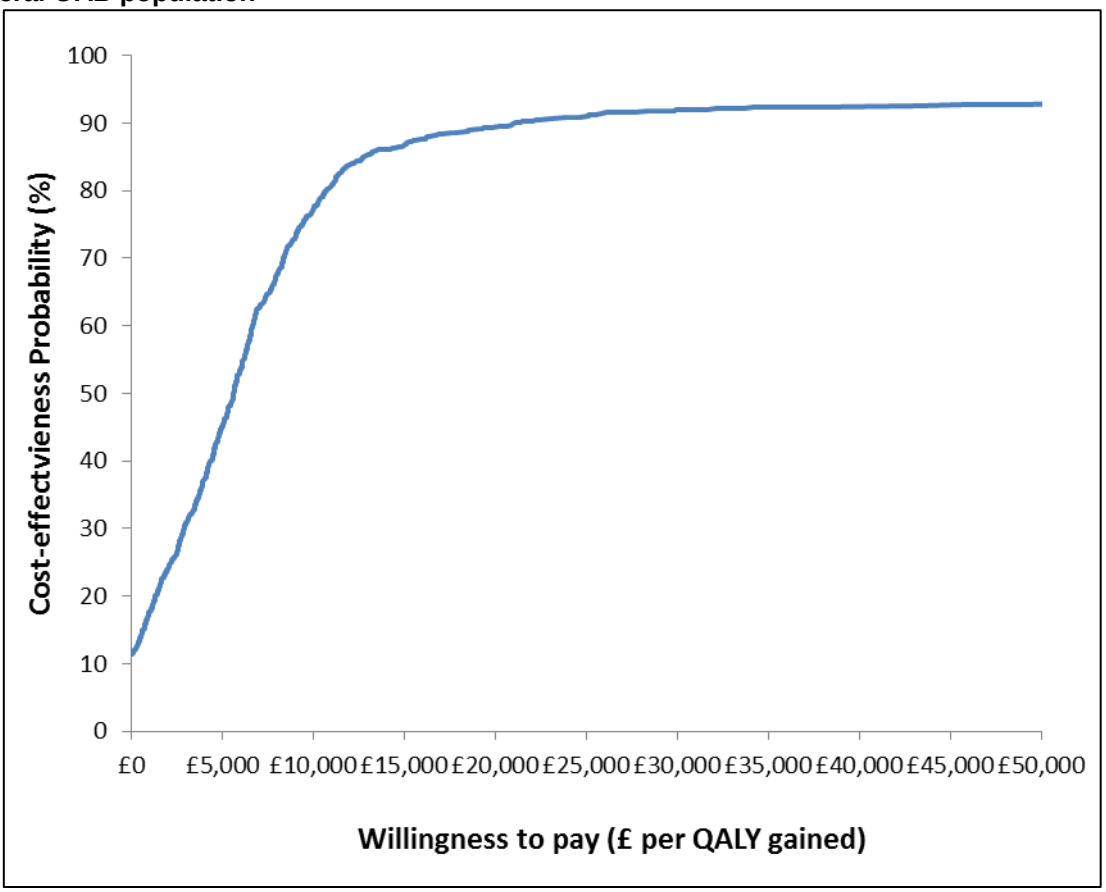
Table 118: PSA results for general OAB population

Treatment	Incremental		ICER (£)
	Costs (£)	QALYs	
Base case	37.88	0.00864	4,386
Mean	49.86	0.01020	4,886
Minimum	-216.89	-0.01681	Dominant
Q 0.025	-84.07	-0.00841	Dominant
Q 0.975	232.28	0.03238	Dominated
Maximum	414.15	0.06509	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

Figure 50 shows the probability that mirabegron 50 mg is cost-effective against tolterodine ER 4 mg for the different values of the willingness-to-pay per QALY (cost-effectiveness thresholds). At a cost-effectiveness threshold of £20,000 per QALY, the probability of mirabegron 50 mg being cost-effective against tolterodine ER 4 mg is 89.4%.

Figure 50: Cost-effectiveness acceptability curve, mirabegron 50 mg vs tolterodine 4 mg, general OAB population



7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Structural uncertainty was analysed by varying the treatment pathway, as presented in the case of the previously treated population, in which mirabegron had an ICER of £3,836.

Sensitivity analysis on time horizon

As sensitivity analysis was performed on the time horizon. The proportion of patients remaining on treatment at 1, 2, 5 and 10 years is presented in Table 119 and the results using EQ-5D and OAB-5D presented in Table 120.

Table 119: Proportion of patients remaining on treatment at 1, 2, 5 and 10 years

	1 year	2 year	5 year	10 year
Mirabegron	42.0%	20.9%	4.9%	0.6%
Tolterodine	32.3%	13.7%	2.9%	0.3%

Table 120: Sensitivity analysis results on time horizon

Timeframe	Incr. costs	Incr. QALYs (EQ-5D)	ICER (EQ-5D)	Incr. QALYs (OAB-5D)	ICER (OAB-5D)
1 year	£12.37	0.00315	£3,925	0.00452	£2,739
2 years	£25.50	0.00588	£4,338	0.00853	£2,988
5 years	£37.88	0.00864	£4,386	0.01259	£3,008
10 years	£33.60	0.00914	£3,675	0.01331	£2,524

Abbreviations: EQ-5D, European quality of life – 5 dimensions; ICER, incremental cost-effectiveness ratio; Incr., incremental; OAB-5D, overactive bladder – 5 dimensions; QALY, quality adjusted life year.

Sensitivity analysis with comorbidities

Results of cost-effectiveness analyses when considering comorbidities are summarised in Table 121. QALYs were estimated using EQ-5D and OAB-5D utilities and costs were estimated from the NHS perspective. The mirabegron strategy was found to be cost-effective vs tolterodine ER 4mg in all sub-populations, except for men patients with OAB-5D QALYs. The benefit of mirabegron 50 mg is the greatest for patients dissatisfied due to adverse events, with an estimated gain of 0.0272 QALYs (EQ-5D), at a cost of £28.37 over 5 years, yielding an ICER of £1,041 per QALY gained (EQ-5D).

Table 121: Sensitivity analysis results on comorbidities

Population	Incr. costs	Incr. QALYs (EQ-5D)	ICER (EQ-5D)	Incr. QALYs (OAB-5D)	ICER (OAB-5D)
General OAB	£37.88	0.01943	£1,950	0.01279	£2,962
Previously treated	£38.07	0.01853	£2,054	0.01492	£2,551
Treatment-naïve	£40.27	0.01996	£2,018	0.01128	£3,569
Male	£43.96	0.01432	£3,070	0.00115	£38,197
Female	£37.73	0.02092	£1,804	0.01673	£2,255

Abbreviations: EQ-5D, European quality of life – 5 dimensions; ICER, incremental cost-effectiveness ratio; Incr., incremental; OAB, overactive bladder; OAB-5D, overactive bladder – 5 dimensions; QALY, quality adjusted life year.

Results of cost-effectiveness analyses of mirabegron when considering comorbidities compared with solifenacin 5 mg and 10 mg, trospium chloride 60 mg, fesoterodine 4 mg, oxybutynin 10 mg IR and oxybutynin 10 mg ER, in general population with a 5-year timeframe, are shown in Table 122. Mirabegron was found to be cost-effective compared with all treatments assessed.

Table 122: Results of cost-effectiveness analysis against other treatments in the general OAB population

Population	Incr. costs	Incr. QALYs (EQ-5D)	ICER (EQ-5D)	Incr. QALYs (OAB-5D)	ICER (OAB-5D)
Tolterodine 4 mg	-£11.29	0.01060	Dominant	0.01585	Dominant
Solifenacin 5 mg	£57.74	0.00466	£12,386	0.00660	£8,752
Solifenacin 10 mg	-£40.67	0.01075	Dominant	0.01529	Dominant
Trospium chloride 60 mg	£49.05	0.00973	£5,038	0.01427	£3,435
Fesoterodine 4 mg	-£17.80	0.01102	Dominant	0.01648	Dominant
Oxybutynin 10 mg ER	£3.42	0.01118	£306	0.01653	£207
Oxybutynin 10 mg IR	£150.11	0.01511	£9,937	0.02229	£6,736

Abbreviations: EQ-5D, European quality of life – 5 dimensions; ICER, incremental cost-effectiveness ratio; Incr., incremental; OAB-5D, overactive bladder – 5 dimensions; QALY, quality adjusted life year.

7.7.10 What were the main findings of each of the sensitivity analyses?

Results of the one-way sensitivity analysis show that in general the model was relatively insensitive to changes in model parameters, including transition probabilities between health states, the probability of discontinuing treatment or switching to the next line of therapy, health state utilities and disutilities associated with AEs, resource use and costs. Additional sensitivity analyses were carried out to investigate the impact of a reduction in the cost of tolterodine which showed that mirabegron remained cost effective in the general OAB population and previously treated population when a 30% cost reduction was applied to tolterodine. Probabilistic sensitivity analysis was also conducted to investigate combined uncertainty around model parameters on the results which resulted in a mean ICER of £4,886. At a cost-effectiveness threshold of £20,000 per QALY, mirabegron was found to be cost-effective against tolterodine in the general OAB population 89.4% of the time.

7.7.11 Key drivers of the cost-effectiveness results

In the general OAB population, mirabegron had an ICER of £4,386 compared with tolterodine and was therefore cost-effective. In general the results were found to be insensitive to changes in model parameters, however the one-way sensitivity analyses showed that the ICER was sensitive to a reduction in the micturition severity group distribution at baseline. The ICER was also sensitive to a lowering of the transition probabilities between micturition symptom levels for tolterodine, but this was not the case for mirabegron.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The model underwent verification and validation consistent with recommendations by Philips et al (124) and the ISPOR Task Force (125). Verification is defined as the process of determining the model is implemented correctly and accurately. Validation refers to the process of evaluating the degree to which the model represents the real world data. Within the verification process the model was checked for internal consistency, accurate data inputs, and logical and mathematically correct calculations. Calculation checks were carried out in order to identify errors (such as probabilities not summing to 1) and to ensure symmetry was present, i.e. outcomes were the same for treatments in different sections of the model. This included testing the model using null or extreme values and comparing the results to expected results. The validation exercise comprised comparison of model outputs to clinical trial data used in the model, face validity and checking of key assumptions by clinical experts. Section 7.7.1 presents the model predictions compared with observed results. Details of the validation by key opinion leaders is presented in Section 7.5.4.

7.9 Subgroup analysis

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to

known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to Section 6.3.7.

Subgroup analyses were performed for the treatment-naïve vs previously treated and male vs female populations as outlined in the scope. See Section 2.4 for further details.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Details of the patients in the subgroups are presented in Section 6.6.1.5.

7.9.3 Please describe how the statistical analysis was undertaken.

A description of the statistical analysis is given in Section 6.3.7 and results in Section 6.6.1.5.

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in Section 7.7.6 (Base-case analysis).

Results of cost-effectiveness analyses for different subgroups are summarised in Table 123. QALYs were estimated using EQ-5D and OAB-5D utilities and costs estimated from the NHS perspective. The mirabegron strategy was found to be cost-effective vs tolterodine ER 4mg in all subgroups, except for male patients.

Table 123: Cost-effectiveness results in subgroups

Subgroup	Inc. costs	Inc. QALYs (EQ-5D)	ICER (EQ-5D)	Inc. QALYs (OAB-5D)	ICER (OAB-5D)
General OAB population	£37.88	0.0086	£4,386	0.0126	£3,008
Previously treated	£38.07	0.0099	£3,836	0.0148	£2,577
Treatment-naïve	£40.27	0.0076	£5,315	0.011	£3,652
Women	£37.73	0.0122	£3,091	0.0167	£2,266
Men	£43.96	0.0011	£38,708	0.0007	£65,968

Abbreviations: EQ-5D, European quality of life – five dimensions questionnaire; ICER, incremental cost-effectiveness ratio; Inc., incremental; OAB-5D, overactive bladder – five dimensions questionnaire; QALY, quality adjusted life year.

Subgroup analyses are presented in Table 124.

Table 124: Subgroup analyses

Treatment	Total			Incremental			ICER (£) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Previously treated subgroup							
Tolterodine 4 mg	£1,643.26	4.666	3.640	-	-	-	-
Mirabegron 50 mg	£1,681.32	4.666	3.650	£38.07	0	0.0099	£3,836
Treatment-naïve subgroup							
Tolterodine 4 mg	£1,535.76	4.666	3.847	-	-	-	-
Mirabegron 50 mg	£1,576.03	4.666	3.855	£40.27	0	0.0076	£5,315
Male subgroup							
Tolterodine 4 mg	£1,411.85	4.666	3.888	-	-	-	-
Mirabegron 50 mg	£1,455.80	4.666	3.889	£43.96	0	0.0011	£38,708
Female subgroup							
Tolterodine 4 mg	£1,694.47	4.666	3.684	-	-	-	-
Mirabegron 50 mg	£1,732.20	4.666	3.697	£37.73	0	0.0122	£3,091

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality adjusted life years.

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in Section 5.

The analyses considers all obvious subgroups included those mentioned in the NICE scope, namely men and women, previously untreated (treatment-naïve) and previously treated OAB populations.

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

A new model structure was developed for this cost-effectiveness analysis. Previous Markov models, based on a structure developed by Kobelt et al (89) consisted of five health states representing different levels of disease severity, without a single absorbing stated for drop-outs.

The main symptoms of OAB micturitions and incontinence were found to have a significant impact on utility independently of each other. Therefore, the progression of both types of symptoms over time was modelled separately. In addition, modelling of the pathways after treatment discontinuation was deemed important since the rate of discontinuation in patients with OAB is high, and since a large proportion of patients switch between treatments.

Compared with other cost-effectiveness models comparing tolterodine ER 4 mg with other antimuscarinics, our results appear congruent. Speakman et al (94) developed a 1-year Markov model to evaluate the cost-utility of solifenacin (5 mg and 10 mg) compared with tolterodine (IR 2 mg bid/ ER 4 mg) in OAB from the UK NHS.

Another 1-year model developed by Cardozo et al (87) assessing the cost-effectiveness of solifenacin vs other antimuscarinic strategies commonly used in UK clinical practice, including tolterodine. The predicted total annual cost per patient was £526 for tolterodine according to Speakman et al and £480 according to Cardozo et al compared with £620 in our model. This difference is mostly related to expert opinion advising that all patients initiating a new treatment are likely to consult a specialist.

The number of QALYs for one year with tolterodine was 0.705 according to Speakman et al and 0.710 according to Cardozo et al, compared with 0.814 in our model. This difference is due to the fact that a new set of utilities were used, based on EQ-5D data collected in clinical trials of mirabegron. It may be noted that the difference between the maximum and minimum utilities in this new model is similar to the range in previous model by Speakman et al. (0.145 vs 0.144).

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in Section 5?

The economic evaluation is relevant to all groups of patients as identified in the decision problem, namely the general OAB population, previously treated, treatment naïve, male and female population.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The main strengths of the economic evaluation include the quality and applicability of the SCORPIO clinical trial data, the synthesis of data for other antimuscarinics by means of MTC. Quality of life has been assessed using both the broad EQ-5D and disease specific OABq instruments, with mapping reducing uncertainty of utility values used within the model. The model structure represents an improved approach to the previously accepted Kobelt model allowing changes in symptoms to be modelled independently from one another, and capturing costs and outcomes after discontinuation of treatment. A pragmatic approach was taken in measuring the impact of AEs, to preserve clarity in the model, and a real life approach was taken when modelling treatment discontinuation to avoid bias from the trial environment. Subgroup analyses have been conducted in line with the NICE scope, and while data limitations prevented analyses of subgroups versus all antimuscarinic comparators, cost-effectiveness has been established versus all comparators listed in the scope for the general population.

A limitation of this analysis is that probabilities of transition between symptom levels could be estimated from SCORPIO for mirabegron and tolterodine only. For other treatments (solifenacin, oxybutynin, fesoterodine, trospium), probabilities were obtained using a calibration method based on a results of a MTC assessing the effectiveness of antimuscarinics. However the MTC only provided estimates of mean changes in micturitions and incontinence episodes for each treatment included in the analysis. Also, there was no unique solution to the calibration problem. Therefore, three series of coefficients were produced for each symptom and treatment. The ICERs for mirabegron 50 mg vs solifenacin 5 mg based on these three series of coefficients were slightly different, but the conclusions were identical.

A second limitation is that it was assumed that the discontinuation rate was similar for mirabegron and the comparator, conditional upon presence or absence of AEs. However, no real-world data were available on persistence with mirabegron, so this assumption is unavoidable. The impact of this assumption was tested in a sensitivity analysis. It is likely that persistence would be greater on mirabegron than tolterodine, owing to greater efficacy. If a 50% lower discontinuation rate is assumed for patients treated with mirabegron in the general population, the conclusion remains unchanged. Using this 50% lower discontinuation rate, the model predicted that the mirabegron strategy was associated with a gain of 0.0022 QALYs, based on EQ-5D utilities, and an additional cost of approximately £101.35 over the 5-year evaluation period, yielding an incremental cost per QALY gained of £4,585 compared with £4,386 based on EQ-5D.

Lastly, while the number of male patients recruited to the trials was high in comparson to other OAB trials, the small population of male patients meant that more substantial QALY gains could not be shown in this population.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

As recommended by NICE, the utilities based on EQ-5D were used to estimate utilities for the base case analysis. However, it has been argued that the EQ-5D instrument may be insufficiently sensitive to OAB symptoms. This led to the development of another preference-based disease-specific measure of utility (OAB 5D) by Yang et al (104) derived from the

Overactive Bladder Questionnaire (OAB-q). OAB-5D utilities were found to be similar to EQ-5D utilities for the most severe health states, but higher than EQ-5D utilities for less severe health states. Thus, the range of OAB-5D utilities was wider than the range of EQ-5D utilities, leading to more favourable ICERs. In the general population, the ICER for mirabegron vs tolterodine based on OAB-5D was estimated at £3,008 per QALY gained, from the NHS perspective, compared with £4,386 based on EQ-5D.

Additional aspects of OAB, such as UTIs, skin infections, falls and fractures, could also be included. UTIs are observed in 22.5% of patients with OAB, and skin infections in 8% of OAB patients (34). Patients with frequent urge incontinence have a 26% increased risk of falls, and a 34% increased risk of fractures (34). Based on the efficacy data from SCORPIO, it could be speculated that inclusion of these factors would have further improved the cost-effectiveness of mirabegron.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Table 125 outlines the number of eligible patients who will seek treatment for their condition and for whom mirabegron will be a treatment option. The patient population is determined as follows:

- Mirabegron is indicated in adults over 18 years, however, the majority of patients are aged 40 and over (9)
- Approximately 19% of people aged over 40 have clinically significant symptoms (9)
- Of those patients who have clinically significant symptoms, approximately 27% will seek treatment for their condition (9)
- The current number of patients eligible for treatment in the population aged 40 and over is calculated to be 5.2 million
- The number of patients likely to present for treatment is calculated to be approximately 1.42 million
- The number of patients eligible for treatment in England and Wales is assumed to stay constant for Years 1 to 5.

Table 125: Estimation of patients eligible for treatment

	Years 1 to 5
Population (≥ 18 years) (126)	44,197,700
Population (≥ 40 years) (126)	27,685,400
Prevalence (clinically significant symptoms in adults ≥ 40 years) (9)	19.00%
Patients currently on medication (9)	27.00%
Patients eligible for treatment, n	5,260,226
Patients likely to present for treatment, n	1,420,261

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

The assumptions are:

- All eligible patients will receive treatment
- The calculations include present cases only (i.e. no incidence has been included)
- No mortality is included (as treatment does not affect mortality)
- An equal uptake (so equal current prescribing) is assumed across the three treatments with the highest market share to ensure simplicity and transparency in the calculations. These treatments are solifenacin, oxybutynin and tolterodine.

8.3 What assumption(s) were made about market share (when relevant)?

- Market share data shows that for current treatments, solifenacin, oxybutynin and tolterodine have the majority of the market share (87%) (Table 126) (18). For simplicity the market share was assumed to be equal across all three treatments.
- The annual cost of medication is based on 180 days of treatment due to patients discontinuing and rarely receiving prescriptions to cover the whole year (22). This is an assumption chosen to balance a plausible treatment duration with a clear and concise budget impact estimate.
- The budget impact assumes that mirabegron will displace each of the three therapies outlined equally.
- Market share for mirabegron is assumed to be 1% in the first year rising to 9% in the fifth year. Table 128 outlines the projected uptake of mirabegron assuming a positive recommendation for use in patients with OAB presenting for treatment.

Table 126: Current competitor market share

	Prescriptions MAT July 2012	Prescriptions MAT July 2012 (% volume)
Urinary incontinence prd	5,379,930	100.0%
Solifenacin	1,924,512	35.8%
Oxybutynin	1,531,443	28.5%
Tolterodine	1,200,779	22.3%
Fesoterodine	222,058	4.1%
Trospium	187,734	3.5%
Other/unknown	313,404	5.8%

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

No other significant costs are associated with treatment.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

The only unit costs used in the calculations were for treatments (Table 128).

Table 127: Unit costs of treatments

Key comparators	Pack price	Annual cost (based on 180 days treatment)	Cost difference vs mirabegron
Solifenacin (5 mg OD 30 tablet pack price)	£27.62	£165.72	£8.28
Tolterodine (XL 4 mg OD 28 tablet pack price)	£25.78	£165.73	£8.27
Oxybutynin, non-proprietary (5 mg TDS 84 tablet pack price)	£11.60	£74.57	£99.43
Mirabegron (50 mg OD 30 tablet pack)	£29.00	£174.00	£0.00
Average price difference			**£38.66**

Abbreviations: mg, milligram; OD, once daily; TDS, three times daily.

8.6 Were there any estimates of resource savings? If so, what were they?

No, while savings may be realised from reduced GP visits and pad usage, the budget impact presented here represents drug costs only.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated annual budget impact for the NHS in England and Wales is approximately £0.5 million in Year 1 rising to approximately £5 million in Year 5 (Table 128).

Table 128: Annual budget impact for NHS in England and Wales

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible patient group	1,420,261				
Predicted mirabegron share of antimuscarinic market	1%	2%	3.50%	5.75%	9%
Average cost difference per patient (based on mirabegron displacing solifenacin, oxybutynin and tolterodine equally)	£38.66				
Annual budget impact	£549,072	£1,098,145	£1,921,755	£3,157,169	£4,941,656

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No.

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10 Appendices

10.1 Appendix 1

10.1.1 ANNEX I - SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Betmiga 25 mg prolonged-release tablets

Betmiga 50 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg 50 mg of mirabegron.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

Oval, brown tablet, debossed with the company logo and “325” on the same side.

Oval, yellow tablet, debossed with the company logo and “355” on the same side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

4.2 Posology and method of administration

Posology

Adults (including elderly patients)

The recommended dose is 50 mg once daily with or without food.

Special populations

Renal and hepatic impairment

Betmiga has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m^2 or patients requiring haemodialysis) or severe hepatic impairment (Child-Pugh Class C) and it is therefore not recommended for use in these patient populations (see sections 4.4 and 5.2).

The following table provides the daily dosing recommendations for subjects with renal or hepatic impairment in the absence and presence of strong CYP3A inhibitors (see sections 4.4, 4.5 and 5.2).

		Strong CYP3A inhibitors[3]	
		Without inhibitor	With inhibitor
Renal impairment[1]	Mild	50 mg	25 mg
	Moderate	50 mg	25 mg
	Severe	25 mg	Not recommended
Hepatic impairment[2]	Mild	50 mg	25 mg
	Moderate	25 mg	Not recommended

1. Mild: GFR 60 to 89 mL/min/1.73 m^2; moderate: GFR 30 to 59 mL/min/1.73 m^2; severe: GFR 15 to 29 mL/min/1.73 m^2.
2. Mild: Child-Pugh Class A; Moderate: Child-Pugh Class B.
3. Strong CYP3A inhibitors see section 4.5

Gender

No dose adjustment is necessary according to gender.

Paediatric population

The safety and efficacy of mirabegron in children below 18 years of age have not yet been established.

No data are available.

Method of administration

The tablet is to be taken once daily, with liquids, swallowed whole and is not to be chewed, divided, or crushed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Renal impairment

Betmiga has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m^2 or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population. Data are limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2); based on a pharmacokinetic study (see section 5.2) a dose reduction to 25 mg is recommended in this population. Betmiga is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2) concomitantly receiving strong CYP3A inhibitors (see section 4.5).

Hepatic impairment

Betmiga has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. Betmiga is not

recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors (see section 4.5).

Hypertension

Betmiga has not been evaluated in severe uncontrolled hypertensive patients (systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg); therefore it is not recommended for use in this patient population. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg).

Patients with congenital or acquired QT prolongation

Mirabegron, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies (see section 5.1). However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro data

Mirabegron is transported and metabolised through multiple pathways. Mirabegron is a substrate for cytochrome P450 (CYP) 3A4, CYP2D6, butyrylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT), the efflux transporter P-glycoprotein (P-gp) and the influx organic cation transporters (OCT) OCT1, OCT2, and OCT3. Studies of mirabegron using human liver microsomes and recombinant human CYP enzymes showed that mirabegron is a moderate and time-dependent inhibitor of CYP2D6 and a weak inhibitor of CYP3A. Mirabegron inhibited P-gp-mediated drug transport at high concentrations.

In vivo data

CYP2D6 polymorphism

CYP2D6 genetic polymorphism has minimal impact on the mean plasma exposure to mirabegron (see section 5.2). Interaction of mirabegron with a known CYP2D6 inhibitor is

not expected and was not studied. No dose adjustment is needed for mirabegron when administered with CYP2D6 inhibitors or in patients who are CYP2D6 poor metabolisers.

Drug-drug interactions

The effect of co-administered medicinal products on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of other medicinal products was studied in single and multiple dose studies. Most drug-drug interactions were studied using a dose of 100 mg mirabegron given as oral controlled absorption system (OCAS) tablets. Interaction studies of mirabegron with metoprolol and with metformin used mirabegron immediate-release (IR) 160 mg.

Clinically relevant drug interactions between mirabegron and medicinal products that inhibit, induce or are a substrate for one of the CYP isozymes or transporters are not expected except for the inhibitory effect of mirabegron on the metabolism of CYP2D6 substrates.

Effect of enzyme inhibitors

Mirabegron exposure (AUC) was increased 1.8-fold in the presence of the strong inhibitor of CYP3A/P-gp ketoconazole in healthy volunteers. No dose-adjustment is needed when Betmiga is combined with inhibitors of CYP3A and/or P-gp. However, in patients with mild to moderate renal impairment (GFR 30 to 89 mL/min/1.73 m^2) or mild hepatic impairment (Child-Pugh Class A) concomitantly receiving strong CYP3A inhibitors, such as itraconazole, ketoconazole, ritonavir and clarithromycin, the recommended dose is 25 mg once daily with or without food (see section 4.2). Betmiga is not recommended in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2) or patients with moderate hepatic impairment (Child-Pugh Class B) concomitantly receiving strong CYP3A inhibitors (see sections 4.2 and 4.4).

Effect of enzyme inducers

Substances that are inducers of CYP3A or P-gp decrease the plasma concentrations of mirabegron. No dose adjustment is needed for mirabegron when administered with therapeutic doses of rifampicin or other CYP3A or P-gp inducers.

Effect of mirabegron on CYP2D6 substrates

In healthy volunteers, the inhibitory potency of mirabegron towards CYP2D6 is moderate and the CYP2D6 activity recovers within 15 days after discontinuation of mirabegron. Multiple once daily dosing of mirabegron IR resulted in a 90% increase in C_{max} and a 229% increase in AUC of a single dose of metoprolol. Multiple once daily dosing of mirabegron

resulted in a 79% increase in C_{max} and a 241% increase in AUC of a single dose of desipramine.

Caution is advised if mirabegron is co-administered with medicinal products with a narrow therapeutic index and significantly metabolised by CYP2D6, such as thioridazine, Type 1C antiarrhythmics (e.g., flecainide, propafenone) and tricyclic antidepressants (e.g., imipramine, desipramine). Caution is also advised if mirabegron is co-administered with CYP2D6 substrates that are individually dose titrated.

Effect of mirabegron on transporters

Mirabegron is a weak inhibitor of P-gp. Mirabegron increased C_{max} and AUC by 29% and 27%, respectively, of the P-gp substrate digoxin in healthy volunteers. For patients who are initiating a combination of Betmiga and digoxin, the lowest dose for digoxin should be prescribed initially. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect. The potential for inhibition of P-gp by mirabegron should be considered when Betmiga is combined with sensitive P-gp substrates e.g. dabigatran.

Other interactions

No clinically relevant interactions have been observed when mirabegron was co-administered with therapeutic doses of solifenacin, tamsulosin, warfarin, metformin or a combined oral contraceptive medicinal product containing ethinylestradiol and levonorgestrel. Dose-adjustment is not recommended.

Increases in mirabegron exposure due to drug-drug interactions may be associated with increases in pulse rate.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of mirabegron in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Betmiga is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

Mirabegron is excreted in the milk of rodents and therefore is predicted to be present in human milk (see section 5.3). No studies have been conducted to assess the impact of mirabegron on milk production in humans, its presence in human breast milk, or its effects on the breast-fed child.

Mirabegron should not be administered during breast-feeding.

Fertility

There were no treatment-related effects of mirabegron on fertility in animals (see section 5.3). The effect of mirabegron on human fertility has not been established.

4.7 Effects on ability to drive and use machines

Betmiga has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of mirabegron was evaluated in 8433 patients with OAB, of which 5648 received at least one dose of mirabegron in the phase 2/3 clinical program, and 622 patients received mirabegron for at least 1 year (365 days). In the three 12-week phase 3 double blind, placebo controlled studies, 88% of the patients completed treatment with mirabegron, and 4% of the patients discontinued due to adverse events. Most adverse reactions were mild to moderate in severity.

The most common adverse reactions reported for patients treated with mirabegron 50 mg during the three 12-week phase 3 double blind, placebo controlled studies are tachycardia and urinary tract infections. The frequency of tachycardia was 1.2% in patients receiving mirabegron 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving mirabegron 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving mirabegron 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving mirabegron 50 mg. Serious adverse reactions included atrial fibrillation (0.2%).

Adverse reactions observed during the 1-year (long term) active controlled (muscarinic antagonist) study were similar in type and severity to those observed in the three 12-week phase 3 double blind, placebo controlled studies.

Tabulated list of adverse reactions

The table below reflects the adverse reactions observed with mirabegron in the three 12-week phase 3 double blind, placebo controlled studies.

The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA **System organ class**	**Common**	**Uncommon**	**Rare**
Infections and infestations	Urinary tract infection	Vaginal infection Cystitis	
Eye disorders			Eyelid oedema
Cardiac disorders	Tachycardia	Palpitation Atrial fibrillation	
Gastrointestinal disorders		Dyspepsia Gastritis	Lip oedema
Skin and subcutaneous tissue disorders		Urticaria Rash Rash macular Rash papular Pruritus	Leukocytoclastic vasculitis Purpura
Musculoskeletal and connective tissue disorders		Joint swelling	
Reproductive system and breast disorders		Vulvovaginal pruritis	
Investigations		Blood pressure increased GGT increased AST increased ALT increased	

4.9 Overdose

Mirabegron has been administered to healthy volunteers at single doses up to 400 mg. At this dose, adverse events reported included palpitations (1 of 6 subjects) and increased pulse rate exceeding 100 beats per minute (bpm) (3 of 6 subjects). Multiple doses of mirabegron up to 300 mg daily for 10 days showed increases in pulse rate and systolic blood pressure when administered to healthy volunteers.

Treatment for overdose should be symptomatic and supportive. In the event of overdose, pulse rate, blood pressure, and ECG monitoring is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, Urinary antispasmodics ATC code: G04BD12.

Mechanism of action

Mirabegron is a potent and selective beta 3-adrenoceptor agonist. Mirabegron showed relaxation of bladder smooth muscle in rat and human isolated tissue, increased cyclic adenosine monophosphate (cAMP) concentrations in rat bladder tissue and showed a bladder relaxant effect in rat urinary bladder function models. Mirabegron increased mean voided volume per micturition and decreased the frequency of non-voiding contractions, without affecting voiding pressure, or residual urine in rat models of bladder overactivity. In a monkey model, mirabegron showed decreased voiding frequency. These results indicate that mirabegron enhances urine storage function by stimulating beta 3-adrenoceptors in the bladder.

During the urine storage phase, when urine accumulates in the bladder, sympathetic nerve stimulation predominates. Noradrenaline is released from nerve terminals, leading predominantly to beta adrenoceptor activation in the bladder musculature, and hence bladder smooth muscle relaxation. During the urine voiding phase, the bladder is predominantly under parasympathetic nervous system control. Acetylcholine, released from pelvic nerve terminals, stimulates cholinergic M2 and M3 receptors, inducing bladder contraction. The activation of the M2 pathway also inhibits beta 3-adrenoceptor induced increases in cAMP. Therefore beta 3-adrenoceptor stimulation should not interfere with the voiding process. This was confirmed in rats with partial urethral obstruction, where

mirabegron decreased the frequency of non-voiding contractions without affecting the voided volume per micturition, voiding pressure, or residual urine volume.

Pharmacodynamic effects

Urodynamics

Mirabegron at doses of 50 mg and 100 mg once daily for 12 weeks in men with lower urinary tract symptoms (LUTS) and bladder outlet obstruction (BOO) showed no effect on cystometry parameters and was safe and well tolerated. The effects of mirabegron on maximum flow rate and detrusor pressure at maximum flow rate were assessed in this urodynamic study consisting of 200 male patients with LUTS and BOO. Administration of mirabegron at doses of 50 mg and 100 mg once daily for 12 weeks did not adversely affect the maximum flow rate or detrusor pressure at maximum flow rate. In this study in male patients with LUTS/BOO, the adjusted mean (SE) change from baseline to end of treatment in post void residual volume (mL) was 0.55 (10.702), 17.89 (10.190), 30.77 (10.598) for the placebo, mirabegron 50 mg and mirabegron 100 mg treatment groups.

Effect on QT interval

Mirabegron at doses of 50 mg or 100 mg had no effect on the QT interval individually corrected for heart rate (QTcI interval) when evaluated either by sex or by the overall group.

A thorough QT (TQT) study (n = 164 healthy male and n = 153 healthy female volunteers with a mean age of 33 years) evaluated the effect of repeat oral dosing of mirabegron at the indicated dose (50 mg once daily) and two supra-therapeutic doses (100 and 200 mg once daily) on the QTcI interval. The supra-therapeutic doses represent approximately 2.6- and 6.5-fold the exposure of the therapeutic dose, respectively. A single 400 mg dose of moxifloxacin was used as a positive control. Each dose level of mirabegron and moxifloxacin was evaluated in separate treatment arms each including placebo-control (parallel cross-over design). For both males and females administered mirabegron at 50 mg and 100 mg, the upper bound of the one-sided 95% confidence interval did not exceed 10 msec at any time point for the largest time-matched mean difference from placebo in the QTcI interval. In females administered mirabegron at the 50 mg dose, the mean difference from placebo on QTcI interval at 5 hours post dose was 3.67 msec (upper bound of the one-sided 95% CI 5.72 msec). In males, the difference was 2.89 msec (upper bound of the one-sided 95% CI 4.90 msec). At a mirabegron dose of 200 mg, the QTcI interval did not exceed 10 msec at any time point in males, while in females the upper bound of the one-sided 95% confidence interval did exceed 10 msec between 0.5–6 hours, with a maximum difference from placebo at 5 hours where the mean effect was 10.42 msec (upper bound of the one-sided 95% CI 13.44 msec). Results for QTcF and QTcIf were consistent with QTcI.

In this TQT study, mirabegron increased heart rate on ECG in a dose dependent manner across the 50 mg to 200 mg dose range examined. The maximum mean difference from

placebo in heart rate ranged from 6.7 bpm with mirabegron 50 mg up to 17.3 bpm with mirabegron 200 mg in healthy subjects.

Effects on pulse rate and blood pressure in patients with OAB

In OAB patients (mean age of 59 years) across three 12-week phase 3 double blind, placebo controlled studies receiving mirabegron 50 mg once daily, an increase in mean difference from placebo of approximately 1 bpm for pulse rate and approximately 1 mm Hg or less in systolic blood pressure/ diastolic blood pressure (SBP/DBP) was observed. Changes in pulse rate and blood pressure are reversible upon discontinuation of treatment.

Effect on intraocular pressure (IOP)

Mirabegron 100 mg once daily did not increase IOP in healthy subjects after 56 days of treatment. In a phase 1 study assessing the effect of mirabegron on IOP using Goldmann applanation tonometry in 310 healthy subjects, a dose of mirabegron 100 mg was non-inferior to placebo for the primary endpoint of the treatment difference in mean change from baseline to day 56 in subject-average IOP; the upper bound of the two-sided 95% CI of the treatment difference between mirabegron 100 mg and placebo was 0.3 mm Hg.

Clinical efficacy and safety

Efficacy of mirabegron was evaluated in three phase 3 randomized, double blind, placebo controlled, 12-week studies for the treatment of overactive bladder with symptoms of urgency and frequency with or without incontinence. Female (72%) and male (28%) patients with a mean age of 59 years (range 18 – 95 years) were included. The study population consisted of approximately 48% antimuscarinic treatment naïve patients as well as approximately 52% patients previously treated with antimuscarinic medication. In one study, 495 patients received an active control (tolterodine prolonged release formulation).

The co-primary efficacy endpoints were (1) change from baseline to end of treatment in mean number of incontinence episodes per 24 hours and (2) change from baseline to end of treatment in mean number of micturitions per 24 hours based on a 3-day micturition diary. Mirabegron demonstrated statistically significant larger improvements compared to placebo for both co-primary endpoints as well as secondary endpoints (see Tables 1 and 2).

Table 1: Co-primary and Selected Secondary Efficacy Endpoints at End of Treatment for Pooled Studies

Parameter	Pooled studies (046, 047, 074)	
	Placebo	**Mirabegron 50 mg**
Mean number of incontinence episodes per 24 hours (FAS-I) (Co-primary)		
n	878	862
Mean baseline	2.73	2.71
Mean change from baseline†	-1.10	-1.49
Mean difference from placebo† (95% CI)	--	-0.40 (-0.58, -0.21)
p-value	--	<0.001#
Mean number of micturitions per 24 hours (FAS) (Co-primary)		
n	1328	1324
Mean baseline	11.58	11.70
Mean change from baseline†	-1.20	-1.75
Mean difference from placebo† (95% CI)	--	-0.55 (-0.75, -0.36)
p-value	--	<0.001#
Mean volume voided (mL) per micturition (FAS) (Secondary)		
n	1328	1322
Mean baseline	159.2	159.0
Mean change from baseline†	9.4	21.4
Mean difference from placebo† (95% CI)	--	11.9 (8.3, 15.5)
p-value	--	<0.001#
Mean level of urgency (FAS) (Secondary)		
n	1325	1323
Mean baseline	2.39	2.42
Mean change from baseline†	-0.15	-0.26
Mean difference from placebo† (95% CI)	--	-0.11 (-0.16, -0.07)
p-value	--	<0.001#
Mean number of urgency incontinence episodes per 24 hours (FAS-I) (Secondary)		
n	858	834
Mean baseline	2.42	2.42
Mean change from baseline†	-0.98	-1.38
Mean difference from placebo† (95% CI)	--	-0.40 (-0.57, -0.23)
p-value	--	<0.001#
Mean number of episodes with urgency grades 3 or 4 per 24 hours (FAS) (Secondary)		
n	1324	1320
Mean baseline	5.61	5.80
Mean change from baseline†	-1.29	-1.93
Mean difference from placebo† (95% CI)	--	-0.64 (-0.89, -0.39)
p-value	--	<0.001#
Treatment satisfaction – visual analogue scale (FAS) (Secondary)		
n	1195	1189
Mean baseline	4.87	4.82
Mean change from baseline†	1.25	2.01
Mean difference from placebo† (95% CI)	--	0.76 (0.52, 1.01)
p-value	--	<0.001*

Pooled studies consisted of studies 046 (Europe / Australia), 047 (North America [NA]) and 074 (Europe / NA).

† Least squares mean adjusted for baseline, gender, and study.

* Statistically significantly superior compared to placebo at the 0.05 level without multiplicity adjustment.

Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment.

FAS: Full analysis set, all randomized patients who took at least 1 dose of double blind study drug and who had a micturition measurement in the baseline diary and at least 1 post-baseline visit diary with a micturition measurement.

FAS-I: Subset of FAS who also had at least 1 incontinence episode in the baseline diary.

CI: Confidence Interval

Table 2: Co-primary and Selected Secondary Efficacy Endpoints at End of Treatment for Studies 046, 047 and 074

Parameter	Study 046			Study 047		Study 074	
	Placebo	Mirabegron 50 mg	Tolterodine ER 4 mg	Placebo	Mirabegron 50 mg	Placebo	Mirabegron 50 mg
Mean number of incontinence episodes per 24 hours (FAS-I) (Co-primary)							
n	291	293	300	325	312	262	257
Mean baseline	2.67	2.83	2.63	3.03	2.77	2.43	2.51
Mean change from baseline†	-1.17	-1.57	-1.27	-1.13	-1.47	-0.96	-1.38
Mean difference from placebo†	--	-0.41	-0.10	--	-0.34	--	-0.42
95% Confidence Interval	--	(-0.72, -0.09)	(-0.42, 0.21)	--	(-0.66, -0.03)	--	(-0.76, -0.08)
p-value	--	0.003#	0.11	--	0.026#	--	0.001#
Mean number of micturitions per 24 hours (FAS) (Co-primary)							
n	480	473	475	433	425	415	426
Mean baseline	11.71	11.65	11.55	11.51	11.80	11.48	11.66
Mean change from baseline†	-1.34	-1.93	-1.59	-1.05	-1.66	-1.18	-1.60
Mean difference from placebo†	--	-0.60	-0.25	--	-0.61	--	-0.42
95% Confidence Interval	--	(-0.90, -0.29)	(-0.55, 0.06)	--	(-0.98, -0.24)	--	(-0.76, -0.08)
p-value	--	<0.001#	0.11	--	0.001#	--	0.015#
Mean volume voided (mL) per micturition (FAS) (Secondary)							
n	480	472	475	433	424	415	426
Mean baseline	156.7	161.1	158.6	157.5	156.3	164.0	159.3
Mean change from baseline†	12.3	24.2	25.0	7.0	18.2	8.3	20.7
Mean difference from placebo†	--	11.9	12.6	--	11.1	--	12.4
95% Confidence Interval	--	(6.3, 17.4)	(7.1, 18.2)	--	(4.4, 17.9)	--	(6.3, 18.6)
p-value	--	<0.001#	<0.001*	--	0.001#	--	<0.001#
Mean level of urgency (FAS) (Secondary)							
n	480	472	473	432	425	413	426
Mean baseline	2.37	2.40	2.41	2.45	2.45	2.36	2.41
Mean change from baseline†	-0.22	-0.31	-0.29	-0.08	-0.19	-0.15	-0.29
Mean difference from placebo†	--	-0.09	-0.07	--	-0.11	--	-0.14
95% Confidence Interval	--	(-0.17, -0.02)	(-0.15, 0.01)	--	(-0.18, -0.04)	--	(-0.22, -0.06)
p-value	--	0.018*	0.085	--	0.004*	--	<0.001‡
Mean number of urgency incontinence episodes per 24 hours (FAS-I) (Secondary)							
n	283	286	289	319	297	256	251
Mean baseline	2.43	2.52	2.37	2.56	2.42	2.24	2.33
Mean change from baseline†	-1.11	-1.46	-1.18	-0.89	-1.32	-0.95	-1.33
Mean difference	--	-0.35	-0.07	--	-0.43	--	-0.39

Parameter	Study 046			Study 047		Study 074	
	Placebo	**Mirabegron 50 mg**	**Tolterodine ER 4 mg**	**Placebo**	**Mirabegron 50 mg**	**Placebo**	**Mirabegron 50 mg**
from placebo†							
95% Confidence Interval	--	(-0.65, -0.05)	(-0.38, 0.23)	--	(-0.72, -0.15)	--	(-0.69, -0.08)
p-value	--	0.003*	0.26	--	0.005*	--	0.002‡
Mean number of episodes with urgency grades 3 or 4 per 24 hours (FAS) (Secondary)							
n	479	470	472	432	424	413	426
Mean baseline	5.78	5.72	5.79	5.61	5.90	5.42	5.80
Mean change from baseline†	-1.65	-2.25	-2.07	-0.82	-1.57	-1.35	-1.94
Mean difference from placebo†	--	-0.60	-0.42	--	-0.75	--	-0.59
95% Confidence Interval	--	(-1.02, -0.18)	(-0.84, -0.00)	--	(-1.20, -0.30)	--	(-1.01, -0.16)
p-value	--	0.005*	0.050*	--	0.001*	--	0.007‡
Treatment satisfaction – visual analogue scale (FAS) (Secondary)							
n	428	414	425	390	387	377	388
Mean baseline	4.11	3.95	3.87	5.5	5.4	5.13	5.13
Mean change from baseline†	1.89	2.55	2.44	0.7	1.5	1.05	1.88
Mean difference from placebo†	--	0.66	0.55	--	0.8	--	0.83
95% Confidence Interval	--	(0.25, 1.07)	(0.14, 0.95)	--	(0.4, 1.3)	--	(0.41, 1.25)
p-value	--	0.001*	0.008*	--	<0.001*	--	<0.001*

† Least squares mean adjusted for baseline, gender and geographical region.

* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment.

Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustment.

‡ Not statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment.

FAS: Full analysis set, all randomized patients who took at least 1 dose of double blind study drug and who had a micturition measurement in the baseline diary and at least 1 post-baseline visit diary with a micturition measurement.

FAS-I: Subset of FAS who also had at least 1 incontinence episode in the baseline diary.

Mirabegron 50 mg once daily was effective at the first measured time point of week 4, and efficacy was maintained throughout the 12-week treatment period. A randomized, active controlled, long term study demonstrated that efficacy was maintained throughout a 1-year treatment period.

Subjective improvement in health-related quality of life measurements

In the three 12-week phase 3 double blind, placebo controlled studies, treatment of the symptoms of OAB with mirabegron once daily resulted in a statistically significant improvement over placebo on the following health-related quality of life measures: treatment satisfaction and symptom bother.

Efficacy in patients with or without prior OAB antimuscarinic therapy

Efficacy was demonstrated in patients with and without prior OAB antimuscarinic therapy. In addition mirabegron showed efficacy in patients who previously discontinued OAB antimuscarinic therapy due to insufficient effect (see Table 3).

Table 3: Co-primary efficacy endpoints for patients with prior OAB antimuscarinic therapy

Parameter	Pooled studies (046, 047, 074)		Study 046		
	Placebo	Mirabegron 50 mg	Placebo	Mirabegron 50 mg	Tolterodine ER 4 mg
Patients with prior OAB antimuscarinic therapy					
Mean number of incontinence episodes per 24 hours (FAS-I)					
n	518	506	167	164	160
Mean baseline	2.93	2.98	2.97	3.31	2.86
Mean change from baseline†	-0.92	-1.49	-1.00	-1.48	-1.10
Mean difference from placebo†	--	-0.57	--	-0.48	-0.10
95% Confidence Interval	--	(-0.81, -0.33)	--	(-0.90, -0.06)	(-0.52, 0.32)
Mean number of micturitions per 24 hours (FAS)					
n	704	688	238	240	231
Mean baseline	11.53	11.78	11.90	11.85	11.76
Mean change from baseline†	-0.93	-1.67	-1.06	-1.74	-1.26
Mean difference from placebo†	--	-0.74	--	-0.68	-0.20
95% Confidence Interval	--	(-1.01, -0.47)	--	(-1.12, -0.25)	(-0.64, 0.23)
Patients with prior OAB antimuscarinic therapy who discontinued due to insufficient effect					
Mean number of incontinence episodes per 24 hours (FAS-I)					
n	336	335	112	105	102
Mean baseline	3.03	2.94	3.15	3.50	2.63
Mean change from baseline†	-0.86	-1.56	-0.87	-1.63	-0.93
Mean difference from placebo†	--	-0.70	--	-0.76	-0.06
95% Confidence Interval	--	(-1.01, -0.38)	--	(-1.32, -0.19)	(-0.63, 0.50)
Mean number of micturitions per 24 hours (FAS)					
n	466	464	155	160	155
Mean baseline	11.60	11.67	11.89	11.49	11.99
Mean change from baseline†	-0.86	-1.54	-1.03	-1.62	-1.11
Mean difference from placebo†	--	-0.67	--	-0.59	-0.08
95% Confidence Interval	--	(-0.99, -0.36)	--	(-1.15, -0.04)	(-0.64, 0.47)

Pooled studies consisted of 046 (Europe / Australia), 047 (North America [NA]) and 074 (Europe / NA).

† Least squares mean adjusted for baseline, gender, study, subgroup, and subgroup by treatment interaction for Pooled Studies and least squares mean adjusted for baseline, gender, geographical region, subgroup, and subgroup by treatment interaction for Study 046.

FAS: Full analysis set, all randomized patients who took at least 1 dose of double blind study drug and who had a micturition measurement in the baseline diary and at least 1 post-baseline visit diary with a micturition measurement.

FAS-I: Subset of FAS who also had at least 1 incontinence episode in the baseline diary.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Betmiga in one or more subsets of the paediatric population in “Treatment of idiopathic overactive bladder” and “Treatment of neurogenic detrusor overactivity” (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

After oral administration of mirabegron in healthy volunteers mirabegron is absorbed to reach peak plasma concentrations (C_{max}) between 3 and 4 hours. The absolute bioavailability increased from 29% at a dose of 25 mg to 35% at a dose of 50 mg. Mean C_{max} and AUC increased more than dose proportionally over the dose range. In the overall population of males and females, a 2-fold increase in dose from 50 mg to 100 mg mirabegron increased C_{max} and AUC_{tau} by approximately 2.9- and 2.6-fold, respectively, whereas a 4-fold increase in dose from 50 mg to 200 mg mirabegron increased C_{max} and AUC_{tau} by approximately 8.4- and 6.5-fold. Steady state concentrations are achieved within 7 days of once daily dosing with mirabegron. After once daily administration, plasma exposure of mirabegron at steady state is approximately double that seen after a single dose.

Effect of food on absorption

Co-administration of a 50 mg tablet with a high-fat meal reduced mirabegron C_{max} and AUC by 45% and 17%, respectively. A low-fat meal decreased mirabegron C_{max} and AUC by 75% and 51%, respectively. In the phase 3 studies, mirabegron was administered with or without food and demonstrated both safety and efficacy. Therefore, mirabegron can be taken with or without food at the recommended dose.

Distribution

Mirabegron is extensively distributed. The volume of distribution at steady state (V_{ss}) is approximately 1670 L. Mirabegron is bound (approximately 71%) to human plasma proteins, and shows moderate affinity for albumin and alpha-1 acid glycoprotein. Mirabegron distributes to erythrocytes. *In vitro* erythrocyte concentrations of ^{14}C-mirabegron were about 2-fold higher than in plasma.

Biotransformation

Mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. Mirabegron is the major circulating component following a single dose of ^{14}C-mirabegron. Two major metabolites were observed in human plasma; both are phase 2 glucuronides representing 16% and 11% of total exposure. These metabolites are not pharmacologically active.

Based on *in vitro* studies, mirabegron is unlikely to inhibit the metabolism of co-administered medicinal products metabolized by the following cytochrome P450 enzymes: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2E1 because mirabegron did not inhibit the activity of these enzymes at clinically relevant concentrations. Mirabegron did not induce CYP1A2 or CYP3A. Mirabegron is predicted not to cause clinically relevant inhibition of OCT-mediated drug transport.

Although *in vitro* studies suggest a role for CYP2D6 and CYP3A4 in the oxidative metabolism of mirabegron, *in vivo* results indicate that these isozymes play a limited role in the overall elimination. *In vitro* and *ex vivo* studies have shown the involvement from butyrylcholinesterase, UGT and possibly alcohol dehydrogenase (ADH) in the metabolism of mirabegron, in addition to CYP3A4 and CYP2D6.

CYP2D6 polymorphism

In healthy subjects who are genotypically poor metabolisers of CYP2D6 substrates (used as a surrogate for CYP2D6 inhibition), mean C_{max} and AUC_{inf} of a single 160 mg dose of a mirabegron IR formulation were 14% and 19% higher than in extensive metabolisers, indicating that CYP2D6 genetic polymorphism has minimal impact on the mean plasma exposure to mirabegron. Interaction of mirabegron with a known CYP2D6 inhibitor is not expected and was not studied. No dose adjustment is needed for mirabegron when administered with CYP2D6 inhibitors or in patients who are CYP2D6 poor metabolisers.

Elimination

Total body clearance (CL_{tot}) from plasma is approximately 57 L/h. The terminal elimination half-life ($t_{1/2}$) is approximately 50 hours. Renal clearance (CL_R) is approximately 13 L/h, which corresponds to nearly 25% of CL_{tot}. Renal elimination of mirabegron is primarily through active tubular secretion along with glomerular filtration. The urinary excretion of unchanged mirabegron is dose-dependent and ranges from approximately 6.0% after a daily dose of 25 mg to 12.2% after a daily dose of 100 mg. Following the administration of 160 mg ^{14}C-mirabegron to healthy volunteers, approximately 55% of the radiolabel was recovered in the urine and 34% in the faeces. Unchanged mirabegron accounted for 45% of the urinary radioactivity, indicating the presence of metabolites. Unchanged mirabegron accounted for the majority of the faecal radioactivity.

Age

The C_{max} and AUC of mirabegron and its metabolites following multiple oral doses in elderly volunteers (≥ 65 years) were similar to those in younger volunteers (18–45 years).

Gender

The C_{max} and AUC are approximately 40% to 50% higher in females than in males. Gender differences in C_{max} and AUC are attributed to differences in body weight and bioavailability.

Race

The pharmacokinetics of mirabegron are not influenced by race.

Renal impairment

Following single dose administration of 100 mg mirabegron in volunteers with mild renal impairment (eGFR-MDRD 60 to 89 mL/min/1.73 m^2), mean mirabegron C_{max} and AUC were increased by 6% and 31% relative to volunteers with normal renal function. In volunteers with moderate renal impairment (eGFR-MDRD 30 to 59 mL/min/1.73 m^2), C_{max} and AUC were increased by 23% and 66%, respectively. In volunteers with severe renal impairment (eGFR-MDRD 15 to 29 mL/min/1.73 m^2), mean C_{max} and AUC values were 92% and 118% higher. Mirabegron has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m^2 or patients requiring haemodialysis).

Hepatic impairment

Following single dose administration of 100 mg mirabegron in volunteers with mild hepatic impairment (Child-Pugh Class A), mean mirabegron C_{max} and AUC were increased by 9% and 19% relative to volunteers with normal hepatic function. In volunteers with moderate hepatic impairment (Child-Pugh Class B), mean C_{max} and AUC values were 175% and 65% higher. Mirabegron has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

5.3 Preclinical safety data

Pre-clinical studies have identified target organs of toxicity that are consistent with clinical observations. Transient increases in liver enzymes and hepatocyte changes (necrosis and decrease in glycogen particles) were seen in rats. An increase in heart rate was observed in rats, rabbits, dogs and monkeys. Genotoxicity and carcinogenicity studies have shown no genotoxic or carcinogenic potential *in vivo*.

No effects on fertility were seen at sub-lethal doses (human equivalent dose was 19-fold higher than the maximum human recommended dose (MHRD)). The main findings in rabbit embryofetal development studies included malformations of the heart (dilated aorta, cardiomegaly) at systemic exposures 36-fold higher than observed at the MHRD. In addition, malformations of the lung (absent accessory lobe of the lung) and increased post-implantation loss were observed in the rabbit at systemic exposures 14-fold higher than observed at the MHRD, while in the rat reversible effects on ossification were noted (wavy ribs, delayed ossification, decreased number of ossified sternebrae, metacarpi or metatarsi) at systemic exposures 22-fold higher than observed at the MHRD. The observed embryofetal toxicity occurred at doses associated with maternal toxicity. The cardiovascular malformations observed in the rabbit were shown to be mediated via activation of the beta 1-adrenoceptor.

Pharmacokinetic studies performed with radio-labelled mirabegron have shown that the parent compound and/or its metabolites are excreted in the milk of rats at levels that were approximately 1.7-fold higher than plasma levels at 4 hours post administration (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<u>Core tablet 25 mg</u>

Macrogols

Hydroxypropylcellulose

Butylhydroxytoluene

Magnesium stearate

Film coating 25 mg

Hypromellose

Macrogol

Iron oxide yellow (E172)

Iron oxide red (E172)

Core tablet 50 mg

Macrogols

Hydroxypropylcellulose

Butylhydroxytoluene

Magnesium stearate

Film coating 50 mg

Hypromellose

Macrogol

Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Shelf life after first opening of the bottle: 6 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu-Alu blisters in cartons containing 10, 20, 30, 60, 90 or 200 tablets.

HDPE bottles with child-resistant polypropylene (PP) caps and a silica gel desiccant containing 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.

Sylviusweg 62

2333 BE Leiden

The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

10.2 Appendix 2: Search strategy for Section 6.1 (Identification of studies)

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***The Cochrane Library***

The following databases were searched:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
- EMBASE (Ovid)
- The Cochrane Library.

10.2.2 The date on which the search was conducted

The searches were conducted on the 13th June 2012.

10.2.3 The date span of the search

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
- EMBASE (Ovid), 1980 to 2010 Week 23.
- The Cochrane Library, to present.

10.2.4 The complete search strategy used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

All the following searches were combined and inclusion/exclusion criteria applied.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present; Searched on 13th June 2012

	Searches	Results
1	exp Urinary Bladder, Overactive/	1731
2	exp Urinary Incontinence, Urge/	423
3	((overactive adj3 bladder*) or (urge adj3 incontinence) or (detrusor adj3 dyssynergia) or urinary frequency or bladder irritation or DESD).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	6810
4	or/1-3	6810
5	exp Muscarinic Antagonists/	47967
6	(solifenacin or Vesicare or Vesikur or Vesiker or Vesitirim).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	269
7	(tolterodine or Detrusitol or Detrol or Detrol LA).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	703
8	(mirabegron or YM-178 or Betanis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	12
9	(darifenacin or Enablex or Emselex).mp. [mp=title, abstract, original title, name of substance	246

	word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	
10	(fesoterodine or Toviaz).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	88
11	(oxybutynin or Ditropan or Lyrinel XL).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1143
12	(propiverine or Detrunorm).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	250
13	(trospium or Regurin or Flotros or Sanctura or Tropez or Trosec or Spasmex).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	197
14	or/5-13	49127
15	Randomized controlled trials as Topic/	80681
16	Randomized controlled trial/	329523
17	Random allocation/	74636
18	Double blind method/	115177
19	Single blind method/	16222
20	Clinical trial/	470549
21	exp Clinical Trials as Topic/	256314
22	or/15-21	822447
23	(clinic$ adj trial$1).tw.	179880
24	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	116506
25	Placebos/	31000
26	Placebo$.tw.	141589
27	Randomly allocated.tw.	14430
28	(allocated adj2 random).tw.	689
29	or/23-28	364340
30	22 or 29	945575
31	Case report.tw.	179155
32	Letter/	766994
33	Historical article/	283529
34	Review of reported cases.pt.	0
35	Review, multicase.pt.	0
36	or/31-35	1219140
37	30 not 36	918974
38	Epidemiologic studies/	5401
39	exp case control studies/	555529
40	exp cohort studies/	1180139
41	Case control.tw.	63573
42	(cohort adj (study or studies)).tw.	64838
43	Cohort analy$.tw.	2879
44	(Follow up adj (study or studies)).tw.	33974
45	(observational adj (study or studies)).tw.	33492
46	Longitudinal.tw.	117312
47	Retrospective.tw.	224489
48	Cross sectional.tw.	131853
49	Cross-sectional studies/	141275
50	or/38-49	1614542
51	37 or 50	2343086
52	4 and 14 and 51	736
53	limit 52 to (humans and yr="2000 -Current")	**642**

EMBASE 1980 to 2010 Week 36; Searched on 13th June 2012

	Searches	Results
1	exp overactive bladder/ or exp detrusor dyssynergia/	7942
2	exp urinary urgency/ or exp urge incontinence/	5981
3	exp urinary frequency/	3292
4	exp bladder irritation/	585
5	((overactive adj3 bladder*) or (urge adj3 incontinence) or (detrusor adj3 dyssynergia) or	12551

	DESD).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	
6	or/1-5	16257
7	exp solifenacin/ or exp tolterodine/ or exp mirabegron/ or exp darifenacin/ or exp fesoterodine/ or exp oxybutynin/ or exp propiverine/ or exp trospium chloride/	6302
8	(solifenacin or Vesicare or Vesikur or Vesiker or Vesitirim).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	948
9	(tolterodine or Detrusitol or Detrol or Detrol LA).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2508
10	(mirabegron or YM-178 or Betanis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	78
11	(darifenacin or Enablex or Emselex).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	960
12	(fesoterodine or Toviaz).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	325
13	(oxybutynin or Ditropan or Lyrinel XL).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	4235
14	(propiverine or Detrunorm).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	910
15	(trospium or Regurin or Flotros or Sanctura or Tropez or Trosec or Spasmex).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1018
16	exp muscarinic receptor blocking agent/	52144
17	or/7-16	54543
18	Clinical trial/	866364
19	Randomized controlled trial/	323003
20	Randomization/	58330
21	Single blind procedure/	15953
22	Double blind procedure/	109131
23	Crossover procedure/	34020
24	Placebo/	199298
25	Randomi?ed controlled trial$.tw.	75150
26	Rct.tw.	9305
27	Random allocation.tw.	1147
28	Randomly allocated.tw.	17143
29	Allocated randomly.tw.	1807
30	(allocated adj2 random).tw.	706
31	Single blind$.tw.	12185
32	Double blind$.tw.	127866
33	((treble or triple) adj blind$).tw.	269
34	Placebo$.tw.	174830
35	Prospective study/	205050
36	or/18-35	1249368
37	Case study/	15738
38	Case report.tw.	225200
39	Abstract report/ or letter/	833427
40	or/37-39	1069815
41	36 not 40	1214471
42	Clinical study/	39131
43	Case control study/	67405
44	Family study/	9563
45	Longitudinal study/	53058
46	Retrospective study/	280717
47	Prospective study/	205050
48	Randomized controlled trials/	16604
49	47 not 48	204650
50	Cohort analysis/	123539
51	(Cohort adj (study or studies)).mp.	83251
52	(Case control adj (study or studies)).tw.	61192
53	(follow up adj (study or studies)).tw.	39369

54	(observational adj (study or studies)).tw.	44662
55	(epidemiologic$ adj (study or studies)).tw.	64601
56	(cross sectional adj (study or studies)).tw.	61034
57	or/42-46,49-56	928654
58	41 or 57	1889175
59	6 and 17 and 58	1697
60	limit 59 to (human and yr="2000 -Current")	**1464**

The Cochrane Library, to present; Searched on 13th June 2012

ID	Search	Hits
#1	MeSH descriptor **Urinary Bladder, Overactive** explode all trees	222
#2	MeSH descriptor **Urinary Incontinence, Urge** explode all trees	57
#3	(overactive NEAR/3 bladder*) or (urge NEAR/3 incontinence) or (detrusor NEAR/3 dyssynergia) or (urinary frequency) or (bladder irritation) or DESD	2691
#4	(#1 OR #2 OR #3)	2691
#5	MeSH descriptor **Muscarinic Antagonists** explode all trees	500
#6	solifenacin or Vesicare or Vesikur or Vesiker or Vesitirim	87
#7	tolterodine or Detrusitol or Detrol or Detrol LA	340
#8	mirabegron or YM-178 or Betanis	0
#9	darifenacin or Enablex or Emselex	55
#10	fesoterodine or Toviaz	53
#11	oxybutynin or Ditropan or Lyrinel XL	343
#12	propiverine or Detrunorm	74
#13	trospium or Regurin or Flotros or Sanctura or Tropez or Trosec or Spasmex	102
#14	(#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)	1067
#15	(#4 AND #14)	541
#16	(#15), from 2000 to 2012	**478**

10.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Additional studies were identified by hand searching the following resources:

- Reference lists of previous trials and systematic reviews
- Conference proceedings (2010 – 2012)
  - International Continence Society (ICS) (2010-2012) - http://www.icsoffice.org/
  - American Urological Association (AUA) (2010-2012) - http://www.auanet.org/
  - European Association of Urology (EAU) (2010-2012) - http://www.uroweb.org/
  - International Urogynecological Association (IUGA) (2010-2012) - http://www.iuga.org/
- Trial databases
  - clinicaltrials.gov http://clinicaltrials.gov/
  - ISRCTN Register http://www.controlled-trials.com/mrct/
  - UK Clinical Trials Gateway http://www.ukctg.nihr.ac.uk/
  - metaRegister (mRCT) of Controlled Trials http://www.controlled-trials.com/mrct/
- NICE website

Unpublished studies (i.e. clinical study reports) were provided by the manufacturer.

10.2.6 The inclusion and exclusion criteria.

	Description	Justification
Inclusion criteria		
Population	Adults with symptoms of OAB	As specified by final scope
Interventions	Mirabegron Oxybutynin (including modified-release preparations)	As specified by final scope
Outcomes	Symptoms of urgency Urinary frequency Frequency of urge urinary incontinence Nocturia Adverse effects of treatment	As specified by final scope
Study design	Prospective RCTs	Non-RCT studies were identified through a separate search.
Language restrictions	Non-English publications without an English abstract to be excluded at first pass stage. English abstracts of non-English publications, to be reviewed to assess eligibility.	
Exclusion criteria		
Population	Patients <18 years of age. Patients with LUTS	
Interventions	Studies not investigating Mirabegron or a relevant comparator	
Outcomes	Studies not reporting the outcomes listed in the scope.	
Study design	Non-randomised controlled studies. Observational studies	Non-RCT studies were identified through a separate search.
Language restrictions	Non-English publications	

Abbreviations: LUTS, lower urinary tract symptoms; OAB, overactive bladder; RCT randomised controlled trial.

10.2.7 The data abstraction strategy.

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party. Relevant information was abstracted into the STA template/ into a pre-defined Microsoft Word® document by a reviewer.

10.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

Study question	Study question reference
Was randomisation carried out appropriately?	(1)
Was the concealment of treatment allocation adequate?	(2)
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	(3)
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	(4)
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	(5)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	(6)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	(7)

DRAGON, 178-CL-044		
Study question reference	**How was the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
(1)	Randomisation sequences prepared by the Contract Research Organisation IFE Europe GmbH, Essen, Germany, under responsibility of Biometrics Department of APEB.	Yes
(2)	IVRS used to control the randomisation and clinical supply distribution. IVRS assigned medication numbers to patients fulfilling all selection criteria at Visit 2. Study medication packed in blister cards. Each card contained medication (mirabegron, tolterodine or placebo) for 1 week treatment for 1 patient.	Yes
(3)	Treatment groups well balanced for all demographic characteristics. No relevant differences between treatment groups with respect to medication and alcohol history at study entry. Proportion of patients with urge incontinence only also comparable across treatment groups.	Yes
(4)	Each patient randomised to any treatment group was administered (swallowed) 3 tablets and 1 capsule each morning after breakfast throughout study. All treatments taken orally with glass of water and swallowed intact. Mirabegron tablets, tolterodine SR capsules and corresponding placebo tablets and capsules were indistinguishable (double dummy technique).	Yes
(5)	Proportion of patients discontinuing study ranged from 4–10% across treatment groups. 32 patients with AEs leading to discontinuations (placebo, 5; 25 mg mirabegron, 10; 50 mg mirabegron, 3; 100 mg mirabegron, 5; 200 mg mirabegron, 7; 4 mg tolterodine, 2.	No
(6)	All outcomes planned to be measured in the study protocol appear to be reported in CSR.	No
(7)	FAS (randomised patients who had taken ≥ 1 dose of double-blind study medication and provided primary efficacy data at baseline and endpoint visit) was primary population for efficacy analysis. Safety population (all patients who had taken ≥ 1 dose of double-blind study medication) used for safety summaries and analyses. Per- protocol set included all patients in the FAS with no major protocol violations. For efficacy and safety data there was no imputation for missing data. Only patients with symptoms at baseline other than 0 were included in analysis of corresponding symptom.	Yes

178-CL-045		
Study question reference	**How was the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
(1)	Randomisation manager allocated study drugs randomly (1 subject in each group for each set, 4 patients in total) and retained sealed key code until code breaking.	Yes
(2)	The mirabegron placebo tablet and its package were indistinguishable from the respective study drug tablets and their package, and only the randomisation manager knew the key code.	Yes
(3)	Overall, subject backgrounds were similar in all groups. No statistically significant imbalance was found between the groups in any of the items (the criterion for the	Yes

	two-sided significance level was 0.05).	
(4)	Randomisation manager confirmed appearance and package of the study drugs were indistinguishable before randomisation and code breaking.	Yes
(5)	Major reasons for discontinuation during treatment period were AEs (6, 6, 8, and 8), protocol deviations (5, 1, 2, and 4), and consent withdrawal (1, 3, 2, and 0 in placebo, 25 mg, 50 mg, and 100 mg groups, respectively); no substantial difference between groups.	No
(6)	All outcomes planned to be measured in the study protocol appear to be reported in the CSR.	No
(7)	The FAS included all patients who received at least one dose of the study drug for treatment period and provided at least one efficacy data before initiation of the treatment period and during the treatment period. The SAF included all patients who received at least one dose of the study drug for treatment period. For patients who discontinued the study during the treatment period, the data obtained on the last day of each visit window (at Visits 2, 3, 4, 5, and 6) or the last day of the study medication + 7 days (whichever was the earliest) was adopted as the data of the visit. Those who did not discontinue during the treatment period were handled in the same manner.	Yes

SCORPIO, 178-CL-046		
Study question reference	**How was the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
(1)	Patients randomised using computer-generated randomisation scheme prepared by Pierrel Research Europe GmbH. Randomisation stratified by country.	Yes
(2)	Patient numbers and randomised treatment allocated by the CIRT system. Study drugs provided in wallet (folded blister card) containing sufficient supply of study medication for 1 week. Each time study drug was dispensed, number of weekly wallets packed in box of study drug was equal to number of weeks between clinic visits plus 1 additional spare wallet. At the end of the screening visit, 1 box of study drugs containing 3 weekly wallets was dispensed.	Yes
(3)	Demographic and baseline characteristics consistent across treatment groups for patients in FAS and SAS populations. Observations for demographic and baseline characteristics for per protocol set were similar to those for the FAS.	Yes
(4)	Throughout study (placebo run-in period and post-randomisation), 2 study drug tablets (mirabegron 50 mg or matching placebo, mirabegron 100 mg or matching placebo) and 1 study capsule (tolterodine SR 4 mg or matching placebo) were taken by mouth with glass of water with or without food in the morning. Mirabegron (OCAS formulation) and placebo tablets to match the OCAS formulation were manufactured by Astellas Pharma Technologies. Tolterodine SR 4 mg capsules were over-encapsulated to maintain blind in a hard gelatine capsule shell. Investigator, study site personnel, patients, sponsor and sponsor representative blinded to identity of randomised drug assignment.	Yes
(5)	Discontinuation rates similar across treatment groups. Placebo, 8.9%; mirabegron 50 mg, 11.5%; mirabegron 100 mg, 9.0%; tolterodine SR 4 mg, 10.1%.	No
(6)	All outcomes planned to be measured in the study protocol appear to be reported in the CSR.	No
(7)	ITT (all randomised patients who took ≥ 1 dose of double-blind study drug and who had a baseline diary with micturition measurements), FAS (all randomised patients who took ≥ 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and ≥ 1 post baseline visit diary with a micturition measurement), SAF (all randomised patients who took ≥ 1 dose of double-blind study drug). LOCF methodology used where no values present for final visit.	Yes

ARIES, 178-CL-047		
Study question reference	**How was the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
(1)	Patients randomised to 1 of 3 treatment groups (mirabegron 50 mg, mirabegron 100 mg or placebo) in 1:1:1 ratio using computer-generated randomisation scheme prepared by Pierrel Research Europe GmbH. Randomisation stratified by centre.	Yes
(2)	Patient numbers and randomised treatment allocated by the CIRT system. Study drugs packaged using double-dummy blinded method. They were provided in wallet (folded blister card) containing a sufficient supply of tablets for 1 week.	Yes

(3)	Demographic and baseline characteristics consistent across treatment groups for patients in SAF population. Generally, demographic and baseline characteristics were similar across treatment groups in the FAS. Observations for demographic and baseline characteristics for the per protocol set were similar to those for the FAS.	Yes
(4)	Investigator, study site personnel, patients, sponsor and sponsor representatives blinded to identity of randomised drug assignment. 2 tablets taken each day (mirabegron 50 mg or matching placebo, mirabegron 100 mg or matching placebo).	Yes
(5)	Proportion of patients randomised into double-blind treatment period that discontinued study was comparable across treatment groups. In each treatment group, the 2 most frequently cited primary reasons for discontinuation were an AE and consent withdrawal. The incidence of discontinuation due to an AE (primary reason) was 3.7%, 4.1% and 4.4% in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively.	No
(6)	All outcomes planned to be measured in the study protocol appear to be reported in the CSR.	No
(7)	ITT (all randomised patients who took ≥ 1 dose of double-blind study drug and who had a baseline diary with micturition measurements), FAS (all randomised patients who took ≥ 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and ≥ 1 post baseline visit diary with a micturition measurement), SAF (all randomised patients who took ≥ 1 dose of double-blind study drug. The values for the final visit were handled using LOCF methodology.	Yes

178-CL-048		
Study question reference	**How was the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
(1)	Randomisation manager randomised study drugs (2 patients from each group per set; 6 patients total) and retained sealed randomisation code until code was broken.	Yes
(2)	Investigators or sub-investigators assigned study medication to patients confirmed eligible for the study. Drug dispensed sequentially by allocated drug number.	Yes
(3)	Patient background factors generally similar in all treatment groups; no statistically significant imbalances between groups (significance level: 0.05, two-sided).	Yes
(4)	Dosage forms and packaging for mirabegron placebo and tolterodine placebo indistinguishable from those of the active mirabegron 50 mg tablets and tolterodine 4 mg capsules. Randomisation managers confirmed that study drugs and their packaging were indistinguishable in appearance before randomisation and before code breaking after the study drugs were retrieved.	Yes
(5)	In the respective treatment groups, 31, 31 and 23 patients withdrew from the treatment period. The most common reasons for withdrawal were AEs (9, 15 and 13 patients, respectively) and withdrawal of consent (12, 8 and 1 patients, respectively). The highest number of patients withdrawing consent was in the placebo group.	Yes
(6)	All outcomes planned to be measured in the study appear to be reported in the publication.	No
(7)	FAS (patients that took the study medication ≥ 1 and provided evaluable efficacy data for ≥ 1 variable before and after initiation of the treatment period), SAF (patients who took the study medication ≥ 1). Final decisions on disposition of missing data and outliers were made before code breaking, taking into account opinions and advice of medical expert and medical statistical advisor. If multiple observations were obtained within the same visit window for a patient, a value obtained close to the target date was used. If deviations from the scheduled date were the same, the value obtained on the later date was used. The day that the study medication was dispensed was counted as day 0 and the next day as day 1. This was considered appropriate.	Yes

TAURUS, 178-CL-049		
Study question reference	**How was the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
(1)	Patients randomised to 1 of the 3 treatment groups using computer-generated randomisation scheme prepared by Pierrel Research Europe GmbH.	Yes
(2)	Patient numbers allocated by the CIRT system. Study drugs provided in a wallet (folded blister card) containing a sufficient supply of study medication for 1 week.	Yes
(3)	Demographic and baseline characteristics (from baseline for this study and not	Yes

	previous data from patients who rolled over from 178-CL-046 or 178-CL-047) consistent across treatment groups for patients in SAF. Generally, demographic and baseline characteristics were similar across treatment groups in FAS.	
(4)	During the double-blind treatment period, investigator, study site personnel, patients, sponsor and sponsor's representatives were blinded to the identity of randomised drug assignment. Study drugs packaged using double-dummy blinded method. 2 tablets (mirabegron 50 mg or matching placebo, mirabegron 100 mg or matching placebo) and 1 capsule (tolterodine ER 4 mg or matching placebo) taken each day.	Yes
(5)	Incidence of patients who discontinued study drug due to a TEAE was 5.9% in the mirabegron 50 mg group, 6.1% in the mirabegron 100 mg group and 5.7% in the tolterodine ER 4 mg group.	No
(6)	All outcomes planned to be measured in the study appear to be reported in the publication.	No
(7)	RAS (all randomised patients), FAS (all randomised patients who took ≥ 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and ≥ 1 post-baseline visit diary with a micturition measurement), SAF (all randomised patients who took ≥ 1 dose of double-blind study drug). For the safety and efficacy data, analysis based on Final Visit took into account patients who withdrew before month 12 and therefore did not have safety or efficacy measurements available for that month. The Final Visit analysis used a LOCF approach. This was considered appropriate.	Yes

CAPRICORN, 178-CL-074		
Study question reference	**How was the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
(1)	Patients randomised using computer-generated randomisation scheme prepared by Pierrel Research Europe GmbH. Randomisation stratified by centre.	Yes
(2)	Patient numbers and randomised treatment allocated by the CIRT system. Study drugs provided in a wallet (folded blister card) containing a sufficient supply of tablets for 1 week.	Yes
(3)	Demographic and baseline characteristics consistent across treatment groups for patients in SAF. Generally, demographic and baseline characteristics similar across treatment groups in FAS. Demographic and baseline characteristics for per protocol set population similar to those for FAS.	Yes
(4)	During double-blind treatment and follow-up periods, investigator, study site personnel, patients, sponsor and sponsors representatives were blinded to identity of randomised drug assignment. Throughout the study, 2 study drug tablets (mirabegron 25 mg or matching placebo, mirabegron 50 mg or matching placebo) taken by mouth with glass of water with or without food in the morning.	Yes
(5)	Proportion of patients randomised into double-blind treatment period that discontinued the study was numerically higher in the placebo group compared with mirabegron 25 mg and mirabegron 50 mg (15.2%, 10.6% and 12.3%, respectively). In each treatment group, the 2 most frequently cited primary reasons for discontinuation were an AE and withdrawal of consent. The incidence of discontinuation due to an AE (primary reason) was 3.5%, 3.9% and 2.7% in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively.	No
(6)	All outcomes planned to be measured in the study protocol appear to be reported in the CSR.	No
(7)	ITT-I (all randomised patients who took ≥ 1 dose of double-blind study drug and who had micturition measurements and ≥ 1 incontinence episode in the baseline diary), FAS (all randomised patients who took ≥ 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and ≥ 1 post baseline visit diary with a micturition measurement), SAF (all randomised patients who took ≥ 1 dose of double-blind study drug). For patients without a value at week 12 for an efficacy or safety variable, LOCF methodology was utilised for deriving final visit value.	Yes

10.4 Appendix 4: Search strategy for Section 6.7 (Indirect and mixed treatment comparisons)

The clinical search described in Section 6.1 and Section 10.2 was also designed to identify eligible studies for the MTC, relevant to the decision problem.

Additional inclusion/exclusion criteria were applied when assessing suitability of studies for the missed treatment comparison. These are outlined in section 6.7.2.

10.5 Appendix 5: Quality assessment of comparator RCT(s) in Section 6.7 (Indirect and mixed treatment comparisons)

Study question	Study question reference
Was randomisation carried out appropriately?	(1)
Was the concealment of treatment allocation adequate?	(2)
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	(3)
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	(4)
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	(5)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	(6)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	(7)

Study question reference	How was the question addressed in the study?	Grade (yes/no/not clear/NA)
BLOSSOM, 178-CL-008 (44)		
(1)	Randomisation sequences prepared by the Biometrics Department of APEB using APEB Randomisation Application. Randomisation was not stratified by centre.	Yes
(2)	IVRS used to control randomisation and clinical supply distribution. IVRS assigned medication numbers to the patients fulfilling all selection criteria at Visit 2.	Yes
(3)	FAS population at baseline. Treatment groups well balanced for all demographic characteristics.	Yes
(4)	In order to ensure blinding, study medication was packed using a double-dummy method, i.e. the same number of tablets (2 large and 2 small ones) and a capsule was taken each study day.	Yes
(5)	No single AE preferred term led to discontinuation from the double-blind treatment period of ≥ 1 patient in any treatment group. However, 3 patients in the mirabegron mg BID group discontinued prematurely due to a moderate skin reaction (i.e. urticaria, rash, and allergic exanthema).	Yes
(6)	All outcomes planned to be measured in the study appear to be reported in the publication.	No
(7)	Patients who took ≥ 1 dose of double-blind study medication and for whom any data was reported after first dose of double blind study medication were included in the safety population. Patients who took ≥ 1 dose of the double-blind study medication and providing efficacy data at baseline (Visit 2) and endpoint visit were included in the FAS. Patients from the FAS who completed the study without major violations of the protocol were included in the PP set.	Yes
Abrams 2006 (45)		
(1)	No description of randomisation given.	Unclear
(2)	No description of concealment of treatment allocation given.	Unclear
(3)	Authors report that baseline characteristics were broadly similar across treatment groups. However there are no tables to verify that.	Not clear
(4)	No description of blinding to treatment allocation reported.	Unclear
(5)	The authors report that 8 patients were not included in the analysis. However, there is no clarification as to how those patients are spread across the treatment groups.	Not clear

(6)	All outcomes planned to be measured in the study appear to be reported in the publication.	No
(7)	The safety analysis included all patients who were enrolled in the study and received ≥ 1 dose of study medication. The ambulatory urodynamic monitoring parameter analysis only included 69 patients who received study drug and were assessed at baseline and for one or more endpoints while on treatment. There was an adequate description of why the data for eight patients was missing and the statistical analysis methods used to account for that.	Yes
Appell 2001 (46)		
(1)	To help ensure a similar distribution of baseline urge incontinence a stratified randomisation based on the severity of urge incontinence at baseline was used. No further description of randomisation given.	Unclear
(2)	No description of concealment allocation given.	Unclear
(3)	Baseline characteristics and urinary symptoms were similar/comparable between the 2 groups.	Yes
(4)	Study medications delivered in a double-blind, double-dummy fashion. All medications encased in identical gelatine capsules, with each subject receiving 2 capsules in the morning and 1 in the evening.	Yes
(5)	No unexpected imbalances in discontinuations between the groups. To address bias from dropouts, additional analyses performed by using efficacy results obtained at all time-points (weeks 2, 4, 8 and 12).	No
(6)	All outcomes planned to be measured in the study appear to be reported in the publication.	No
(7)	All patients who completed diaries at least once while on treatment were included in these analyses. This was considered appropriate.	Yes
Birns 2000 (47)		
(1)	Randomisation carried out for the 10 hospital centres using blocks of 2 patients while the additional 5 GP centres which were opened later in the study, received randomised blocks of study drugs in blocks of 5. Randomisation produced using Statistical Analysis System procedure	Yes
(2)	No description of concealment of treatment allocation given.	Unclear
(3)	Baseline characteristics similar between groups for most of the genitourinary diagnosis.	Yes
(4)	Each patient provided with 2 tablets to be taken in the morning and 1 tablet to be taken in the evening. This ensured that although each patient took 3 tablets a day, neither they nor their doctors were aware of the contents.	Yes
(5)	No unexpected imbalances in drop-outs between groups.	No
(6)	All outcomes planned to be measured in the study appear to be reported in the publication.	No
(7)	128 patients were analysed on an ITT basis, of whom 62 were treated with study drug and 66 with reference drug. This was considered appropriate as there was no data available for the 2 patients who discontinued soon after randomisation.	Yes
Cardozo 2004 (48)		
(1)	No description of randomisation given.	Unclear
(2)	No description of concealment allocation given.	Unclear
(3)	Three treatment groups well balanced for all demographic characteristics.	Yes
(4)	Study described as double blind but no description of blinding given	Unclear
(5)	Within each treatment group discontinuation rates were low and comparable (10.3% for placebo, 7.4% for solifenacin 5mg and 7.8% for solifenacin 10mg). A dropout rate of 20% was assumed when calculating study numbers.	No
(6)	All outcomes planned to be measured in the study appear to be reported in the publication.	No
(7)	Efficacy analysis included all randomised patients who received ≥ 1 dose of study medication and who had efficacy data from the baseline and ≥ 1 on treatment visit. All patients who received ≥ 1 dose of medication were included in safety evaluation. This was considered appropriate.	Yes
Chapple 2004 (51)		
(1)	No description of randomisation given.	No
(2)	No description of allocation concealment given.	No
(3)	The 4 groups were well balanced for all demographic characteristics. With respect to clinical characteristics, the mean number of voids/24 h was similar among treatment groups. The mean time from start of symptoms and previous drug treatment for OAB were more variable.	No
(4)	To maintain blinding, all patients continued to take medication BID (using placebo tablets and capsules as necessary. No further description of blinding given.	Unclear

(5)	20% discontinuation rate assumed when calculating study numbers. 10% of patients discontinued treatment. Highest discontinuation rate was in placebo group. The discontinuation rate for AEs was low and comparable across the 4 treatment arms.	Yes
(6)	All outcomes planned to be measured in the study appear to have been reported in the publication.	No
(7)	Although the authors reported discontinuations, there was no mention of statistical methods used to account for these. No ITT analysis was reported.	Unclear
Chapple 2004 (50)		
(1)	No description of randomisation given	Unclear
(2)	No description of allocation concealment given	Unclear
(3)	Treatment groups described as demographically comparable. The groups were also similar with respect to the presence of urge incontinence	Yes
(4)	Study is described as double-blind, but no description of blinding given	Unclear
(5)	No notable differences in discontinuation rates between treatment groups	No
(6)	All outcomes planned to be measured in the study protocol appear to be reported in the clinical study	Yes
(7)	Primary efficacy analysis derived from FAS (all randomised patients who received ≥ 1 dose of study medication and for whom data were available at baseline and one additional visit). Secondary efficacy analysis included data from both the FAS and the per-protocol set. This was considered appropriate.	Yes
Chapple 2007 (49)		
(1)	No description of randomisation given.	Unclear
(2)	No description of allocation concealment given.	Unclear
(3)	The 2 treatment groups were well balanced with respect to both baseline demographic and disease characteristics.	Yes
(4)	To ensure adequate blinding, placebo had to be given in both forms in the run-in phase. In the double-blind phase, placebo was given as a capsule to the fesoterodine group and as a tablet to the tolterodine group. While it is clear that the patients were blinded, it is unclear whether it was the carers or outcome assessors that were blinded.	Not clear
(5)	Discontinuations because of an AE were low in all groups. AEs observed in any of the active treatment groups were low and similar to placebo, except for dry mouth, which occurred at a higher rate with fesoterodine 8 mg.	No
(6)	All outcomes planned to be measured in the study protocol appear to be reported in the publication.	No
(7)	Primary subject population for statistical analyses of efficacy was FAS (all subjects who were randomised, received any study medication, and for whom baseline and double-blind micturition data were available). Safety analyses were conducted on the safety set (all subjects who took ≥ 1 dose of trial medication after randomisation). This was considered appropriate.	Unclear
Choo 2008 (52)		
(1)	No description of randomisation given.	Unclear
(2)	No description of allocation concealment given.	Unclear
(3)	Baseline characteristics and demographics similar among all treatment groups.	Yes
(4)	To maintain blinding, all patients continued to take medication BID using placebo tablets and capsules as necessary. The study is described as double blind, but blinding of carers/ investigators is not described.	Unclear
(5)	No unexpected imbalances in drop-outs between groups. There were 22, 22 and 18 discontinuations in the solifenacin 5mg, 10mg and tolterodine 2mg groups respectively. Data available at the point of withdrawal were analysed. Missing data was accepted as such.	No
(6)	All outcomes planned to be measured as listed in the methodology section appear to be reported in the publication.	No
(7)	The efficacy analysis included all randomised patients who had efficacy data available from baseline and ≥ 1 on-treatment visit. Data analysis with the LOCF method was performed and presented for efficacy analysis. This was considered appropriate.	Yes
Chu 2009 (53)		
(1)	Randomisation performed at centre level to provide a balance of treatment groups within a centre. PROC PLAN used to generate the randomisation codes. Sealed copies of randomisation code were kept by Covance Drug Safety Coordination US.	Yes
(2)	Each pack had a blinded tear-off label containing the name of the product and dose, to be used only if it was necessary to unblind a patient.	Yes
(3)	The 2 groups were comparable with respect to baseline demographic and clinical characteristics.	Yes

(4)	Solifenacin 10mg or placebo orally were supplied in identical blister packs. Solifenacin and placebo tablets were also identical in appearance to maintain blinding.	Yes
(5)	Discontinuation rates were comparable between groups; 20.6% in the solifenacin group and 17.5% in the placebo group. Sample size calculated assuming a 20% drop-out rate.	No
(6)	All outcomes planned to be measured in the methodology section appear to be reported in the results.	No
(7)	The efficacy analysis was performed using the FAS. The safety analyses were performed using all patients who were randomised and received ≥1 dose of double-blind treatment.	Yes
Corcos 2006 (54)		
(1)	Randomisation was carried out using a block size of six within each stratum.	Yes
(2)	No description of allocation concealment given.	Unclear
(3)	Treatment groups were demographically comparable, with no statistically significant differences among the three groups in age, previous anticholinergic exposure and baseline symptoms of urgency, voiding frequency or total UI	Yes
(4)	Randomised patients took 1 tablet of the relevant strength daily and 2 placebo tablets. Placebo tablets for the 5, 10 and 15 mg doses were identical in size, colour and composition to active tablets but with no active ingredient.	Yes
(5)	There were 9, 20 and 18 discontinuations in the oxybutynin 5mg, 10 mg and 15 mg groups respectively. The differences in discontinuations were explained. There were 3 AEs in the 5 mg group and 11 and 12 AEs in the 10 and 15 mg groups.	No
(6)	All outcomes planned to be measured in the methodology section appear to be reported in the results.	No
(7)	An ITT analysis of efficacy and safety was used for all randomised patients. This was considered appropriate.	Yes
Diokno 2003 (55)		
(1)	No description of randomisation given.	No
(2)	No description of concealment allocation given.	No
(3)	The 2 treatment groups were well balanced with respect to baseline demographic characteristics as well as baseline averages of weekly episodes of urinary urge incontinence episodes, weekly micturition frequency and history of prior anticholinergic treatment.	Yes
(4)	Medication was over-encapsulated to ensure both participants and investigators were blinded to the assigned treatment.	Yes
(5)	Although more participants in the oxybutynin vs tolterodine group were lost to follow up, at last observation they had better mean responses on all measures and fewer AEs for the number of dropouts. The authors suggest that efficacy or tolerability did not determine the difference between groups.	Yes
(6)	All outcomes planned to be measured in the methodology section appear to be reported in the results.	No
(7)	All efficacy analysis were based on an ITT population (all participants who took a study drug and completed ≥ 1 efficacy assessment while receiving treatment). This was considered appropriate.	Yes
Dmochowski 2003 (56)		
(1)	No description of randomisation given	No
(2)	No description of blinding given	No
(3)	Treatment groups were comparable with respect to demographic and disease characteristics and prior antimuscarinic treatment	Yes
(4)	No description of blinding given	No
(5)	The imbalances in discontinuations were explained. AEs led to treatment discontinuations in 13 oxybutynin patients and two tolterodine patients. The LOCF imputation was used for patients who did not complete the treatment period.	No
(6)	All outcomes planned to be measured, appear to be reported in the results	No
(7)	The ITT population was analysed. This included all patients who received medication and at least one efficacy assessment. This was considered appropriate.	Yes
Herschorn 2008 (77)		
(1)	No description of randomisation given.	Unclear
(2)	No description of allocation concealment given.	Unclear
(3)	Baseline demographics and baseline OAB parameters were comparable between the study groups.	Yes
(4)	No description of blinding given	Unclear
(5)	22/207 subjects discontinued in the placebo group while 36/410 discontinued in the tolterodine group. In the tolterodine group 3% of subjects discontinued because of an	No

	AE. In the placebo group 1% of subjects discontinued because of an AE.	
(6)	All outcomes planned to be measured appear to be reported in the results	No
(7)	ITT population analysed for the efficacy evaluation. This included all subjects who had ≥1 dose of study drug and ≥1 post-baseline assessment. The safety population included all subjects who received ≥1 dose of study drug regardless of whether they had a post-baseline assessment. This was considered appropriate.	Yes
Herschorn 2010 (58)		
(1)	Simple randomisation schedule with a block of 5 implemented using centralised system.	Yes
(2)	The randomisation schedule was generated, secured distributed and stored by Pfizer Global Clinical Data Services; neither the investigator nor the patient was aware of which treatment was administered.	Yes
(3)	Baseline demographic and clinical characteristics were similar among the groups.	Yes
(4)	No description of blinding was given, except that all medications were taken once daily in the morning.	Unclear
(5)	Overall rates of discontinuations were low. 2% receiving placebo, 4% receiving tolterodine and 6% receiving fesoterodine discontinued due to treatment-emergent AE. The most frequently reported TEAE in the tolterodine and fesoterodine groups were dry mouth, headache and constipation. Investigators assumed that ~90% of the randomised patients would contribute to the FAS, so 1,675 patients were randomised even though sample size calculations required 1,515.	No
(6)	All outcomes planned to be measured appear to be reported in the results	No
(7)	Efficacy was analysed using FAS (randomised patients who took ≥1 dose of study drug and had ≥1 baseline or post-baseline efficacy assessment). The safety analysis set included all patients who were randomised and took ≥1 dose of study drug. This was considered appropriate.	Yes
Herschorn 2010 (57)		
(1)	Eligible patients were randomised using a computerised randomisation list consisting of 48 blocks of four patients each.	Yes
(2)	No description of concealment of treatment allocation given.	Unclear
(3)	There were no significant demographic differences between the groups.	Yes
(4)	The solifenacin groups received 1 active tablet and 3 placebo capsules daily, while the oxybutynin group received 1 placebo tablet and 3 active capsules daily.	Yes
(5)	Overall discontinuation rate did not differ significantly between the solifenacin and oxybutynin groups, (24% vs38%, p=0.081). However, significantly fewer solifenacin treated patients withdrew due to dry mouth (3% vs 19%, p=0.003 An additional 21 patients per arm were recruited in anticipation of patients lost of follow-up.	No
(6)	All outcomes planned to be measured appear to be reported in the results	No
(7)	All safety and efficacy analysis were done in the ITT population. Data imputation for missing data was not done for the efficacy analysis. This was appropriate as the study was not powered to detect treatment related differences in diary variables.	Yes
Ho 2010 (59)		
(1)	No description of randomisation was given.	Unclear
(2)	No description of concealment of treatment allocation was given.	Unclear
(3)	The two treatment groups were not significantly different in demographic characteristics.	Yes
(4)	Open label study.	No
(5)	One patient in the solifenacin group withdrew because of dizziness and one patient in the tolterodine group withdrew because of palpitations. Between the two groups, the incidence of each AE was not significantly different.	No
(6)	All outcomes planned to be measured appear to be reported in the results.	No
(7)	Safety population- patients who took at least one dose of study medication. FAS (patients who took ≥ 1 dose of study medication and provided efficacy data at baseline and endpoint), PP (patients in the FAS who completed the study without major deviation from the protocol). All efficacy analysis were based on PP. No explanation given for dealing with missing data.	No
Homma 2003 (60)		
(1)	Patients were randomised using the method of random permuted blocks.	Yes
(2)	No description of concealment of treatment allocation was given.	Unclear
(3)	Baseline and demographic characteristics well matched among the 3 treatment groups.	Yes
(4)	Blinding was achieved by providing matching placebos for both tolterodine and oxybutynin. Patients were instructed to take one tolterodine or placebo capsule in the morning, plus one oxybutynin or placebo tablet three times daily.	Yes
(5)	A higher incidence of withdrawal was reported for oxybutynin (23.2%) than placebo	No

	(16.4%) and tolterodine groups (10.4%). This was due to the higher frequency of withdrawals for AEs with oxybutynin than with placebo or tolterodine. Other reasons for withdrawals were similar between treatment groups.	
(6)	All outcomes planned to be measured appear to be reported in the results.	No
(7)	Efficacy was analysed on an ITT basis for all randomised patients who received at least one dose of study drug, using the LOCF for any missing 12-week values. This was considered appropriate.	Yes
Jacquetin 2001 (61)		
(1)	No description of randomisation was given.	Unclear
(2)	No description of concealment of allocation was given.	Unclear
(3)	The baseline demographic and clinical characteristics were similar in each treatment group with the exception of body mass index which was significantly	
(4)	Placebo was given as physically indistinguishable tablets.	Yes
(5)	Six patients were withdrawn from the study as a result of AEs, with a similar proportion (2-3%) coming from each group. Dry mouth was the reason from withdrawal for four patients (two from each of the tolterodine treatment groups).	No
(6)	All outcomes planned to be measured appear to be reported in the results.	No
(7)	Analysis of efficacy was made on an ITT basis using all randomised patients who had taken at least one dose of study drug. This was considered appropriate.	Yes
Kaplan 2011 (62)		
(1)	A randomisation schedule with a block size of five was implemented. It was generated, secured, distributed and stored by Pfizer Global Clinical Data Services.	Yes
(2)	No description of concealment of treatment allocation was given.	Unclear
(3)	Baseline demographic and clinical characteristics similar among treatment groups.	Yes
(4)	All subjects instructed to take 1 tablet (fesoterodine 4 or 8 mg, or matching placebo) and 1 capsule (tolterodine ER 4 mg, or matching placebo) daily in the morning.	Yes
(5)	In the placebo, tolterodine and fesoterodine groups, 2%, 3% and 5% of subjects respectively, were discontinued owing to treatment emergent AEs. The most frequently reported TEAE in all groups was dry mouth.	No
(6)	All outcomes planned to be measured appear to be reported in the results.	No
(7)	Efficacy analyses were initially planned to include all subjects taking one or more dose of double blind study drug and having at least one valid post-baseline efficacy assessment. Safety analysis set included all subjects who took one or more doses or double-blind study drug. 77 subjects from 3 sites with practice violations and data irregularities were excluded from the full analysis set, but included in the safety analysis set. Missing post-baseline data were imputed based on the last-observation-carried-forward principle. This was considered appropriate.	Yes
Khullar 2004 (63)		
(1)	Random permuted blocks with a computer generated randomisation list was prepared by a trial-independent statistician.	Yes
(2)	Trial drugs of identical appearance were pre-packaged according to randomisation list and a multiple block size distributed to each study centre. Investigator at each centre allocated treatment by assigning subject numbers in strict consecutive order.	Yes
(3)	Treatment groups well matched for demographic and baseline disease characteristics.	Yes
(4)	Trial drugs were pre-packaged and were identical in appearance. No further description of blinding was given.	Unclear
(5)	In the tolterodine group, 4.6% of patients withdrew because of AEs compared with 5.6% in the placebo group. The AE frequency was similar between groups (tolterodine 39%, placebo 34%; p=0.14).	No
(6)	All outcomes planned to be measured appear to be reported in the results.	No
(7)	The analysis of efficacy was performed on intent to treat basis with the last observation after randomisation carried forward method. This was considered appropriate.	Yes
Lackner 2008 (64)		
(1)	Participants were randomised by the investigational pharmacy using a computer generated randomisation program.	Yes
(2)	No description of concealment of treatment allocation was given.	Unclear
(3)	There were no group differences in baseline demographic, functional or neuropsychiatric characteristics.	Yes
(4)	Oxybutynin tablets or placebo (identical-appearing sham tablet) OD were supplied. Study personnel blinded to group assignment until data collection was complete.	Yes
(5)	96% of patients receiving drug completed the trial (4% discontinued) and 92% of patients receiving placebo completed the trial (8% discontinued) P=055.	No
(6)	All outcomes planned to be measured appear to be reported in the results.	No

(7)	Where participants discontinued, the method of LOCF was not employed in order to most reliably reflect change at the time point of participant withdrawal.	No
Lee 2002 (65)		
(1)	Patients randomised using computer generated, random permuted blocks.	Yes
(2)	No description of concealment of treatment allocation was given.	Unclear
(3)	There were no statistically significant differences between the two treatment groups with respect to baseline demographic and clinical characteristics.	Yes
(4)	Double-dummy technique was used to maintain blinding. No further description of blinding was given.	Unclear
(5)	29 patients (tolterodine 11/112; oxybutynin 18/115) withdrew from the study due to AEs, mainly due to dry mouth.	No
(6)	All outcomes planned to be measured appear to be reported in the results	No
(7)	Analysis of efficacy was performed for all randomised patients (ITT), using all the last observed data. Missing micturition data were extrapolated by the principle of LOCF from baseline. Safety analysis was performed for all patients who took at least one dose of study medication. This was considered appropriate.	Yes
Malone-Lee 2001 (66)		
(1)	No description of randomisation was given.	Unclear
(2)	No description of concealment of treatment allocation was given.	Unclear
(3)	No statistically significant differences in demographic characteristics between groups. Baseline mean volume voided per micturition was also comparable in the three treatment groups. However, compared with the placebo group, the baseline mean number of micturitions/24 hours was significantly higher in the 2 tolterodine treatment groups. Compared with the placebo group, the mean number of urge incontinence episodes/24 hours was significantly lower than in the 2 tolterodine groups.	No
(4)	To maintain blinding, all study medication was supplied in physically indistinguishable tablets. No further description of blinding was given.	Unclear
(5)	The number of patients who withdrew because of AEs was higher in the tolterodine treatment groups, although these changes were not statistically significant (placebo 2%; tolterodine 1 mg bid 7%; tolterodine 2 mg bid 10%).	No
(6)	All outcomes planned to be measured appear to be reported in the results.	No
(7)	No description is given of the analysis sets used for efficacy and safety analyses. No description was given of how missing data was accounted for.	Yes
Nitti 2007 (67)		
(1)	A computer generated randomisation schedule was used and was stratified by site.	Yes
(2)	No description of concealment of treatment allocation was given.	Unclear
(3)	The groups appeared to be similar in baseline and clinical characteristics.	Yes
(4)	Placebo tablets were identical in appearance to the 4 mg and 8 mg fesoterodine tablets. No further description of blinding was given.	Unclear
(5)	19% of subjects (155 of 836) discontinued the study prematurely. 53 subjects withdrew because of AEs (4% on placebo; 6% on 4 mg fesoterodine and 9% on 8 mg fesoterodine).	No
(6)	All outcomes planned to be measured appear to be reported in the results	No
(7)	The full analysis set included all randomised subjects receiving trial medication for whom a baseline and double-blind treatment measure was obtained. The safety population included all subjects who received one or greater doses. Missing responses were imputed via LOCF. This was considered appropriate.	Yes
Nitti 2010 (68)		
(1)	No description of randomisation was given.	Unclear
(2)	No description of concealment of treatment allocation was given.	Unclear
(3)	Demographic characteristics were similar for patients randomised to placebo, fesoterodine 4, 8 and 12 mg, and for patients assigned to strata A and B based on urodynamic assessment.	Yes
(4)	No description of blinding was given.	Unclear
(5)	Ten patients discontinued during the double-blind treatment period: placebo 5%, fesoterodine 4-, 8- and 12 mg groups 2%, 4% and 13%. Dry mouth was the most common cause of discontinuation.	No
(6)	All outcomes planned to be measured appear to be reported in the results	No
(7)	FAS (all patients who had received ≥ 1 doses of trial medication after randomisation and had one or more assessment after baseline). Safety set (all patients who had received ≥ 1 doses of trial medication after randomisation). Missing data for primary and secondary variables were imputed using LOCF.	Yes
Rackley 2006 (69)		
(1)	No description of randomisation was given.	Unclear
(2)	No description of concealment of treatment allocation was given.	Unclear

(3)	Baseline demographic and clinical characteristics comparable between treatment groups.	Yes
(4)	No description of blinding was given.	Unclear
(5)	No description of drop-outs was given.	Unclear
(6)	All outcomes planned to be measured appear to be reported in the results.	No
(7)	The intent to treat population (all randomised patients) was used for the efficacy analysis. The safety population was defined as all randomised patients who received any study medication. Missing post-baseline data was imputed using the last-observation-carried forward technique. This was considered appropriate.	Yes
Rogers 2008 (70)		
(1)	The randomisation schedule was generated with a fixed block size of four.	Yes
(2)	No description of concealment of treatment allocation was given.	Unclear
(3)	Demographic and clinical characteristics were similar in the two treatment groups.	Yes
(4)	No description of blinding was given.	Unclear
(5)	Discontinuation rates were similar in the two treatment groups.	No
(6)	All outcomes planned to be measured appear to be reported in the results.	No
(7)	Modified ITT (all subjects who took ≥ 1 dose of study drug and had ≥ 1 post baseline efficacy assessment). The MITT population excluded one subject who was determined to be an extreme outlier; safety population (all subjects who took ≥ 1 dose of study drug). Missing post baseline data were imputed using the LOCF.	Yes
Rudy 2006 (71)		
(1)	No description of randomisation was given.	Unclear
(2)	No description of concealment of treatment allocation was given.	Unclear
(3)	The treatment groups did not differ significantly in baseline characteristics.	Yes
(4)	Ne description of blinding was given.	Unclear
(5)	Overall in the placebo group 9.7% of patients discontinued treatment, while 12.8% of patients in the trospium group discontinued. AEs led to discontinuation in 4.6% of the placebo group and 7.3% in the trospium group.	No
(6)	All outcomes planned to be measured appear to be reported in the results	No
(7)	Efficacy was assessed using the ITT patient sample, LOCF dataset. Efficacy was also analysed with no data imputation (observed cases dataset) to assess the potential impact of missing data on outcomes.	Yes
Staskin 2007 (72)		
(1)	Randomisation was accomplished with an interactive voice response system (Kronos Communication Data). No further description of randomisation was given.	Unclear
(2)	No description was given of concealment of treatment allocation.	Unclear
(3)	Baseline characteristics were comparable in the 2 groups.	Yes
(4)	No description of blinding was given.	Unclear
(5)	The treatment groups were similar with respect to the rates of and reasons for discontinuations. The most common reason for discontinuations were AEs (trospium 4% and placebo 3.6%) or the withdrawal of participant consent.	No
(6)	All outcomes planned to be measured appear to be reported in the results.	No
(7)	All primary and secondary efficacy assessments were performed using the intent to treat subject sample. Efficacy analyses were performed using LOCF data set. This was considered appropriate.	Yes
van Kerrebroeck 2001 (73)		
(1)	Patients were randomised using the procedure of random permuted blocks.	Yes
(2)	No description of concealment of treatment allocation was given.	Unclear
(3)	Treatment groups well matched with regard to demographic and baseline disease characteristics.	Yes
(4)	Double-dummy drug packaging technique used to maintain blinding. No further description of blinding was given.	Unclear
(5)	187 (12%) of patients prematurely withdrawn from the study. Main reason for withdrawal in all treatment groups was AEs; 88 patients (5% tolterodine ER; 5% tolterodine IR and 6% placebo) were withdrawn from the study due to AEs. Aside from dry mouth, all other side effects were seen with a similar frequency in the treatment and placebo groups.	No
(6)	All outcomes planned to be measured appear to be reported in the results.	No
(7)	Efficacy analysis was performed for all randomised patients on an ITT basis using the LOCF to estimate the values for patients that dropped out of the study early. This was considered appropriate.	Yes
Yamaguchi 2007 (74)		
(1)	No description of randomisation was given.	Unclear
(2)	No description of concealment of treatment allocation was given.	Unclear
(3)	The baseline characteristics were comparable across all treatment groups.	Yes

(4)	No description of blinding was given.	Unclear
(5)	Discontinuation rates were low and comparable within each treatment group. Those due to AEs were also similar in the active treatment groups. Discontinuation rates due to AEs were 2.7% placebo, 5.1% solifenacin 5 mg, 6.8% solifenacin 10 mg, 6.5% propiverine 20 mg groups.	No
(6)	All outcomes planned to be measured appear to be reported in the results.	No
(7)	The efficacy analysis population comprised all randomised patients with data available at baseline and for at least one visit after, who received at least one dose of study medication. Safety analyses were conducted for all patients who received at least one dose of study medication. LOCF approach was used to determine end-point values if week 12 data was not available.	Yes
Yamaguchi 2011 (75)		
(1)	No description of randomisation was given.	Unclear
(2)	No description of concealment of treatment allocation was given.	Unclear
(3)	All demographic characteristics were comparable at baseline among the three treatment groups. The mean (standard deviation) number of UUI episodes per 24 hours at baseline was also comparable across the three treatment groups.	Yes
(4)	No description of blinding was given.	Unclear
(5)	Percentage of subjects who permanently discontinued the study due to AEs was similar among the treatment groups (3.5%, placebo; 4.7% fesoterodine 4 mg; and 4.5%, fesoterodine 8 mg).	No
(6)	All outcomes planned to be measured appear to be reported in the results.	No
(7)	FAS for efficacy analyses (all subjects who took ≥ 1 dose of study drug after randomisation and had efficacy observations at baseline and post baseline). Safety analyses were conducted on the SAS comprising all subjects who took ≥ 1 dose of study drug after randomisation. LOCF used to impute missing data at week 12.	Yes
Zinner 2002 (76)		
(1)	Randomisation list prepared by a trial independent statistician through the method of random permuted blocks using a computer software program. It was kept secure until the database was locked and subsequently unblended for analysis.	Yes
(2)	No description of concealment of treatment allocation was given.	Unclear
(3)	Both treatment groups within each age cohort were well matched in terms of demographic and baseline disease characteristics.	Yes
(4)	No description of blinding was given.	Unclear
(5)	No difference was noted between the age cohorts in reasons for discontinuations. The most common reason for treatment discontinuation was AEs (placebo, 6.5%; tolterodine mg OD, 5.3%).	No
(6)	All outcomes planned to be measured appear to be reported in the results	No
(7)	Analysis of efficacy was performed for all randomised patients on an ITT basis. The “carry forward” approach was used. This was considered appropriate.	Yes

10.6 Appendix 6: Search strategy for Section 6.8 (Non-RCT evidence)

10.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***The Cochrane Library***

The following databases were searched:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
- EMBASE (Ovid).

10.6.2 The date on which the search was conducted.

The searches were conducted on the 13th June 2012.

10.6.3 The date span of the search.

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
- EMBASE (Ovid), 1980 to 2012 Week 23.

10.6.4 The complete search strategies used. including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

EMBASE 1980 to 2012 Week 23; Searched on 13th June 2012

	Searches	Results
1	overactive bladder.mp. or exp overactive bladder/	6716
2	dry overactive bladder.mp.	5
3	detrusor dyssynergia.mp. or exp detrusor dyssynergia/	2512
4	bladder instability.mp. or exp bladder instability/	765
5	urinary urgency.mp. or exp urinary urgency/	3106
6	urge incontinence.mp. or exp urge incontinence/	4819
7	urinary frequency.mp. or exp urinary frequency/	4115
8	exp urine incontinence/ or urin* incontin*.mp.	48042
9	stress incontinence.mp. or exp stress incontinence/	14392
10	unstable bladder.mp.	281
11	((overactive adj3 bladder) or (urge adj3 incontinence) or (detrusor adj3 dyssynergia) or (urge adj3 syndrome) or (urin* adj3 freq*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	18114
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	58913
13	exp mirabegron/	35
14	(mirabegron or YM-178 or Betanis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	79
15	13 or 14	79
16	Clinical study/	39716
17	Case control study/	67754
18	Family study/	9577
19	Longitudinal study/	53366

20	Retrospective study/	282319
21	Prospective study/	206317
22	Randomized controlled trials/	17196
23	21 not 22	205902
24	Cohort analysis/	124503
25	(Cohort adj (study or studies)).mp.	83889
26	(Case control adj (study or studies)).tw.	61460
27	(follow up adj (study or studies)).tw.	39490
28	(observational adj (study or studies)).tw.	45068
29	(epidemiologic$ adj (study or studies)).tw.	64810
30	(cross sectional adj (study or studies)).tw.	61424
31	or/16-20,23-30	934159
32	12 and 15 and 31	4
33	limit 32 to human	4
34	limit 33 to yr="2000 -Current"	4

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; Searched on 13th June 2012

	Searches	Results
1	overactive bladder.mp. or exp Urinary Bladder, Overactive/	3209
2	exp Urinary Incontinence/ or detrusor dyssynergia.mp.	24193
3	exp Urinary Incontinence, Urge/ or urinary urgency.mp.	896
4	urinary frequency.mp.	1081
5	dry overactive bladder.mp.	4
6	bladder irritation.mp.	155
7	bladder instability.mp.	354
8	unstable bladder.mp.	234
9	exp Urinary Incontinence, Stress/ or stress incontinence.mp.	9678
10	((urin* adj3 incontinence) or (overactive adj3 bladder) or (urge adj3 incontinence) or (urge adj3 syndrome) or (urin* adj3 freq)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	31012
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	32748
12	mirabegron.mp.	14
13	(mirabegron or YM-178 or Betanis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	16
14	12 or 13	16
15	Epidemiologic studies/	5416
16	exp case control studies/	558091
17	exp cohort studies/	1184639
18	Case control.tw.	63861
19	(cohort adj (study or studies)).tw.	65236
20	Cohort analy$.tw.	2895
21	(Follow up adj (study or studies)).tw.	34054
22	(observational adj (study or studies)).tw.	33710
23	Longitudinal.tw.	117797
24	Retrospective.tw.	225646
25	Cross sectional.tw.	132559
26	Cross-sectional studies/	142214
27	or/15-26	1621110
28	11 and 14 and 27	0

10.6.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Additional studies were identified by hand searching the following resources:

- Reference lists of previous trials and systematic reviews

- Conference proceedings (2010 – 2012)
- International Continence Society (ICS) (2010-2012) - http://www.icsoffice.org/
- American Urological Association (AUA) (2010-2012) -
- European Association of Urology (EAU) (2010-2012) - http://www.uroweb.org/
- International Urogynecological Association (IUGA) (2010-2012).

10.6.6 The inclusion and exclusion criteria.

	Description	Justification
Inclusion criteria		
Population	Adults with symptoms of OAB	As outlined in draft scope
Interventions	Mirabegron	As outlined in draft scope
Outcomes	Symptoms of urgency Urinary frequency Frequency of urge urinary incontinence Nocturia Adverse effects of treatment	As outlined in draft scope
Study design	Prospective observational studies	RCT studies were identified through a separate search
Language restrictions	English publications or non-English publications with an English abstract	
Exclusion criteria		
Population	Patients <18 years of age. Patients with LUTS	
Interventions	Studies not investigating Mirabegron or a relevant comparator	
Outcomes	Studies not reporting the outcomes listed in the scope.	
Study design	Randomised controlled studies Observational studies with a retrospective design.	RCT studies were identified through a separate search.
Language restrictions	Non-English publications	

Abbreviations: LUTS, lower urinary tract symptoms; OAB, overactive bladder; RTC, randomised controlled trial.

10.6.7 The data abstraction strategy.

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party. Relevant information was abstracted into the STA template/ into a pre-defined Microsoft Word® document by a reviewer. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion.

10.7 Appendix 7: Quality assessment of non-RCT(s) in Section 6.8 (Non-RCT evidence)

Table 129: Quality assessment for non-RCT, 178-CL-051

178-CL-051	**Grade (yes/no/not clear/NA)**
Study question	
Were selection/eligibility criteria adequately reported?	Yes
Was the selected population representative of that seen in normal practice?	Yes
Was an appropriate measure of variability reported?	Yes
Was loss to follow-up reported or explained?	Not clear
Were at least 90% of those included at baseline followed up?	Not clear
Were patients recruited prospectively?	Yes
Were patients recruited consecutively?	Yes
Did the study report relevant prognostic factors?	Yes

10.8 Appendix 8: Search strategy for Section 6.9 (Adverse events)

The clinical search described in Section 6.1 and Section 10.2 was also designed to identify eligible studies for AEs associated with mirabegron.

10.9 Appendix 9: Quality assessment of adverse event data in Section 6.9 (Adverse events)

10.9.1 Please tabulate the quality assessment of each of studies identified.

A quality assessment of relevant studies can be found in Section 10.3.

10.10 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

10.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***EconLIT***
- ***NHS Economic Evaluation Database (NHS EED)***

The databases searched were Medline, Embase and NHS EED.

10.10.2 The date on which the search was conducted.

The search was conducted on 26th November 2011.

10.10.3 The date span of the search.

There was no restriction on the date of publication.

10.10.4 The complete search strategies used, including all the search term textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Economic search strategy for Medline and Embase

No.	Query	Results
#1	'overactive bladder'/exp OR 'urge incontinence'/exp OR 'detrusor dyssynergia'/exp OR 'urinary urgency'/exp OR 'urinary frequency'/exp OR 'bladder irritation'/exp	15,713
#2	'economics' OR 'economics'/exp OR economics OR 'economic value of life'/exp OR 'economic value of life' OR 'health economics'/exp OR 'health economics' OR 'economic evaluation'/exp OR 'economic evaluation' OR 'pharmacoeconomics' OR 'pharmacoeconomics'/exp OR pharmacoeconomics OR 'health care cost'/exp OR 'health care cost' OR 'health care costs'/exp OR 'health care costs' OR resource NEAR/2 (use OR utilization OR utilisation OR trend OR trends) OR 'budget impact' OR (economic AND burden) OR 'cost of illness'/exp OR 'cost of illness' OR 'cost analysis'/exp OR 'cost analysis' OR 'cost effectiveness'/exp OR 'cost effectiveness' OR 'cost utility'/exp OR 'cost utility' OR 'cost benefit'/exp OR 'cost benefit' OR 'cost minimization'/exp OR 'cost minimization' OR 'markov model' OR 'decision tree'/exp OR 'decision tree' OR 'decision analytic model' OR 'discrete event model'	803,788
#3	[humans]/lim	12,695,366
#4	#1 AND #2 AND #3	778

Economic search strategy for NHS EED

No.	Query	Results
#1	"overactive bladder" OR "urge incontinence" OR "detrusor dyssynergia" OR "urinary urgency" OR "urinary frequency" OR "bladder irritation"	23

10.10.5 Details of any additional searches, (for example, searches of company databases [include a description of each database]).

None.

10.10.6 The inclusion and exclusion criteria.

Studies were included in the review based on the following criteria:

- Study design: all cost-effectiveness and cost-utility studies, budget impact analyses and other forms of economic evaluations were included, whether based on models, observational studies or RCTs.
- Study design: all costing studies that reported cost or resource use by pharmacological treatment.
- Population: only adults (age ≥ 18 years old) diagnosed with OAB.
- Treatment: only pharmacological treatment for OAB.
- Publication date: no restriction on the time.

Studies were excluded from the review based on the following criteria:

- Case report study
- Published only as an abstract
- Database studies
- Literature reviews
- Patients were not OAB
- Treatment was not pharmacological treatment: botulinum toxin A, bladder retraining or devices were excluded.
- Study did not report costs of OAB by treatment or did not report any economic evaluation outcome.

10.10.7 The data abstraction strategy.

All abstracts were reviewed by two independent reviewers.

10.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

Study question	Study name															
	Arikian 2000 (1)	Arlandis-Guzman 2011 (1)	Cardozo 2010 (3)	Getsios 2004 (4)	Getsios 2004 (5)	Guest 2004 (6)	Hakkaart 2009 (7)	Herschorn 2010 (8)	Hughes 2004 (9)	Ko 2006 (10)	Kobelt 1998 (11)	Milsom 2009 (12)	Nilsson 2012 (13)	O'Brien 2001 (14)	Pradelli 2009 (15)	Speakman 2008 (16)
Study design																
1. Was the research question stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Was the economic importance of the research question stated?	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	Y	Y	N
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Y	Y	Y	U	U	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y
5. Were the alternatives being compared clearly described?	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y
6. Was the form of economic evaluation stated?	Y	Y	Y	U	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Data collection																
8. Was/were the source(s) of effectiveness estimates used stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N	N	N/A	Y	Y	N	Y	Y	Y	N/A	Y	Y	N/A	Y	Y	Y
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N	Y	Y	U	N/A	U	Y	N/A	Y	Y	Y	Y	N/A	Y	Y	N/A
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
12. Were the methods used to value health states and other benefits stated?	N/A	Y	Y	Y	Y	N/A	Y	N	N/A	Y	Y	Y	Y	Y	Y	Y

Study question	Study name															
	Arikian 2000 (1)	Arlandis-Guzman 2011 (1)	Cardozo 2010 (3)	Getsios 2004 (4)	Getsios 2004 (5)	Guest 2004 (6)	Hakkaart 2009 (7)	Herschorn 2010 (8)	Hughes 2004 (9)	Ko 2006 (10)	Kobelt 1998 (11)	Milsom 2009 (12)	Nilsson 2012 (13)	O'Brien 2001 (14)	Pradelli 2009 (15)	Speakman 2008 (16)
13. Were the details of the subjects from whom valuations were obtained given?	N/A	Y	N	Y	Y	N/A	Y	N	N/A	N	Y	Y	U	Y	Y	Y
14. Were productivity changes (if included) reported separately?	N/A	Y	N/A	N	N	Y	N/A	N	N/A	N/A	N/A	U	N/A	N/A	N/A	N/A
15. Was the relevance of productivity changes to the study question discussed?	N	Y	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N
16. Were quantities of resources reported separately from their unit cost?	N	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	N	N	N
17. Were the methods for the estimation of quantities and unit costs described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
18. Were currency and price data recorded?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	N	Y
19. Were details of price adjustments for inflation or currency conversion given?	N/A	N/A	N/A	Y	Y	N	N/A	N/A	Y	Y	U	N/A	Y	N	N	Y
20. Were details of any model used given?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y
Analysis and interpretation of results																
22. Was the time horizon of cost and benefits stated?	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y
23. Was the discount rate stated?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N	N/A	N/A	N/A	N/A	N	N/A	N/A
24. Was the choice of rate justified?	N	Y	Y	Y	Y	N	N	Y	N	N	N	N	N	N	Y	N
25. Was an explanation given if cost or benefits were not discounted?	N	Y	Y	Y	Y	N	N	Y	N	N	N	N	N	N	Y	N
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N	N/A	Y	N/A	N/A	U	N/A	Y	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Study question	Study name															
	Arikian 2000 (1)	Arlandis-Guzman 2011 (1)	Cardozo 2010 (3)	Getsios 2004 (4)	Getsios 2004 (5)	Guest 2004 (6)	Hakkaart 2009 (7)	Herschorn 2010 (8)	Hughes 2004 (9)	Ko 2006 (10)	Kobelt 1998 (11)	Milsom 2009 (12)	Nilsson 2012 (13)	O'Brien 2001 (14)	Pradelli 2009 (15)	Speakman 2008 (16)
27. Was the approach to sensitivity analysis described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
28. Was the choice of variables for sensitivity analysis justified?	Y	Y	Y	N	N	Y	N	Y	Y	N	N	Y	Y	Y	Y	Y
29. Were the ranges over which the parameters were varied stated?	N	Y	Y	U	U	U	U	Y	Y	Y	Y	N	Y	Y	Y	Y
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
31. Was an incremental analysis reported?	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
32. Were major outcomes presented in a disaggregated as well as aggregated form?	N	N	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	N	N
33. Was the answer to the study question given?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
34. Did conclusions follow from the data reported?	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	N/A	U	Y	N/A
35. Were conclusions accompanied by the appropriate caveats?	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y	Y	N	N	Y
36. Were generalisability issues addressed?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Abbreviations: N, no; N/A, not applicable; U, unclear; Y, yes.

10.12 Appendix 12: Search strategy for Section 7.4 (Measurement and valuation of health effects)

10.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***NHS EED***
- ***EconLIT***

Relevant studies were identified by searching the following electronic databases:

- MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R), 1946 to present
- EMBASE, 1980 to present
- EconLit, 1961 to present
- Cochrane library, 1968 to present (NHS Economics Evaluation Database, Health Technology Assessment Database).

10.12.2 The date on which the search was conducted.

Searches were conducted on the 7th August 2012.

10.12.3 The date span of the search.

The searches were not limited by date.

10.12.4 The complete search strategies used, including all the search terms textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

QoL search strategy for Embase

	Searches	Results
1	exp overactive bladder/ or exp detrusor dyssynergia/	8149
2	exp urinary urgency/ or exp urge incontinence/	6108
3	exp urinary frequency/	3384
4	exp bladder irritation/	593
5	((overactive adj3 bladder*) or (urge adj3 incontinence) or (detrusor adj3 dyssynergia) or DESD).mp.	12812
6	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	4662
7	(Health utilities index or HUI).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1929
8	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	837

9	(short form 6D or short-form 6D).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	124
10	(standard gamble or ("SG" adj2 "standard gamble")).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	710
11	(15D or 16D or 17D).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2261
12	or/6-11	9692
13	(QoL or HRQoL or HRQL).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	34027
14	exp "quality of life"/	212114
15	(health related quality of life or health-related quality of life).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	23555
16	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	47581
17	or/13-16	217286
18	health state$.mp.	4475
19	utilit*.mp.	130474
20	Patient Preference/ or preference.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	77034
21	(map$ or regression).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	836314
22	or/18-21	1031125
23	17 and 22	21867
24	12 or 23	28722
25	or/1-5	16604
26	24 and 25	241

QoL search strategy for MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

	Searches	Results
1	exp Urinary Bladder, Overactive/	1781
2	exp Urinary Incontinence, Urge/	426
3	((overactive adj3 bladder*) or (urge adj3 incontinence) or (detrusor adj3 dyssynergia) or urinary frequency or bladder irritation or DESD).mp.	6917
4	*Urinary Bladder/	23784
5	or/1-4	29851
6	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	2954
7	(Health utilities index or HUI).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	895
8	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	654
9	(short form 6D or short-form 6D).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	66

10	(standard gamble or ("SG" adj2 "standard gamble")).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	603
11	(15D or 16D or 17D).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1699
12	or/6-11	6244
13	(QoL or HRQoL or HRQL).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	22362
14	quality of life.mp. or exp "Quality of Life"/	162075
15	(health related quality of life or health-related quality of life).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	17502
16	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	34953
17	or/13-16	162749
18	health state$.mp.	3199
19	utilit$.mp.	102634
20	Patient Preference/ or preference.mp.	59896
21	(map$ or regression).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	814263
22	or/18-21	965717
23	17 and 22	16627
24	12 or 23	20735
25	5 and 24	124

QoL search strategy for Cochrane library, 1968 to present (NHS Economics Evaluation Database, Health Technology Assessment Database)

	Searches	Results
1	exp Urinary Bladder, Overactive/	17
2	exp Urinary Incontinence, Urge/	2
3	((overactive adj3 bladder*) or (urge adj3 incontinence) or (detrusor adj3 dyssynergia) or urinary frequency or bladder irritation or DESD).mp.	36
4	urinary bladder.mp. [mp=ti, tx, hw]	103
5	or/1-4	119
6	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp. [mp=ti, tx, hw]	602
7	(Health utilities index or HUI).mp. [mp=ti, tx, hw]	98
8	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp. [mp=ti, tx, hw]	328
9	(short form 6D or short-form 6D).mp. [mp=ti, tx, hw]	6
10	(standard gamble or ("SG" adj2 "standard gamble")).mp. [mp=ti, tx, hw]	188
11	(15D or 16D or 17D).mp. [mp=ti, tx, hw]	16
12	or/6-11	1097
13	(QoL or HRQoL or HRQL).mp. [mp=ti, tx, hw]	250
14	quality of life.mp. or exp "Quality of Life"/	5523
15	(health related quality of life or health-related quality of life).mp. [mp=ti, tx, hw]	411
16	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp. [mp=ti, tx, hw]	642
17	or/13-16	5548
18	health state$.mp.	1310
19	utilit$.mp.	3940

20	Patient Preference/ or preference.mp.	456
21	(map$ or regression).mp. [mp=ti, tx, hw]	946
22	or/18-2	5003
23	17 and 22	3259
24	12 or 23	3311
25	5 and 24	21

QoL search strategy for EconLit

	Searches	Results
1	[exp Urinary Bladder, Overactive/]	0
2	[exp Urinary Incontinence, Urge/]	0
3	((overactive adj3 bladder*) or (urge adj3 incontinence) or (detrusor adj3 dyssynergia) or urinary frequency or bladder irritation or DESD).mp.	5
4	urinary bladder.mp. [mp=heading words, abstract, title, country as subject]	0
5	or/1-4	5

10.12.5 Details of any additional searches, such as searches of company databases (include a description of each database).

- Reference lists of included publications were hand-searched
- Reference lists of relevant systematic review publications of the last three years were searched
- The Cost-Effectiveness Analysis Registry (https://research.tufts-nemc.org/cear4/Default.aspx), EQ-5D website (www.euroqol.org) and Research Papers in Economics (RePEc) website (http://repec.org/docs/RePEcIntro.html) were hand-searched for relevant utility studies
- NICE Health Technology Assessment submission/appraisal data was searched but no relevant publications were identified.

10.12.6 The inclusion and exclusion criteria.

Table 130: Inclusion and exclusion for QoL search strategy

Criteria	Include	Exclude
Population	Patients with OAB	Patients with detrusor activity only, or patients with LUTS suggestive of other diseases
Intervention	The SR was not restricted by any particular intervention	The SR was not restricted by any particular intervention
Comparator	The SR was not restricted by any particular comparator	The SR was not restricted by any particular comparator
Outcomes	The HRQoL outcomes of interest were EQ-5D utility values, and mapping studies that would allow a condition-specific measure to be mapped to EQ-5D	Studies that did not report EQ-5D utility values, or mapping studies that would allow a condition-specific measure to be mapped to EQ-5D
Study design	The type of study design was not limited	The type of study design was not limited. Abstracts were excluded if they did not

Criteria	Include	Exclude
		report any EQ-5D HSUVs or mapping algorithms.
Language of publication	Only English language publications were included. English abstracts of foreign publications were included.	Non-English publications were excluded
Date of publication	The searches were not limited by date	The searches were not limited by date

Abbreviations: EQ-5D, European quality of life – 5 dimensions; HSUVs, health state utility values; LUTS, lower urinary tract symptoms; HRQoL, health-related quality of life; OAB, overactive bladder; SR, systematic review.

10.12.7 The data abstraction strategy.

At first pass, on the basis of the title and abstract, studies were excluded if obviously not satisfying the selection criteria in Table 130 or if they were a (non-systematic) review or commentary.

At second pass, on the basis of the full text, studies were evaluated according to the above PICOS criteria.

Data extraction was conducted by a researcher/senior researcher and quality checked by a second researcher or project lead. Disputes were referred to a third party (strategic advisor).

The quality of life DET column headings included: country, study design, study population, inclusion and exclusion criteria, QoL measure, valuation and elicitation technique, weight tariff, source of utilities, health states described, utilities, response rate, and whether the paper includes utility or utilities that meet the reference case for NICE.

10.13 Appendix 13: Resource identification, measurement and valuation (section 7.5)

Costing studies were identified through the systematic review using the methodology detailed in Section 10.10.

10.14 Appendix 14: Summary of supporting RCTs for mirabegron

10.14.1 178-CL-044 (DRAGON)

Table 131: Summary of methodology, DRAGON

Study no. (acronym)	178-CL-044 (DRAGON)
Study objective	Evaluation of dose-response relationship of mirabegron efficacy in patients with OAB
Location	97 sites in 14 European countries (Belgium, Czech Republic, Denmark, France, Germany, Hungary, Italy, Netherlands, Norway, Poland, Russian Federation, Spain, Sweden, UK)
Design	Phase IIb, randomised, parallel group, placebo- and active-controlled study of 928 randomised patients (857 completed)
Inclusion criteria	Inclusion criteria were the same as the primary trials and have been described previously (Table 9).
Exclusion criteria	Criteria in common with the primary trials have been described previously (Table 9) (with the exception of hypertension). In addition, the following exclusion criteria were applied: **At screening** • Clinically significant bladder outflow obstruction at risk of urinary retention. • Uncontrolled narrow angle glaucoma, urinary or gastric retention, severe colitis ulcerosa, toxic megacolon, myasthenia gravis or any other medical condition that, in the opinion of the investigator, made the use of anticholinergics contraindicated. • Known or suspected hypersensitivity to tolterodine, other anticholinergics. • Significant PVR (PVR >200mL). • Clinically significant cardiovascular or cerebro vascular diseases within 6 months prior to Visit 1. **At baseline** • Abnormal serum bilirubin. • ECG on visit 1 showing a QTc interval >470msec, patients with Torsades de Pointes, patients receiving co-medication with QT-prolonging drugs.
Duration of study	• 2-week single-blind placebo run-in • 12 weeks on double-blind randomised treatment
Method of randomisation	• 2:2:2:2:2:1 (tolterodine) • Randomisation by IVRS
Method of blinding (care provider, patient and outcome assessor)	• Study drugs packaged using double-dummy blinding • During double-blind treatment, the investigator, study site personnel and patients were blinded to the identity of the randomised drug assignment
Interventions, N randomised	• 25 mg mirabegron, N=169 • 50 mg mirabegron, N=169 • 100 mg mirabegron, N=169 • 200 mg mirabegron, N=167
Comparators, N randomised	• 4 mg tolterodine SR, N=85 • Placebo, N=169
Permitted concomitant medications	• Antidepressants • Antihistamines/antiemetics • Loop diuretics • Neuroleptics • Type I antiarrhythmics • ß-adrenergic antagonists • Opioids These medications were permitted provided patient had been taking them on a long-term basis (i.e. not stopped, started or changed dose in the month prior to study entry)

Study no. (acronym)	178-CL-044 (DRAGON)
Disallowed concomitant medications	• Anticholinergics • Antispasmodics • Alpha-adrenergic antagonists • Anti-Parkinson drugs • Drugs known to be substrates of cytochrome P450 (CYP) enzyme CYP2D6 or CYP3A4 with narrow therapeutic indices • Inhibitors of CYP3A4 and CYP2D6 • CYP3A4 inducers • Tricyclic antidepressants • Drugs known to prolong QT • Oral formulations of ß-adrenergic agonists
Discontinuation of study therapy	• Patient request/withdrawn consent • (Intolerable) AE • Decision by investigator that termination was in the patient's best medical interest • Patient experienced lack of efficacy • Patient lost to follow-up • Death
Assessments	Visits at baseline and Weeks 1, 4, 8, 12
Primary outcomes (including scoring methods and timings of assessments)	• Reduction in number of micturitions per 24 hours based on a 3-day micturition diary
Secondary outcomes (including scoring methods and timings of assessments)	**Secondary efficacy endpoints** CFB to endpoint in: • urgency episodes per 24 hours (Grade 3 or 4) • level of urgency • volume voided per micturition • (urge) incontinence episodes per 24 hours • nocturia episodes per 24 hours • severity of urgency • patient perception of bladder condition • patient assessment of treatment benefit **Safety endpoints** • Adverse events
Duration of follow-up	Patients were not contacted after Visit 6 (Week 12)
Analysis populations	FAS, PPS, SAS

Study no. (acronym)	178-CL-044 (DRAGON)
Statistical methods	**Statistical analysis** • All statistical testing was performed by 2-sided tests at the α = 0.05 significance level, with 2-sided alternative hypotheses. • All summaries, analyses, and data listings were generated using SAS version 9.1.3 on UNIX. • Proc StatXact 6 running under SAS version 9.1 in a UNIX environment was used for some additional statistical analyses. **Sample size, power calculation** • Assuming a common SD of 2.7, and the requirement to detect with 80% power at the alpha = 0.05 level, a difference in means characterised by a variance of means of 0.126, it was necessary to recruit 140 patients to each of the 5 treatment arms. • Assuming 10% of randomised patients would not be evaluable it was planned to randomise 856 patients in order to have 770 evaluable patients. With an assumed a dropout rate of 20% during the placebo run-in period, it was expected that 1,070 patients should be enrolled in order to have 856 patients randomised. **Data management, patient withdrawals** • For efficacy and safety data there was no imputation for missing data, except for sum of symptom scores (assessed by ICIQ-OAB) and sum of QoL scores (assessed by ICIQ-OABqol). • For secondary variables (urge) incontinence, (level of) urgency and nocturia, all patients with value 0 or missing value (.) at baseline were excluded from analysis (i.e. only patients with symptoms at baseline were included). • For the analysis of patient's perception of treatment benefit, only patients answering "No" or "Yes, a little" at baseline were taken into account. • If at a particular visit the sum of the scores (assessed by ICIQ-OAB or ICIQ-OABqol) could not be calculated because the answer was missing on ≥ 1 question, the answer on that question from the previous visit was imputed. If the answer on that question was missing on all previous visits, the answer on that question of the next visit was imputed. If the answer on that question was missing for all visits, the answer on that question was to remain blank with no calculation of a sum of scores.

Abbreviations: AE, adverse event; CFB, change from baseline; FAS, full analysis set; IVRS, interactive voice recognition system; mg, milligram; OAB, overactive bladder; PPS, per protocol set; SAS, safety analysis set; SR, slow-release.

Table 132: Baseline characteristics, DRAGON

178-CL-044 (DRAGON)	Placebo N=166	Mirabegron				Tolterodine SR 4mg N=85	N=919
		25 mg N=167	50 mg N=167	100 mg N=168	200 mg N=166		
Sex, n (%)							
Male	15 (9.0)	20 (12.0)	18 (10.8)	17 (10.1)	12 (7.2)	16 (18.8)	98 (10.7)
Female	151 (91.0)	147 (88.0)	149 (89.2)	151 (89.9)	154 (92.8)	69 (81.2)	821 (89.3)
Age in years							
Mean (SD)	57.1 (12.9)	57.2 (12.1)	56.9 (12.5)	57.1 (12.5)	58.0 (13.7)	56.6 (12.8)	57.2 (12.7)
Range	21-80	20-78	26-84	21-91	18-82	27-78	18-91
Age group in years, n (%)							
≤ 65	122 (73.5)	117 (70.1)	125 (74.9)	126 (75.0)	113 (68.1)	64 (75.3)	667 (72.6)
>65	44 (26.5)	50 (29.9)	42 (25.1)	42 (25.0)	53 (31.9)	21 (24.7)	252 (27.4)
>75	11 (6.6)	5 (3.0)	9 (5.4)	14 (8.3)	13 (7.8)	5 (5.9)	57 (6.2)
Race, n (%)							
Caucasian	166 (100)	162 (97.0)	162 (97.0)	167 (99.4)	164 (98.8)	81 (95.3)	902 (98.2)
Black	0	2 (1.2)	0	0	0	0	2 (0.2)
Asian	0	1 (0.6)	0	1 (0.6)	0	2 (2.4)	4 (0.4)
Other	0	1 (0.6)	3 (1.8)	0	0	1 (1.2)	5 (0.5)
Missing	0	1 (0.6)	2 (1.2)	0	2 (1.2)	1 (1.2)	6 (0.7)
Weight in Kg							
Mean (SD)	75.1 (14.3)	75.8 (13.2)	72.9 (13.2)	73.0 (12.8)	73.7 (14.2)	73.9 (14.7)	74.1 (13.7)
Range	46-132	49-129	47-121	49-120	40-125	45-129	40-132
Height in cm							
Mean (SD)	164.5 (7.1)	165.2 (7.7)	164.7 (8.2)	164.2 (7.2)	163.2 (7.8)	165.3 (7.1)	164.5 (7.6)
Range	149-184	145-190	131-190	150-190	147-199	148-183	131-199

Table 133: OAB-related history, DRAGON

178-CL-044 (DRAGON)	Placebo N=166	Mirabegron					Total N=919
		25 mg N=167	50 mg N=167	100 mg N=168	200 mg N=166	Tolterodine SR 4mg N=85	
Type of OAB, n (%)							
Urge incontinence only	74 (44.6)	79 (47.3)	67 (40.1)	67 (39.9)	63 (38.0)	38 (44.7)	388 (42.2)
Mixed incontinence (urge as predominant factor)	52 (31.3)	41 (24.6)	47 (28.1)	54 (32.1)	63 (38.0)	24 (28.2)	281 (30.6)
Without incontinence	52 (31.3)	47 (28.1)	53 (31.7)	47 (28.0)	40 (24.1)	23 (27.1)	250 (27.2)
Previous OAB drug within 1 year of study start, n (%)							
Yes, at least 1 effective	41 (24.7)	40 (24.0)	39 (23.4)	42 (25.0)	34 (20.5)	19 (22.4)	215 (23.4)
Yes, none effective	30 (18.1)	42 (25.1)	38 (22.8)	39 (23.2)	38 (22.9)	16 (18.8)	203 (22.1)
No	95 (57.2)	85 (50.9)	90 (53.9)	87 (51.8)	94 (56.6)	50 (58.8)	501 (54.5)
Duration of OAB symptoms (months)							
	N=63	*N=63*	*N=53*	*N=67*	*N=54*	*N=31*	*N=331*
Mean (SD)	54.2 (66.9)	48.0 (35.7)	45.1 (53.7)	40.6 (48.8)	43.4 (32.9)	46.5 (44.7)	46.3 (48.9)
Median	35.0	44.0	31.0	27.0	33.0	43.0	34.0
Range	6-390	3-241	6-343	6-357	4-135	3-230	3-390
Treatment other than drug, n (%)	51 (30.7)	7 (34.1)	49 (29.3)	44 (26.2)	40 (24.1)	22 (25.9)	263 (28.6)

Table 134: OAB baseline characteristics, DRAGON

178-CL-044 (DRAGON), mean (SD)	Placebo N=166	Mirabegron				Tolterodine SR 4mg N=85
		25 mg N=167	50 mg N=167	100 mg N=168	200 mg N=166	
Mean number of micturitions per 24 hours	11.67 (3.39)	11.87 (2.88)	11.85 (3.30)	11.81 (3.51)	11.34 (2.41)	12.31 (3.68)
Mean volume voided per micturition (mL)	161.38 (53.87)	160.83 (55.04)	153.62 (49.39)	152.67 (55.26)	156.10 (50.17)	157.00 (64.40)
Mean number of urgency episodes (Grade 3 or 4) per 24 hours	5.75 (3.95)	5.77 (4.12)	5.94 (3.87)	5.92 (3.89)	5.75 (3.57)	5.83 (3.72)
Mean level of urgency	2.36 (0.58)	2.32 (0.59)	2.39 (0.55)	2.38 (0.55)	2.34 (0.54)	2.34 (0.56)
Mean number of nocturia episodes per 24 hours	1.77 (1.12)	1.76 (1.17)	1.70 (1.02)	1.82 (1.08)	1.78 (1.17)	1.78 (0.98)
Mean number of incontinence episodes per 24 hours	2.45 (2.35)	2.92 (3.23)	2.41 (2.30)	2.49 (2.48)	2.47 (2.23)	2.85 (2.76)
Mean number of urgency incontinence episodes per 24 hours	2.21 (2.00)	2.88 (3.09)	2.21 (2.17)	2.39 (2.46)	2.36 (2.02)	2.63 (2.53)

Table 135: Efficacy results, DRAGON, mirabegron vs placebo

178-CL-044 (DRAGON)	Placebo N=166	Mirabegron				Tolterodine SR 4 mg N=85
		25 mg N=167	50 mg N=167	100 mg N=168	200 mg N=166	
Change from baseline in mean number of micturitions per 24 hours						
Adjusted mean CFB	-1.44	-1.88	-2.08	-2.12	-2.24	NR
Estimated difference vs placebo	N/A	-0.45	-0.64	-0.68	-0.80	NR
95% CI	N/A	-0.99; 0.10	-1.19; -0.10	-1.22; -0.13	-1.34; -0.25	NR
p-value	N/A	0.1083	0.0205	0.0152	0.0041	NR
Change from baseline in mean number of incontinence episodes per 24 hours						
Adjusted mean CFB to endpoint	-0.53	-1.36	-1.15	-1.06	-1.10	-0.81
Estimated difference vs placebo	N/A	-0.84	-0.62	-0.53	-0.58	NR
95% CI	N/A	-1.45; -0.23	-1.22; -0.02	-1.12;0.06	-1.16;0.01	NR
p-value	N/A	0.0072	0.0416	0.0758	0.0551	NR
Change from baseline in mean volume voided per micturition						
n	*165*	*167*	*167*	*168*	*166*	*85*
Adjusted mean CFB to endpoint	7.29	15.32	27.34	25.56	33.34	23.86
Estimated difference vs placebo	N/A	8.03	20.05	18.28	26.06	NR
95% CI	N/A	-1.54; 17.60	10.48; 29.63	8.66; 27.89	16.49; 35.62	NR
p-value	N/A	0.0998	<0.0001	0.0002	<0.0001	NR
Change from baseline in mean number of urgency episodes (Grade 3/4) per 24 hours						
n	*165*	*167*	*166*	*168*	*165*	*85*
Adjusted mean CFB to endpoint	-1.07	-1.77	-1.67	-2.28	-2.48	-1.46
Estimated difference vs placebo	N/A	-0.70	-0.60	-1.21	-1.42	NR
95% CI	N/A	-1.38; -0.01	-1.29; 0.08	-1.90; -0.52	-2.10; -0.73	NR
p-value	N/A	0.0456	0.0845	0.0006	0.0001	NR
Change from baseline in mean level of urgency						
n	*166*	*166*	*166*	*168*	*166*	*85*
Adjusted mean CFB to endpoint	-0.10	-0.21	-0.18	-0.29	-0.38	-0.14
Estimated difference vs placebo	N/A	-0.12	-0.08	-0.19	-0.28	NR
95% CI	N/A	-0.25; 0.02	-0.22; 0.05	-0.33; -0.06	-0.41; -0.15	NR
p-value	N/A	0.0922	0.2189	0.0047	<0.0001	NR
Change from baseline in mean number of urge incontinence episodes per 24 hours						
Adjusted mean CFB to endpoint	-0.44	-1.31	-1.13	-1.18	-1.24	-0.76
Estimated difference vs placebo	N/A	-0.86	-0.69	-0.74	-0.80	NR
95% CI	N/A	-1.38; -0.35	-1.18; -0.19	-1.23; -0.25	-1.29; -0.31	NR

p-value	N/A	0.0011	0.0068	0.0033	0.0014	NR
Change from baseline in mean number of nocturia episodes per 24 hours						
Adjusted mean CFB to endpoint	-0.38	-0.52	-0.60	-0.42	-0.59	NR
Estimated difference vs placebo	N/A	-0.15	-0.22	-0.04	-0.21	NR
95% CI	N/A	-0.36; 0.07	-0.44; -0.01	-0.26; 0.17	-0.43; 0.00	NR
p-value	N/A	0.1753	0.0426	0.6984	0.0523	NR

Abbreviations: CFB, change from baseline; CI, confidence interval; mg, milligram; N/A, not applicable; NR, not reported; SD, standard deviation; SR slow-release.

Table 136: Efficacy results, DRAGON, mirabegron vs tolterodine

178-CL-044 (DRAGON)	**Placebo N=166**	**Mirabegron**			**Tolterodine SR 4 mg N=85**
		25 mg N=167	**50 mg N=167**	**100 mg N=168**	**200 mg N=166**
Change from baseline in mean number of incontinence episodes per 24 hours					
Adjusted mean CFB to endpoint	-0.53	-1.37	-1.15	-1.05	-1.10	-0.81
Estimated difference vs tolterodine	0.28	-0.56	-0.34	-0.24	-0.29	N/A
95% CI	-0.45; 1.01	-1.29; 0.18	-1.06; 0.39	-0.96; 0.49	-1.02; 0.43	N/A
p-value	0.4468	0.1371	0.3599	0.5228	0.4272	N/A
Change from baseline in mean volume voided per micturition						
n	*165*	*167*	*167*	*168*	*166*	*85*
Adjusted mean CFB to endpoint	7.05	15.13	27.14	25.34	33.06	23.86
Estimated difference vs tolterodine	-16.81	-8.73	3.28	1.48	9.20	N/A
95% CI	-28.5; -5.09	-20.4; 2.91	-8.40; 14.96	-10.1; 13.11	-2.50; 20.90	N/A
p-value	0.0050	0.1412	0.5817	0.8023	0.1232	N/A
Change from baseline in mean number of urgency episodes (Grade 3/4) per 24 hours						
n	*165*	*167*	*166*	*168*	*165*	*85*
Adjusted mean CFB to endpoint	-1.09	-1.77	-1.68	-2.29	-2.50	-1.46
Estimated difference vs tolterodine	0.37	-0.31	-0.22	-0.82	-1.03	N/A
95% CI	-0.47; 1.21	-1.14; 0.52	-1.06; 0.62	-1.66; 0.01	-1.87; -0.20	N/A
p-value	0.3853	0.4642	0.6057	0.0526	0.0156	N/A
Change from baseline in mean level of urgency						
n	*166*	*166*	*166*	*168*	*166*	*85*
Adjusted mean CFB to endpoint	-0.10	-0.21	-0.18	-0.29	-0.38	-0.14
Estimated difference vs tolterodine	0.04	-0.07	-0.04	-0.15	-0.23	N/A
95% CI	-0.12; 0.21	-0.23; 0.10	-0.20; 0.13	-0.31; 0.01	-0.40; -0.07	N/A
p-value	0.6117	0.4182	0.6553	0.0741	0.0048	N/A
Change from baseline in mean number of urge incontinence episodes per 24 hours						

Adjusted mean CFB to endpoint	-0.45	-1.31	-1.13	-1.17	-1.24	-0.76
Estimated difference vs tolterodine	0.31	-0.55	-0.37	-0.41	-0.49	N/A
95% CI	-0.30; 0.92	-1.18; 0.07	-0.99; 0.24	-1.02; 0.20	-1.10; 0.12	N/A
p-value	0.3239	0.0830	0.2324	0.1868	0.1177	N/A

Table 137: Safety results, DRAGON

AEs **Number (%) patients**	**Placebo** **N=169**	**Mirabegron**				**Tolterodine SR** **4 mg** **N=85**	**Total** **N=927**
		25 mg **N=169**	**50 mg** **N=169**	**100 mg** **N=168**	**200 mg** **N=167**		
TEAEs	73 (43.2)	74 (43.8)	74 (43.8)	77 (45.8)	80 (47.9)	41 (48.2)	419 (45.2)
Mild	34 (20.1)	38 (22.5)	37 (21.9)	40 (23.8)	46 (27.5)	19 (22.4)	214 (23.1)
Moderate	37 (21.9)	29 (17.2)	33 (19.5)	32 (19.0)	30 (18.0)	19 (22.4)	180 (19.4)
Severe	2 (1.2)	7 (4.1)	4 (2.4)	5 (3.0)	4 (2.4)	2 (2.4)	24 (2.6)
Missing	0	0	0	0	0	1 (1.2)	1 (0.1)
Total number of TEAEs	132	148	171	148	164	78	841
SAEs	1 (0.6)	1 (0.6)	1 (0.6)	2 (1.2)	3 (1.8)	1 (1.2)	9 (1.0)
Total number of SAEs	2	2	1	2	3	1	11
TEAEs leading to study drug discontinuation	5 (3.0)	9 (5.3)	4 (2.4)	4 (2.4)	7 (4.2)	1 (1.2)	30 (3.2)
Treatment-related TEAEs	26 (15.4)	34 (20.1)	38 (22.5)	36 (21.4)	37 (22.2)	13 (15.3)	184 (19.8)
Deaths	0	0	0	0	0	0	0

Abbreviations: mg, milligram; SAE, serious adverse event; SR, slow-release; TEAE, treatment-emergent adverse event.

10.14.2 Japanese RCTs 178-CL-045 and 178-CL-048

Table 138: Comparative methodology, 178-CL-045 and 178-CL-048

Study no. (acronym)	178-CL-045	178-CL-048
Study objective	Evaluation of dose-response relationship of mirabegron efficacy in patients with OAB	• Evaluation of efficacy (superiority vs placebo), safety and pharmacokinetics of mirabegron in patients with OAB • Evaluation of efficacy and safety mirabegron vs tolterodine
Location	60 sites in Japan	93 sites in Japan
Design	Phase II, randomised, double-blind, parallel group, placebo-controlled study of 842 randomised patients	Phase III, randomised, double-blind, parallel group, placebo- and active-controlled study of 1,139 randomised patients
Duration of study	• 2-week single-blind placebo run-in • 12 weeks on double-blind randomised treatment	
Interventions, N randomised	• 25 mg mirabegron, N=211 • 50 mg mirabegron, N=208 • 100 mg mirabegron, N=209	• 50 mg mirabegron, N=380
Comparators, N randomised	• Placebo, N=214	• Placebo, N=381 • 4 mg tolterodine ER, N=378
Assessments	Visits at Weeks 1, 4, 8, 12	Visits at Weeks 4, 8, 12
Primary outcomes (including scoring methods and timings of assessments)	CFB in mean number of micturitions per 24 hours based on a 3-day micturition diary	
Secondary outcomes (including scoring methods and timings of assessments)	**Secondary efficacy endpoints** CFB to endpoint in: • urgency episodes per 24 hours • incontinence episodes per 24 hours • urge incontinence episodes per 24 hours • volume voided per micturition • nocturia episodes • QoL domain scores on the King's Health questionnaire **Safety endpoints** Adverse events	
Duration of follow-up	Ongoing safety follow up only	2 weeks
Analysis populations	FAS, PPS, QOL, SAS, PKAS The PKAS is defined as patients who had taken the study drug ≥ once and in whom plasma unchanged drug concentration had been measured for ≥ 1 time point.	FAS, PPS, QOL, SAS, PKAS

Abbreviations: AE, adverse event; BPH, benign prostatic hyperplasia; CFB, change from baseline; FAS, full analysis set; mg, milligram; N/A, not applicable; OAB, overactive bladder; PKAS, pharmacokinetic analysis set; PPS, per protocol set; QoL, quality of life; QOL, quality of life analysis set; SAE, serious adverse event; SAS, safety analysis set; SD, standard deviation.

Patient disposition for RCTs 178-CL-045 and 178-CL-048

In study 178-CL-045, 1011 patients consented to participate in the study. Of these, 842 were randomised (214, 211, 208, and 209 in placebo, 25 mg, 50 mg, and 100 mg

groups, respectively); 789 patients completed the study (198, 200, 195, and 196) and 53 discontinued the study (16, 11, 13, and 13 in placebo, 25 mg, 50 mg, and 100 mg groups, respectively).

In study 178-CL-048, 1,381 patients gave informed consent. Of these, 1,139 were randomised to treatment (381, 380, and 378 patients in the placebo, mirabegron and tolterodine groups, respectively); 380, 379 and 378, respectively, received study medication, and 350, 349 and 355 completed the treatment period.

Baseline characteristics and OAB history were similar across treatment groups with no significant differences, for both trials.

Table 139: Efficacy results, 178-CL-045

178-CL-045	Placebo N=211	Mirabegron		
		25 mg N=209	50 mg N=208	100 mg N=207
Mean number of micturitions				
Mean CFB to end of study	−1.18	−1.94	−2.12	−1.97
SD	2.155	2.158	2.383	1.970
p-value	N/A	<0.001	<0.001	<0.001
Mean number of urgency episodes				
n	*211*	*208*	*208*	*207*
Mean CFB to end of study	−1.83	−2.15	−2.24	−2.48
SD	2.965	2.731	3.120	2.605
p-value	N/A	N/A†	0.084	0.011
Mean number of incontinence episodes				
n	*140*	*134*	*144*	*150*
CFB to end of study	−0.64	−1.29	−1.20	−1.28
SD	1.360	1.938	1.455	1.355
p-value	N/A	<0.001	<0.001	<0.001
Mean number of urge incontinence episodes				
n	*132*	*128*	*137*	*142*
CFB to end of study	−0.68	−1.14	−1.09	−1.24
SD	1.358	1.809	1.345	1.278
p-value	N/A	0.006	0.008	<0.001
Mean volume voided				
n	*211*	*209*	*208*	*207*
CFB to end of study	11.184	23.783	27.249	31.231
SD	36.9308	41.6669	39.5137	39.4515
p-value	N/A	<0.001	<0.001	<0.001
Mean number of nocturia episodes				
n	*168*	*179*	*176*	*180*
CFB to end of study	−0.24	−0.49	−0.38	−0.39
SD	0.977	0.977	0.814	0.849
p-value	N/A	N/A†	N/A†	0.035

Abbreviations: CFB, change from baseline; N/A, not applicable; SD, standard deviation
†Not tested, as this was the Williams' multiple comparison test

Table 140: Efficacy results, 178-CL-048

178-CL-048	Placebo N=368	Mirabegron 50 mg N=369	Tolterodine 4 mg N=368
Mean number of micturitions			
n	*368*	*369*	*368*
Mean CFB to end of study	-0.86	-1.67	-1.40
SD	2.354	2.212	2.176
p-value		<0.001	

178-CL-048	Placebo N=368	Mirabegron 50 mg N=369	Tolterodine 4 mg N=368
Mean number of urgency episodes			
n	*368*	*369*	*368*
Mean CFB to end of study	-1.37	-1.85	-1.66
SD	3.191	2.555	2.560
p-value		0.025	
Mean number of incontinence episodes			
n	*264*	*266*	*240*
CFB to end of study	-0.66	-1.12	-0.97
SD	1.861	1.475	1.612
p-value		0.003	
Mean number of urge incontinence episodes			
n	*258*	*254*	*230*
CFB to end of study	-0.60	-1.01	-0.95
SD	1.745	1.338	1.583
p-value		0.008	
Mean volume voided			
n	*364*	*368*	*367*
CFB to end of study	9.715	24.300	28.834
SD	29.0864	35.4767	34.7201
p-value		<0.001	
Mean number of nocturia episodes			
n	*322*	*323*	*332*
CFB to end of study	-0.36	-0.44	-0.42
SD	1.062	0.933	0.845
p-value		0.277	

Abbreviations: CFB, change from baseline; N/A, not applicable; SD, standard deviation

Table 141: QoL results, 178-CL-045

178-CL-045	Placebo N=201	Mirabegron		
		25 mg N=204	50 mg N=200	100 mg N=200
General health perception (Domain 1)				
Mean CFB to study end	−2.2	−3.3	0.3	−4.4
SD	20.49	21.01	21.70	19.96
p-value				0.194
Incontinence impact (Domain 2)				
Mean CFB to study end	−7.3	−16.3	−13.2	−15.2
SD	26.70	29.50	29.49	29.47
p-value		<0.001	0.005	0.004
Role limitations (Domain 3)				
Mean CFB to study end	−6.7	−12.5	−11.3	−12.6
SD	24.73	27.29	25.49	25.70
p-value			0.025	0.013
Physical limitations (Domain 4)				
Mean CFB to study end	−5.7	−12.6	−10.8	−10.6
SD	25.48	26.62	24.55	25.07
p-value		0.003	0.011	0.016
Social limitations (Domain 5)				
Mean CFB to study end	−3.2	−7.8	−4.7	−7.3
SD	21.03	21.94	17.98	18.39
p-value			0.070	0.021
Personal relationships (Domain 6)				
Mean CFB to study end	−0.8	−3.5	−2.6	−3.2
SD	14.38	15.49	13.45	17.19
p-value				0.104
Emotions (Domain 7)				

178-CL-045	Placebo N=201	Mirabegron		
		25 mg N=204	50 mg N=200	100 mg N=200
Mean CFB to study end	−7.4	−13.9	−10.0	−13.7
SD	23.76	24.19	21.19	23.76
p-value			0.029	0.004
Sleep/energy (Domain 8)				
Mean CFB to study end	−6.4	−11.4	−8.4	−9.5
SD	21.13	22.13	19.84	19.16
p-value				0.060
Severity measures (Domain 9)				
Mean CFB to study end	−4.7	−7.9	−8.5	−10.3
SD	13.09	15.91	15.58	16.44
p-value		0.020	0.007	<0.001

Table 142: QoL results, 178-CL-048

178-CL-048	Placebo N=368	Mirabegron 50 mg N=369	Tolterodine 4 mg N=368
General health perception (Domain 1)			
n	*368*	*365*	*365*
Mean CFB to study end	-0.1	-2.2	-2.1
SD	20.13	20.43	20.40
p-value		0.170	
Incontinence impact (Domain 2)			
n	*368*	*365*	*365*
Mean CFB to study end	-6.7	-13.9	-11.0
SD	28.76	28.32	27.98
p-value		<0.001	
Role limitations (Domain 3)			
n	*368*	*365*	*365*
Mean CFB to study end	-4.7	-10.9	-8.6
SD	25.99	23.55	23.91
p-value		<0.001	
Physical limitations (Domain 4)			
n	*368*	*365*	*365*
Mean CFB to study end	-5.1	-10.4	-8.2
SD	23.48	25.32	24.88
p-value		0.004	
Social limitations (Domain 5)			
n	*368*	*365*	*365*
Mean CFB to study end	-1.7	-6.1	-6.0
SD	20.57	21.43	19.32
p-value		0.005	
Personal relationships (Domain 6)			
n	*259*	*263*	*278*
Mean CFB to study end	-0.9	-3.3	-2.7
SD	17.28	13.33	14.64
p-value		0.077	
Emotions (Domain 7)			
n	*368*	*365*	*365*
Mean CFB to study end	-5.3	-10.1	-8.9
SD	25.07	24.77	23.03
p-value		0.009	
Sleep/energy (Domain 8)			
n	*368*	*365*	*365*
Mean CFB to study end	-5.0	-8.9	-8.1
SD	21.54	22.01	21.84
p-value		0.016	

178-CL-048	Placebo N=368	Mirabegron 50 mg N=369	Tolterodine 4 mg N=368
Severity measures (Domain 9)			
n	*368*	*365*	*365*
Mean CFB to study end	-3.3	-8.3	-7.9
SD	15.52	16.83	16.51
p-value		<0.001	

10.14.2.1 Safety results for RCTs 178-CL-045 and 178-CL-048

Table 143: Safety results, 178-CL-045

178-CL-045				
n (%)	**Placebo N=212**	**Mirabegron**		
		25 mg N=210	**50 mg N=208**	**100 mg N=208**
TEAEs†	157 (74.1)	169 (80.5)	171 (82.2)	175 (84.1)
Mild†	148 (69.8)	160 (76.2)	168 (80.8)	168 (80.8)
Moderate†	8 (3.8)	8 (3.8)	3 (1.4)	5 (2.4)
Severe†	0	1 (0.5)	0	0
Treatment-related TEAEs†	40 (18.9)	49 (23.3)	51 (24.5)	54 (26.0)
SAEs	4 (1.9)	3 (1.4)	1 (0.5)	1 (0.5)
Treatment-related SAEs	1 (0.5)	1 (0.5)	0	1 (0.5)
TEAEs resulting in permanent discontinuation	4 (1.9)	5 (2.4)	7 (3.4)	8 (3.8)
Treatment-related TEAEs resulting in permanent discontinuation	2 (0.9)	1 (0.5)	5 (2.4)	6 (2.9)

Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event.
†Mild/moderate/severe categories do not include AEs related to ECGs (where severity was not graded).

Table 144: Safety results, 178-CL-048

178-CL-048			
n (%)	**Placebo N=379**	**Mirabegron 50 mg N=379**	**Tolterodine 4mg N=375**
TEAEs†	292 (77.0)	281 (74.1)	305 (81.3)
Mild†	282 (74.4)	271 (71.5)	287 (76.5)
Moderate†	9 (2.4)	9 (2.4)	13 (3.5)
Severe†	0	0	1 (0.3)
Treatment-related TEAEs†	91 (24.0)	93 (24.5)	131 (34.9)
Mild†	87 (23.0)	93 (24.5)	123 (32.8)
Moderate†	0	0	4 (1.1)
Severe†	0	0	0
SAEs	4 (1.1)	3 (0.8)	4 (1.1)
Treatment-related SAEs	1 (0.3)	0	1 (0.3)
TEAEs resulting in permanent discontinuation	8 (2.1)	12 (3.2)	12 (3.2)
Treatment-related TEAEs resulting in permanent discontinuation	4 (1.1)	6 (1.6)	8 (2.1)

Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event.
†Mild/moderate/severe categories do not include AEs related to ECGs (where severity was not graded).
When the same event occurred in the same patient more than once, the most severe severity grade was tabulated.

10.15 Appendix 15: Description of micturition diary and scales used to assess QoL and treatment satisfaction in mirabegron studies

Micturition diary

A diary day started when the patient awoke with the intention of staying awake and ended on the following day when the patient awoke with the intention of staying awake. Times of micturition, voided volume (minimum of 2 of 3 days required), urgency severity, incontinence episodes and pad use were recorded by the patient in the micturition diary for day time (time interval between awakening with the intention of staying awake and going to bed with the intention to sleep) and night time (time interval between going to bed with the intention to sleep and awakening the following day with the intention of staying awake). Measuring devices for use in measuring the voided urine volume were provided to the patients. If, for practical reasons, the measurement of volume voided was not feasible within the 3-day period prior to the visit, completion of the diary and measurement of the urine volumes could be done within a period of up to 6 days prior to the visit. For each micturition and/or incontinence episode, patients were asked to rate the degree of associated urgency according to the following 5-point categorical scale (Patient Perception of Intensity of Urgency Scale):

0. No urgency, I felt no need to empty my bladder, but did so for other reasons.
1. Mild urgency, I could postpone voiding as long as necessary, without fear of wetting myself.
2. Moderate urgency, I could postpone voiding for a short while, without fear of wetting myself.
3. Severe urgency, I could not postpone voiding, but had to rush to the toilet in order not to wet myself.
4. Urge incontinence, I leaked before arriving to the toilet.

European quality of life – five dimensions (EQ-5D)

The EQ-5D is a two-page questionnaire divided into the EQ-5D descriptive system and the EQ-5D VAS. The descriptive system consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has three levels. The EQ-5D VAS is a 10 cm vertical visual analogue scale with the endpoints labelled as ‘best imaginable health state’ corresponding to a score of 100 and ‘worst imaginable health state’ corresponding to a score of 0.

Patient perception of bladder condition (PPBC)

PPBC is a six-point Likert scale on which a score of 1 indicates “no problems at all” and a score of 6 indicates “many severe problems”. Negative change indicates improvement.

Patient perception of treatment benefit

Patient perception of treatment benefit is a three-point response to treatment scale.

Overactive bladder questionnaire (OABq) (30)

OAB-q consists of 33 items that include coping, concern, sleep, social interaction and a symptom bother scale with eight symptoms. Higher scores on the HRQoL subscales and total score indicate a better QoL, and a positive change in the HRQoL scores indicates improvement. Scores for the symptom bother scale range from 0 to 100, with a score of 100 indicating worst severity. A negative change in symptom bother indicates improvement.

Treatment satisfaction – visual analogue scale (TS-VAS)

In the TS-VAS, patients are asked to put a vertical mark on a line that runs from 0 (No, not at all) to 10 (Yes, completely).

Work productivity and activity impairment: specific health problem (WPAI: SHP) (127)

WPAI: SHP consists of six questions covering employment status, hours absent from work due to a specific health problem, hours absent from work due to other reasons, hours actually worked, impact of the health problem on productivity while working, impact of the health problem on productivity while doing regular daily activities other than work. A negative change from baseline indicates improvement.

10.16 Appendix 16: Winbugs code used for MTC

Continuous outcomes

```
# Normal likelihood, identity link
# Fixed effects model for multi-arm trials
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 #   LOOP THROUGH STUDIES
   mu[i] ~ dnorm(0,.0001)           # vague priors for all trial baselines
   for (k in 1:na[i]) {           #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)   # calculate variances
      prec[i,k] <- 1/var[i,k]      # set precisions
      y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # normal likelihood
# model for linear predictor
      theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]
#Deviance contribution
      dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
    }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
 }
totresdev <- sum(resdev[])           #Total Residual Deviance
d[1]<-0      # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }


for (k in 1:nt) {
  rk[k] <- rank(d[],k)                    # assumes events are “bad”
  best[k] <- equals(rk[k],1)                 #calculate probability that treat k is best
  }

#Ranking the treatment
for (k in 1:nt){ best[k]<- equals(rank[d[],k],1) }

#the effect of treatment Vs trt 2 ."mirabegron 50 mg"
for (c in 1:(nt)) {
      TvMira[c] <- (d[c] - d[2])

}

}                               # *** PROGRAM ENDS


# Normal likelihood, identity link
# Random effects model for multi-arm trials
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 #   LOOP THROUGH STUDIES
   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0           # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)           # vague priors for all trial baselines
   for (k in 1:na[i]) {           #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)   # calculate variances
```

```
        prec[i,k] <- 1/var[i,k]      # set precisions
        y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # normal likelihood
        theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
        dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {            # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
  }
totresdev <- sum(resdev[])            #Total Residual Deviance
d[1]<-0       # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)



for (k in 1:nt) {
   rk[k] <- rank(d[],k)                    # assumes events are “bad”
   best[k] <- equals(rk[k],1)                 #calculate probability that treat k is best
   }

#Ranking
for (k in 1:nt){   best[k]<- equals(rank[d[],k],1) }

#the effect of treatment Vs trt 2 ."mirabegron 50 mg"
for (c in 1:(nt)) {
       TvMira[c] <- (d[c] - d[2])

}

}

                              # *** PROGRAM ENDS
```

Binary data

```
# Binomial likelihood, logit link, MTC
```

```
# Fixed effect model
model{                                                  # *** PROGRAM STARTS
for(i in 1:ns){                                          # LOOP THROUGH STUDIES
  mu[i] ~ dnorm(0,.0001)                                  # vague priors for all trial baselines
  for (k in 1:na[i]) {                                   # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],n[i,k])                         # binomial likelihood
    logit(p[i,k]) <- mu[i] + d[t[i,k]]-d[t[i,1]]          # model for linear predictor


   rhat[i,k] <- p[i,k] * n[i,k]                          # expected value of the numerators
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))        #Deviance contribution
       + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
  }
  resdev[i] <- sum(dev[i,1:na[i]])              # summed residual deviance contribution for this trial
}
totresdev <- sum(resdev[])                       #Total Residual Deviance
d[1]<- 0                                        # treatment effect is zero for reference treatment
for (k in 2:nt)  { d[k] ~ dnorm(0,.0001) }        # vague priors for treatment effects

# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {  for (k in (c+1):nt) {
      or[c,k] <- exp(d[k] - d[c])
      lor[c,k] <- (d[k]-d[c])
     }
}

# ranking
for (k in 1:nt) {
   #rk[k] <- nt+1-rank(d[],k)                 # assumes events are “good”
   rk[k] <- rank(d[],k)                     # assumes events are “bad”
   best[k] <- equals(rk[k],1)                #calculate probability that treat k is best
}

#the effect of treatment Vs trt 2 ."mirabegron 50 mg"
for (c in 1:(nt)) {
      TvMira[c] <- (d[c] - d[2])

}

}                                                        # *** PROGRAM ENDS

# Binomial likelihood, logit link
# Random effect model, multi-arm trials
model{                                                  # *** PROGRAM STARTS
for(i in 1:ns){                                          # LOOP THROUGH STUDIES
  w[i,1] <- 0                                           # adjustment for multi-arm trials is zero for
control arm
  delta[i,1] <- 0                                        # treatment effect is zero for control arm
  mu[i] ~ dnorm(0,.0001)                                  # priors for all trial baselines
  for (k in 1:na[i]) {                                   # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],n[i,k])                         # binomial likelihood
    logit(p[i,k]) <- mu[i] + delta[i,k]                    # model for linear predictor
```

```
    rhat[i,k] <- p[i,k] * n[i,k]                                  # expected value of the numerators
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))          #Deviance contribution
       + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
  }
 resdev[i] <- sum(dev[i,1:na[i]])                  # summed residual deviance contribution for this
trial
  for (k in 2:na[i]) {                                        # LOOP THROUGH ARMS
    delta[i,k] ~ dnorm(md[i,k],taud[i,k])                  # trial-specific LOR distributions
    md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]               # mean of LOR distributions (with multi-arm
correction)
    taud[i,k] <- tau *2*(k-1)/k                              # precision of LOR distributions (with multi-arm
correction)
    w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])           # adjustment for multi-arm RCTs
    sw[i,k] <- sum(w[i,1:k-1])/(k-1)                         # cumulative adjustment for multi-arm trials
   }
}
totresdev <- sum(resdev[])                                    #Total Residual Deviance
d[1]<- 0                                                     # treatment effect is zero for reference
treatment
for (k in 2:nt)  { d[k] ~ dnorm(0,.0001)}                      # priors for treatment effects
sd ~ dunif(0,2)
tau <- pow(sd,-2)

# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {  for (k in (c+1):nt) {
      or[c,k] <- exp(d[k] - d[c])
      lor[c,k] <- (d[k]-d[c])
     }
}

# ranking
for (k in 1:nt) {
  rk[k] <- rank(d[],k)                    # assumes events are “bad”
  best[k] <- equals(rk[k],1)                #calculate probability that treat k is best
}


#the effect of treatment Vs trt 2 ."mirabegron 50 mg"
for (c in 1:(nt)) {
      TvMira[c] <- (d[c] - d[2])

}

}                                                             # *** PROGRAM ENDS
```

10.17 Appendix 17: Inconsistency assessment between direct and indirect evidence for each comparison

Table 145: Inconsistency assessment for MTC, micturitions

Treatment 1	Treatment 2	Inconsistency estimate		
		Mean	SD	Prob
Mirabegron 50 mg	Tolterodine 4 mg	-0.143	0.146	0.164
Mirabegron 50 mg	Placebo	-0.210	0.121	0.042
Tolterodine 4 mg	Fesoterodine 4 mg	-0.205	0.263	0.219
Tolterodine 4 mg	Fesoterodine 8 mg	0.209	0.208	0.844
Tolterodine 4 mg	Oxybutynin 10 mg	-0.239	10.050	0.493
Tolterodine 4 mg	Placebo	0.022	0.105	0.584
Tolterodine 4 mg	Solifenacin 10 mg	0.032	0.215	0.561
Tolterodine 4 mg	Solifenacin 5 mg	0.094	0.209	0.675
Fesoterodine 4 mg	Placebo	0.210	0.158	0.909
Fesoterodine 8 mg	Placebo	-0.041	0.113	0.359
Placebo	Solifenacin 10 mg	-0.245	0.337	0.233
Placebo	Solifenacin 5 mg	-0.159	0.333	0.319
Placebo	Trospium 60 mg	-0.329	10.015	0.488
Fesoterodine 4 mg	Fesoterodine 8 mg	-0.155	0.166	0.177
Solifenacin 10 mg	Solifenacin 5 mg	-0.405	9.995	0.486

Table 146: Inconsistency assessment for MTC, incontinence episodes

Treatment 1	Treatment 2	Inconsistency estimate		
		Mean	SD	Prob
Mirabegron 50 mg	Tolterodine 4 mg	-0.093	0.129	0.235
Mirabegron 50 mg	Placebo	-0.363	0.141	**0.005**
Tolterodine 4 mg	Oxybutynin 10 mg	-0.115	10.031	0.496
Tolterodine 4 mg	Placebo	0.047	0.112	0.660
Tolterodine 4 mg	Solifenacin 10 mg	0.015	0.233	0.525
Tolterodine 4 mg	Solifenacin 5 mg	0.075	0.218	0.637
Fesoterodine 4 mg	Placebo	1.436	6.525	0.593
Fesoterodine 8 mg	Placebo	1.478	6.503	0.597
Placebo	Solifenacin 10 mg	-0.302	10.016	0.486
Placebo	Solifenacin 5 mg	-0.395	9.901	0.484
Fesoterodine 4 mg	Fesoterodine 8 mg	0.110	9.987	0.503
Solifenacin 10 mg	Solifenacin 5 mg	-0.396	9.901	0.484

Table 147: Inconsistency assessment for MTC, urge incontinence

Treatment 1	Treatment 2	Inconsistency estimate		
		Mean	SD	Prob
Mirabegron 50 mg	Tolterodine 4 mg	-0.026	0.136	0.423
Mirabegron 50 mg	Placebo	-0.092	0.115	0.212
Tolterodine 4 mg	Fesoterodine 4 mg	-0.186	0.238	0.218
Tolterodine 4 mg	Fesoterodine 8 mg	0.339	0.163	0.982
Tolterodine 4 mg	Oxybutynin 10 mg	-0.291	10.022	0.490
Tolterodine 4 mg	Placebo	-0.080	0.096	0.200
Tolterodine 4 mg	Solifenacin 10 mg	-0.129	0.218	0.277
Tolterodine 4 mg	Solifenacin 5 mg	0.154	0.211	0.769
Fesoterodine 4 mg	Placebo	0.405	0.138	0.998
Fesoterodine 8 mg	Placebo	-0.120	0.104	0.123
Placebo	Solifenacin 10 mg	0.455	0.282	0.947
Placebo	Solifenacin 5 mg	-0.438	0.248	0.038
Placebo	Trospium 60 mg	-0.207	10.011	0.493

Fesoterodine 4 mg	Fesoterodine 8 mg	-0.439	0.141	0.001
Solifenacin 10 mg	Solifenacin 5 mg	-0.414	10.021	0.484

Table 148: Inconsistency assessment for MTC, dry mouth

Treatment 1	Treatment 2	Inconsistency estimate		
		Mean	SD	Prob
Mirabegron 50 mg	Tolterodine ER 4 mg	0.060	0.476	0.550
Mirabegron 50 mg	Placebo	-0.326	0.261	0.099
Tolterodine ER 4 mg	Fesoterodine 4mg	0.298	0.296	0.853
Tolterodine ER 4 mg	Fesoterodine 8mg	-0.236	0.209	0.122
Tolterodine ER 4 mg	Oxybutynin ER 10 mg	-0.273	0.399	0.243
Tolterodine ER 4 mg	Placebo	0.207	0.174	0.883
Tolterodine ER 4 mg	Oxybutynin IR 9 mg	0.829	10.000	0.534
Tolterodine ER 4 mg	Tolterodine IR 4 mg	-0.267	0.291	0.165
Fesoterodine 4mg	Placebo	-0.041	0.227	0.425
Fesoterodine 8mg	Placebo	0.075	0.198	0.655
Oxybutynin ER 10 mg	Placebo	1.615	10.037	0.564
Oxybutynin ER 5 mg	Placebo	1.172	1.859	0.743
Oxybutynin IR 15 mg	Placebo	0.087	0.911	0.551
Oxybutynin IR 9 mg	Placebo	-0.432	0.428	0.151
Placebo	Solifenacin 10 mg	0.136	0.378	0.648
Placebo	Solifenacin 5 mg	-0.016	0.359	0.482
Placebo	Tolterodine IR 4 mg	0.187	0.297	0.730
Placebo	Trospium 40 mg	0.224	9.950	0.509
Placebo	Trospium 60 mg	0.011	10.006	0.502
Fesoterodine 4mg	Fesoterodine 8mg	0.173	0.220	0.798
Oxybutynin ER 10 mg	Tolterodine IR 4 mg	0.326	0.384	0.807
Oxybutynin ER 10 mg	Oxybutynin ER 15 mg	0.605	9.980	0.523
Oxybutynin ER 10 mg	Oxybutynin ER 5 mg	1.146	1.835	0.743
Oxybutynin ER 10 mg	Oxybutynin IR 10 mg	-1.776	0.590	0.001
Oxybutynin IR 10 mg	Tolterodine IR 4 mg	-1.753	0.601	0.001
Oxybutynin IR 15 mg	Solifenacin 5 mg	-0.102	0.872	0.451
Solifenacin 10 mg	Solifenacin 5 mg	-0.912	0.605	0.063
Solifenacin 10 mg	Tolterodine IR 4 mg	0.462	0.287	0.951

Table 149: Inconsistency assessment for MTC, constipation:

Treatment 1	Treatment 2	Inconsistency estimate		
		Mean	SD	Prob
Mirabegron 50 mg	Tolterodine ER 4 mg	-0.076	0.253	0.385
Mirabegron 50 mg	Placebo	0.174	0.315	0.711
Tolterodine ER 4 mg	Oxybutynin IR 9 mg	-0.167	10.033	0.493
Tolterodine ER 4 mg	Placebo	-0.104	0.226	0.324
Tolterodine ER 4 mg	Tolterodine IR 4 mg	0.502	0.361	0.919
Tolterodine ER 4 mg	Fesoterodine 4mg	0.360	0.460	0.786
Tolterodine ER 4 mg	Fesoterodine 8mg	-0.215	0.305	0.241
Tolterodine ER 4 mg	Oxybutynin ER 10 mg	-0.371	0.531	0.242
Fesoterodine 4mg	Placebo	-0.183	0.311	0.280
Fesoterodine 8mg	Placebo	-0.308	0.300	0.150
Oxybutynin ER 5 mg	Placebo	-1.888	2.325	0.200
Oxybutynin IR 15 mg	Placebo	-2.448	2.189	0.097
Oxybutynin IR 9 mg	Placebo	-0.031	0.520	0.489
Placebo	Solifenacin 10 mg	-0.386	0.434	0.187
Placebo	Solifenacin 5 mg	-0.075	0.402	0.428
Placebo	Tolterodine IR 4 mg	0.454	0.413	0.865
Placebo	Trospium 40 mg	0.433	9.967	0.520
Placebo	Trospium 60 mg	1.648	10.020	0.566

Treatment 1	Treatment 2	Inconsistency estimate		
		Mean	SD	Prob
Fesoterodine 4mg	Fesoterodine 8mg	0.197	0.322	0.731
Oxybutynin ER 10 mg	Tolterodine IR 4 mg	-0.266	0.544	0.311
Oxybutynin ER 10 mg	Oxybutynin ER 15 mg	0.352	10.017	0.513
Oxybutynin ER 10 mg	Oxybutynin ER 5 mg	-1.902	2.326	0.197
Oxybutynin IR 15 mg	Solifenacin 5 mg	2.458	2.202	0.903
Solifenacin 10 mg	Solifenacin 5 mg	-1.369	1.065	0.081
Solifenacin 10 mg	Tolterodine IR 4 mg	-0.081	0.421	0.430
Solifenacin 5 mg	Tolterodine IR 4 mg	-0.208	0.418	0.312

Table 150: Inconsistency assessment for MTC, blurred vision:

Treatment 1	Treatment 2	Inconsistency estimate		
		Mean	SD	Prob
Mirabegron 50 mg	Tolterodine ER 4 mg	0.298	1.085	0.611
Mirabegron 50 mg	Placebo	0.509	0.708	0.764
Tolterodine ER 4 mg	Oxybutynin IR 9 mg	1.109	9.979	0.545
Tolterodine ER 4 mg	Placebo	-0.542	0.643	0.197
Tolterodine ER 4 mg	Tolterodine IR 4 mg	0.560	0.772	0.771
Fesoterodine 4mg	Placebo	1.018	7.096	0.560
Fesoterodine 8mg	Placebo	1.064	7.001	0.560
Oxybutynin ER 5 mg	Placebo	0.532	3.406	0.572
Oxybutynin IR 9 mg	Placebo	-1.645	2.107	0.210
Placebo	Solifenacin 10 mg	0.545	0.394	0.917
Placebo	Solifenacin 5 mg	-0.249	0.410	0.269
Placebo	Tolterodine IR 4 mg	-0.573	0.537	0.140
Placebo	Trospium 60 mg	-0.144	10.064	0.494
Fesoterodine 4mg	Fesoterodine 8mg	-1.251	10.076	0.450
Oxybutynin ER 10 mg	Oxybutynin ER 15 mg	-0.188	10.096	0.493
Oxybutynin ER 10 mg	Oxybutynin ER 5 mg	0.511	3.394	0.572
Oxybutynin ER 10 mg	Oxybutynin IR 10 mg	-0.285	10.076	0.490
Oxybutynin IR 15 mg	Tolterodine IR 4 mg	-1.771	10.209	0.431
Solifenacin 10 mg	Solifenacin 5 mg	-1.686	7.143	0.407
Solifenacin 10 mg	Tolterodine IR 4 mg	-0.498	0.755	0.250

10.18 Appendix 18: Severity levels for micturitions and incontinence; model predictions and comparison with trial data

Proportions of patients by severity level (model predictions)

The predicted proportions of patients at different severity levels for micturitions are presented at baseline and every 6 months in Figure 51 and Figure 52 for mirabegron and tolterodine, respectively and for incontinence in Figure 53 and Figure 54 for mirabegron and tolterodine, respectively. The model predicted that patients treated with mirabegron were more likely to be in severity levels 1 and 2 (i.e. less severe levels) at 12 months, for all symptoms, most notably for micturitions.

Figure 51. Proportion of patients by micturition severity level and month, mirabegron, general OAB population

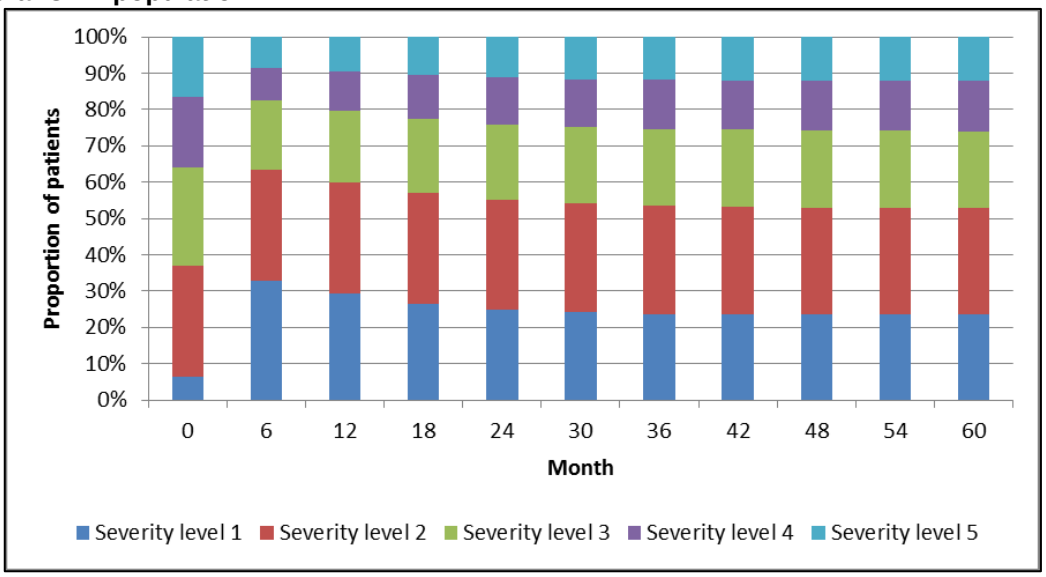


Figure 52. Proportion of patients by micturition severity level and month, tolterodine, general OAB population

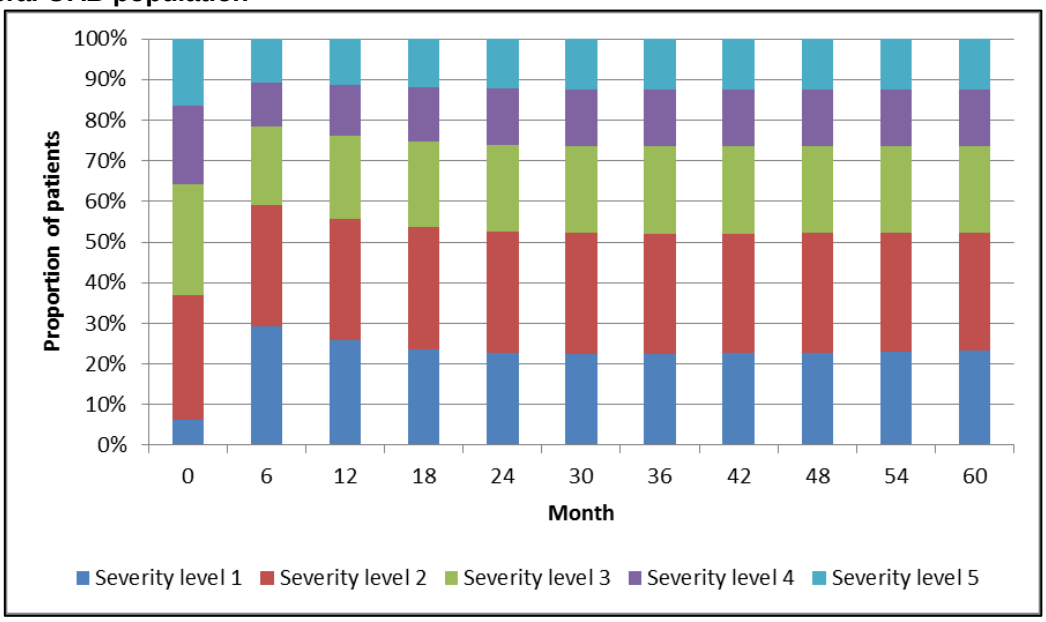


Figure 53. Proportion of patients by incontinence severity level and month, mirabegron, general OAB population

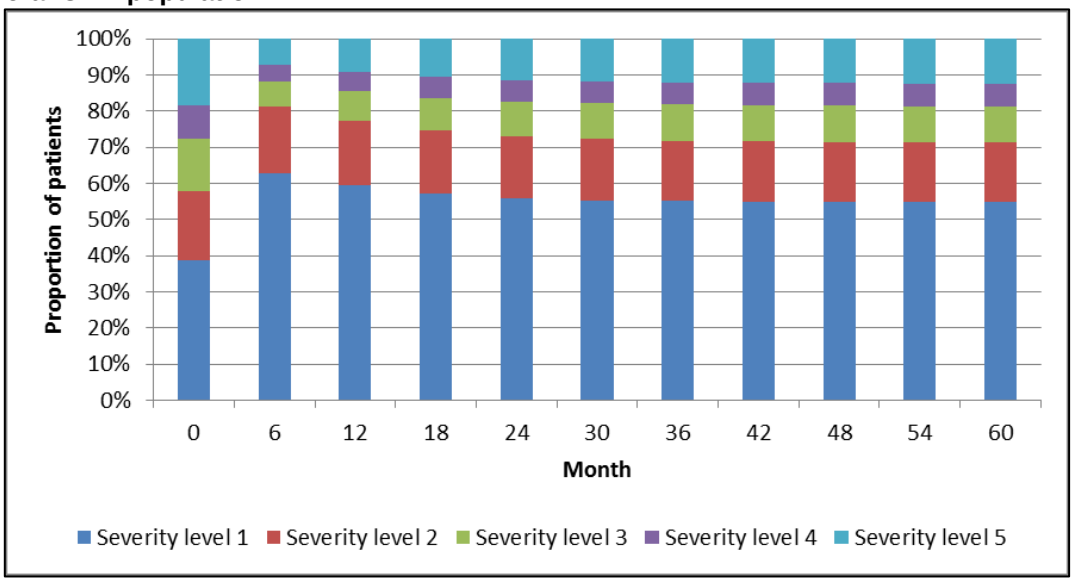
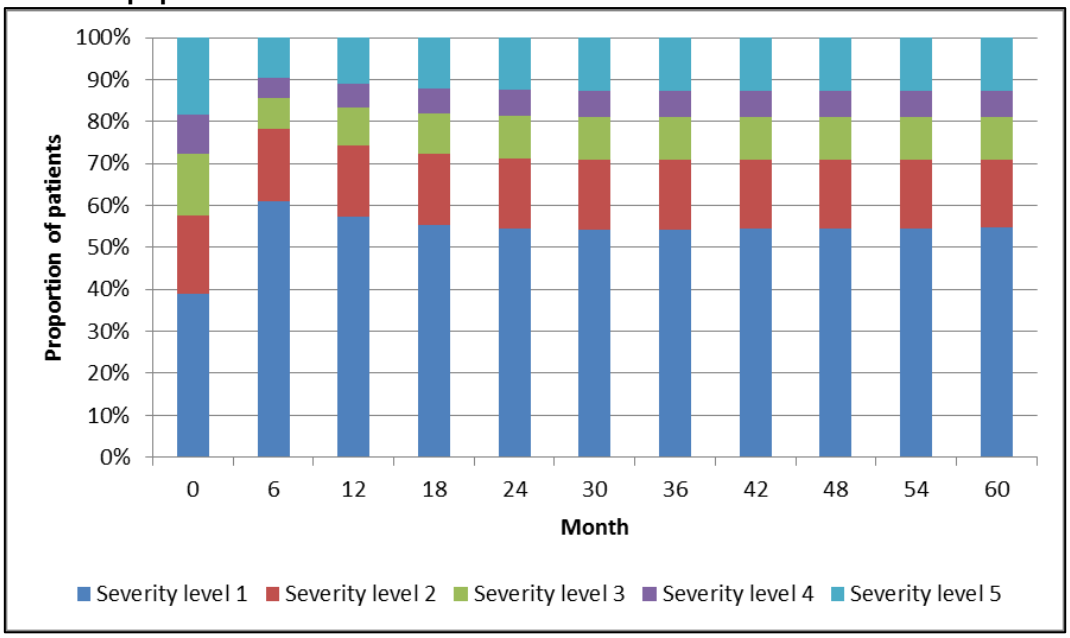


Figure 54. Proportion of patients by incontinence severity level and month, tolterodine, general OAB population



Model prediction compared with trial results (SCORPIO)

Predicted proportions of patients by severity level at 3 months are compared with the estimated proportions from SCORPIO in Table 151, for micturitions and incontinence episodes, and for both treatments. Predicted and observed proportions are not identical, which is partly related to the fact that patients were less likely to discontinue in the trial than in the model, since the model aims to reflect persistence in real practice. However, predicted proportions are all within the limits of the 95% confidence intervals around proportions estimated from the trial.

Table 151: Comparison between proportions of patients in severity levels at 3 months predicted by the model and estimated from SCORPIO

Micturition	Severity level				
	1	2	3	4	5
Mirabegron 50 mg					
Predicted (by model)	31.7%	30.2%	19.9%	9.1%	9.1%
Estimated (SCORPIO)	33.4%	31.4%	18.8%	9.2%	7.3%
95% CI	29.0-37.8%	27.0-35.8%	15.1-22.5%	6.5-11.9%	4.9-9.7%
Tolterodine ER 4 mg					
Predicted (by model)	29.6%	29.4%	19.3%	10.8%	11.0%
Estimated (SCORPIO)	32.4%	29.7%	18.5%	9.4%	10.1%
95% CI	28.0-36.8%	25.4-34.0%	14.9-22.1%	6.7-12.1%	7.3-12.9%
Incontinence	**Severity level**				
	1	**2**	**3**	**4**	**5**
Mirabegron 50 mg					
Predicted (by model)	61.9%	19.3%	6.9%	4.7%	7.2%
Estimated (SCORPIO)	62.7%	19.0%	7.6%	4.4%	6.4%
95% CI	58.2-67.2%	15.3-22.7%	5.1-10.1%	2.5-6.3%	4.1-8.7%
Tolterodine ER 4 mg					
Predicted (by model)	61.4%	17.6%	6.5%	4.9%	9.6%
Estimated (SCORPIO)	63.7%	17.1%	5.9%	4.6%	8.7%
95% CI	59.2-68.2%	13.6-20.6%	3.7-8.1%	2.6-6.6%	6.1-11.3%

Abbreviations: CI, confidence interval; ER, extended-release.

10.19 Appendix 19: Logistic regression models for symptom severity levels

Table 152: Maximum likelihood estimates for mirabegron 50 mg, micturition

Parameter		Class	DF	Estimate	SE	Wald Chi-Square	Pr >ChiSq
Intercept		1	1	-3.3811	0.4566	54.8358	<0.0001
Intercept		2	1	-2.5668	0.3745	46.9707	<0.0001
Intercept		3	1	-1.7892	0.3398	27.7217	<0.0001
Intercept		4	1	-1.3204	0.3369	15.3654	<0.0001
Age		1	1	0.00104	0.00571	0.033	0.8559
Age		2	1	0.00663	0.00535	1.533	0.2157
Age		3	1	0.00939	0.00515	3.3214	0.0684
Age		4	1	0.00987	0.00521	3.5884	0.0582
Sex		1	1	-0.3891	0.1529	6.4792	0.0109
Sex		2	1	-0.4228	0.1418	8.8858	0.0029
Sex		3	1	-0.2782	0.1346	4.2732	0.0387
Sex		4	1	-0.2065	0.1356	2.3197	0.1277
Treatment	Mirabegron 50 mg	1	1	0.6037	0.1938	9.7054	0.0018
Treatment	Mirabegron 50 mg	2	1	0.3803	0.179	4.5143	0.0336
Treatment	Mirabegron 50 mg	3	1	0.1454	0.1699	0.7322	0.3922
Treatment	Mirabegron 50 mg	4	1	0.0665	0.1736	0.1467	0.7017
Treatment	Mirabegron 100 mg	1	1	0.6656	0.1942	11.7517	0.0006
Treatment	Mirabegron 100 mg	2	1	0.4635	0.1792	6.6873	0.0097
Treatment	Mirabegron 100 mg	3	1	0.1593	0.1709	0.8684	0.3514
Treatment	Mirabegron 100 mg	4	1	0.2632	0.1721	2.3389	0.1262
Treatment	Tolterodine ER 4 mg	1	1	0.3667	0.1908	3.696	0.0545
Treatment	Tolterodine ER 4 mg	2	1	0.1826	0.1753	1.0851	0.2976
Treatment	Tolterodine ER 4 mg	3	1	-0.0609	0.1662	0.1344	0.7139
Treatment	Tolterodine ER 4 mg	4	1	0.055	0.1678	0.1073	0.7432
Previous severity level	1	1	1	10.5809	1.044	102.7231	<0.0001
Previous severity level	1	2	1	8.1706	1.0175	64.4794	<0.0001
Previous severity level	1	3	1	4.7618	1.0264	21.5216	<0.0001
Previous severity level	1	4	1	2.4592	1.0983	5.0138	0.0251
Previous severity level	2	1	1	8.0818	0.484	278.8203	<0.0001
Previous severity level	2	2	1	7.3018	0.4215	300.1062	<0.0001
Previous severity level	2	3	1	5.1391	0.4021	163.3865	<0.0001
Previous severity level	2	4	1	2.4679	0.4234	33.9797	<0.0001
Previous severity level	3	1	1	4.6396	0.338	188.3739	<0.0001

Parameter		Class	DF	Estimate	SE	Wald Chi-Square	Pr >ChiSq
Previous severity level	3	2	1	4.6067	0.2327	391.9571	<0.0001
Previous severity level	3	3	1	3.7392	0.1888	392.2008	<0.0001
Previous severity level	3	4	1	1.8994	0.1854	104.9034	<0.0001
Previous severity level	4	1	1	2.021	0.3603	31.4687	<0.0001
Previous severity level	4	2	1	2.4017	0.2187	120.6232	<0.0001
Previous severity level	4	3	1	2.2553	0.1597	199.5183	<0.0001
Previous severity level	4	4	1	1.4332	0.1435	99.8024	<0.0001
Visit	8	1	1	-0.8433	0.1672	25.4507	<0.0001
Visit	8	2	1	-0.6208	0.154	16.2464	<0.0001
Visit	8	3	1	-0.282	0.1466	3.6982	0.0545
Visit	8	4	1	0.0142	0.1462	0.0094	0.9226
Visit	12	1	1	-1.1007	0.1729	40.5093	<0.0001
Visit	12	2	1	-0.7356	0.1588	21.4636	<0.0001
Visit	12	3	1	-0.3613	0.1508	5.7358	0.0166
Visit	12	4	1	-0.2527	0.1541	2.689	0.101

Table 153: Maximum likelihood estimates for tolterodine 4 mg, micturition

Parameter		Class	DF	Estimate	Standard error	Wald Chi-Square	Pr > ChiSq
Intercept		1	1	-3.3811	0.4566	54.8358	<.0001
Intercept		2	1	-2.5668	0.3745	46.9707	<.0001
Intercept		3	1	-1.7892	0.3398	27.7217	<.0001
Intercept		4	1	-1.3204	0.3369	15.3654	<.0001
Age		1	1	0.00104	0.00571	0.033	0.8559
Age		2	1	0.00663	0.00535	1.533	0.2157
Age		3	1	0.00939	0.00515	3.3214	0.0684
Age		4	1	0.00987	0.00521	3.5884	0.0582
Sex		1	1	-0.3891	0.1529	6.4792	0.0109
Sex		2	1	-0.4228	0.1418	8.8858	0.0029
Sex		3	1	-0.2782	0.1346	4.2732	0.0387
Sex		4	1	-0.2065	0.1356	2.3197	0.1277
Treatment	Tolterodine ER 4 mg	1	1	0.3667	0.1908	3.696	0.0545
Treatment	Tolterodine ER 4 mg	2	1	0.1826	0.1753	1.0851	0.2976
Treatment	Tolterodine ER 4 mg	3	1	-0.0609	0.1662	0.1344	0.7139
Treatment	Tolterodine ER 4 mg	4	1	0.055	0.1678	0.1073	0.7432
Treatment	Mirabegron 100 mg	1	1	0.6656	0.1942	11.7517	0.0006
Treatment	Mirabegron 100 mg	2	1	0.4635	0.1792	6.6873	0.0097

Treatment	Mirabegron 100 mg	3	1	0.1593	0.1709	0.8684	0.3514
Treatment	Mirabegron 100 mg	4	1	0.2632	0.1721	2.3389	0.1262
Treatment	Mirabegron 50 mg	1	1	0.6037	0.1938	9.7054	0.0018
Treatment	Mirabegron 50 mg	2	1	0.3803	0.179	4.5143	0.0336
Treatment	Mirabegron 50 mg	3	1	0.1454	0.1699	0.7322	0.3922
Treatment	Mirabegron 50 mg	4	1	0.0665	0.1736	0.1467	0.7017
Previous severity level	1	1	1	10.5809	1.044	102.7231	<.0001
Previous severity level	1	2	1	8.1706	1.0175	64.4794	<.0001
Previous severity level	1	3	1	4.7618	1.0264	21.5216	<.0001
Previous severity level	1	4	1	2.4592	1.0983	5.0138	0.0251
Previous severity level	2	1	1	8.0818	0.484	278.8203	<.0001
Previous severity level	2	2	1	7.3018	0.4215	300.1062	<.0001
Previous severity level	2	3	1	5.1391	0.4021	163.3865	<.0001
Previous severity level	2	4	1	2.4679	0.4234	33.9797	<.0001
Previous severity level	3	1	1	4.6396	0.338	188.3739	<.0001
Previous severity level	3	2	1	4.6067	0.2327	391.9571	<.0001
Previous severity level	3	3	1	3.7392	0.1888	392.2008	<.0001
Previous severity level	3	4	1	1.8994	0.1854	104.9034	<.0001
Previous severity level	4	1	1	2.021	0.3603	31.4687	<.0001
Previous severity level	4	2	1	2.4017	0.2187	120.6232	<.0001
Previous severity level	4	3	1	2.2553	0.1597	199.5183	<.0001
Previous severity level	4	4	1	1.4332	0.1435	99.8024	<.0001
Visit	8	1	1	-0.8433	0.1672	25.4507	<.0001
Visit	8	2	1	-0.6208	0.154	16.2464	<.0001
Visit	8	3	1	-0.282	0.1466	3.6982	0.0545
Visit	8	4	1	0.0142	0.1462	0.0094	0.9226
Visit	12	1	1	-1.1007	0.1729	40.5093	<.0001
Visit	12	2	1	-0.7356	0.1588	21.4636	<.0001
Visit	12	3	1	-0.3613	0.1508	5.7358	0.0166
Visit	12	4	1	-0.2527	0.1541	2.689	0.101

Table 154: Maximum likelihood estimates for mirabegron 50 mg, incontinence

Parameter		Class	DF	Estimate	Standard error	Wald Chi-Square	Pr > ChiSq
Intercept		1	1	-1.5399	0.3702	17.2994	<.0001
Intercept		2	1	-1.627	0.3728	19.0435	<.0001
Intercept		3	1	-0.9374	0.3863	5.89	0.0152
Intercept		4	1	-1.2225	0.4189	8.5146	0.0035

Age		1	1	-0.00728	0.00525	1.9218	0.1657
Age		2	1	-0.0025	0.00531	0.2211	0.6382
Age		3	1	-0.00511	0.00567	0.8114	0.3677
Age		4	1	-0.003	0.00614	0.2393	0.6247
Sex		1	1	1.0042	0.2005	25.0764	<.0001
Sex		2	1	0.2635	0.2089	1.5913	0.2071
Sex		3	1	0.1231	0.2327	0.2798	0.5969
Sex		4	1	0.095	0.2584	0.1351	0.7132
Treatment	Mirabegron 50 mg	1	1	0.3617	0.1818	3.9592	0.0466
Treatment	Mirabegron 50 mg	2	1	0.4634	0.1832	6.4002	0.0114
Treatment	Mirabegron 50 mg	3	1	-0.0251	0.1934	0.0168	0.8968
Treatment	Mirabegron 50 mg	4	1	0.204	0.2122	0.9239	0.3365
Treatment	b: Mirabegron 100 mg	1	1	0.2131	0.1763	1.462	0.2266
Treatment	b: Mirabegron 100 mg	2	1	0.1445	0.1793	0.6494	0.4203
Treatment	b: Mirabegron 100 mg	3	1	-0.1592	0.1867	0.7272	0.3938
Treatment	b: Mirabegron 100 mg	4	1	0.1151	0.2036	0.3193	0.572
Treatment	d: Tolterodine ER 4 mg	1	1	0.1431	0.1765	0.6574	0.4175
Treatment	d: Tolterodine ER 4 mg	2	1	0.1768	0.1787	0.9787	0.3225
Treatment	d: Tolterodine ER 4 mg	3	1	-0.3271	0.1907	2.9428	0.0863
Treatment	d: Tolterodine ER 4 mg	4	1	-0.0298	0.2085	0.0205	0.8861
Previous severity level	1	1	1	6.5207	0.2607	625.7562	<.0001
Previous severity level	1	2	1	4.2602	0.2621	264.2503	<.0001
Previous severity level	1	3	1	2.0943	0.2937	50.8512	<.0001
Previous severity level	1	4	1	1.1226	0.3367	11.1156	0.0009
Previous severity level	2	1	1	4.6908	0.2363	394.0306	<.0001
Previous severity level	2	2	1	4.2494	0.2312	337.7914	<.0001
Previous severity level	2	3	1	2.7019	0.2389	127.8799	<.0001
Previous severity level	2	4	1	1.3854	0.2758	25.2263	<.0001
Previous severity level	3	1	1	3.5642	0.2344	231.1848	<.0001
Previous severity level	3	2	1	3.4919	0.2266	237.4175	<.0001
Previous severity level	3	3	1	2.8324	0.2236	160.3924	<.0001
Previous severity level	3	4	1	1.8855	0.2399	61.7474	<.0001
Previous severity level	4	1	1	1.8445	0.2282	65.3095	<.0001
Previous severity level	4	2	1	2.0808	0.207	101.0375	<.0001
Previous severity level	4	3	1	1.7923	0.1985	81.5436	<.0001
Previous severity level	4	4	1	1.4037	0.2019	48.357	<.0001
Visit	8	1	1	-0.4289	0.1523	7.9311	0.0049
Visit	8	2	1	-0.3704	0.1538	5.8017	0.016
Visit	8	3	1	-0.1569	0.1625	0.9325	0.3342

Visit	8	4	1	0.0234	0.1765	0.0176	0.8944
Visit	12	1	1	-0.4915	0.1605	9.384	0.0022
Visit	12	2	1	-0.2811	0.1611	3.0468	0.0809
Visit	12	3	1	-0.2037	0.1731	1.386	0.2391
Visit	12	4	1	0.0692	0.1856	0.1392	0.7

Table 155: Maximum likelihood estimates for tolterodine 4 mg, incontinence

Parameter		Class	DF	Estimate	Standard error	Wald Chi square	Pr > ChiSq
Intercept		1	1	-1.5399	0.3702	17.2994	<.0001
Intercept		2	1	-1.627	0.3728	19.0435	<.0001
Intercept		3	1	-0.9374	0.3863	5.89	0.0152
Intercept		4	1	-1.2225	0.4189	8.5146	0.0035
Age		1	1	-0.00728	0.00525	1.9218	0.1657
Age		2	1	-0.0025	0.00531	0.2211	0.6382
Age		3	1	-0.00511	0.00567	0.8114	0.3677
Age		4	1	-0.003	0.00614	0.2393	0.6247
Sex		1	1	1.0042	0.2005	25.0764	<.0001
Sex		2	1	0.2635	0.2089	1.5913	0.2071
Sex		3	1	0.1231	0.2327	0.2798	0.5969
Sex		4	1	0.095	0.2584	0.1351	0.7132
Treatment	Tolterodine ER 4 mg	1	1	0.1431	0.1765	0.6574	0.4175
Treatment	Tolterodine ER 4 mg	2	1	0.1768	0.1787	0.9787	0.3225
Treatment	Tolterodine ER 4 mg	3	1	-0.3271	0.1907	2.9428	0.0863
Treatment	Tolterodine ER 4 mg	4	1	-0.0298	0.2085	0.0205	0.8861
Treatment	Mirabegron 100 mg	1	1	0.2131	0.1763	1.462	0.2266
Treatment	Mirabegron 100 mg	2	1	0.1445	0.1793	0.6494	0.4203
Treatment	Mirabegron 100 mg	3	1	-0.1592	0.1867	0.7272	0.3938
Treatment	Mirabegron 100 mg	4	1	0.1151	0.2036	0.3193	0.572
Treatment	Mirabegron 50 mg	1	1	0.3617	0.1818	3.9592	0.0466
Treatment	Mirabegron 50 mg	2	1	0.4634	0.1832	6.4002	0.0114
Treatment	Mirabegron 50 mg	3	1	-0.0251	0.1934	0.0168	0.8968
Treatment	Mirabegron 50 mg	4	1	0.204	0.2122	0.9239	0.3365
Previous severity level	1	1	1	6.5207	0.2607	625.7562	<.0001
Previous severity level	1	2	1	4.2602	0.2621	264.2503	<.0001
Previous severity level	1	3	1	2.0943	0.2937	50.8512	<.0001
Previous severity level	1	4	1	1.1226	0.3367	11.1156	0.0009
Previous severity level	2	1	1	4.6908	0.2363	394.0306	<.0001

Previous severity level	2	2	1	4.2494	0.2312	337.7914	<.0001
Previous severity level	2	3	1	2.7019	0.2389	127.8799	<.0001
Previous severity level	2	4	1	1.3854	0.2758	25.2263	<.0001
Previous severity level	3	1	1	3.5642	0.2344	231.1848	<.0001
Previous severity level	3	2	1	3.4919	0.2266	237.4175	<.0001
Previous severity level	3	3	1	2.8324	0.2236	160.3924	<.0001
Previous severity level	3	4	1	1.8855	0.2399	61.7474	<.0001
Previous severity level	4	1	1	1.8445	0.2282	65.3095	<.0001
Previous severity level	4	2	1	2.0808	0.207	101.0375	<.0001
Previous severity level	4	3	1	1.7923	0.1985	81.5436	<.0001
Previous severity level	4	4	1	1.4037	0.2019	48.357	<.0001
Visit	8	1	1	-0.4289	0.1523	7.9311	0.0049
Visit	8	2	1	-0.3704	0.1538	5.8017	0.016
Visit	8	3	1	-0.1569	0.1625	0.9325	0.3342
Visit	8	4	1	0.0234	0.1765	0.0176	0.8944
Visit	12	1	1	-0.4915	0.1605	9.384	0.0022
Visit	12	2	1	-0.2811	0.1611	3.0468	0.0809
Visit	12	3	1	-0.2037	0.1731	1.386	0.2391
Visit	12	4	1	0.0692	0.1856	0.1392	0.709

10.20 Appendix 20: Transition probabilities; micturitions and incontinence episodes

Table 156: Transition probabilities between micturition levels, on mirabegron 50 mg

		Level 1	Level 2	Level 3	Level 4	Level 5
		Severity level at 1 month				
Severity level at baseline	1	0.805	0.180	0.013	0.002	0.000
	2	0.408	0.465	0.113	0.012	0.002
	3	0.160	0.387	0.343	0.084	0.026
	4	0.055	0.202	0.368	0.251	0.124
	5	0.030	0.074	0.156	0.241	0.500
		Severity level at 2 months				
Severity level at 1 month	1	0.761	0.213	0.021	0.004	0.001
	2	0.334	0.476	0.162	0.023	0.004
	3	0.107	0.321	0.399	0.132	0.040
	4	0.030	0.138	0.352	0.323	0.157
	5	0.014	0.043	0.128	0.268	0.546
		Severity level at 3 months				
Severity level at 2 months	1	0.734	0.237	0.024	0.004	0.001
	2	0.302	0.497	0.175	0.021	0.005
	3	0.094	0.326	0.420	0.115	0.046
	4	0.027	0.140	0.372	0.282	0.179
	5	0.012	0.042	0.129	0.223	0.594

Table 157: Transition probabilities between micturition levels, on tolterodine 4 mg ER

		Level 1	Level 2	Level 3	Level 4	Level 5
		Severity level at 1 month				
Severity level at baseline	1	0.799	0.186	0.013	0.002	0.000
	2	0.397	0.472	0.113	0.015	0.003
	3	0.152	0.381	0.335	0.100	0.031
	4	0.050	0.188	0.340	0.281	0.141
	5	0.025	0.064	0.133	0.251	0.527
		Severity level at 2 months				
Severity level at 1 month	1	0.754	0.219	0.021	0.005	0.001
	2	0.324	0.480	0.162	0.028	0.005
	3	0.100	0.312	0.385	0.155	0.048
	4	0.027	0.126	0.319	0.355	0.175
	5	0.011	0.037	0.109	0.275	0.568
		Severity level at 3 months				
Severity level at 2 months	1	0.726	0.243	0.024	0.005	0.001
	2	0.293	0.501	0.175	0.025	0.006
	3	0.088	0.317	0.405	0.135	0.055
	4	0.024	0.128	0.337	0.311	0.200
	5	0.004	0.020	0.086	0.243	0.646

Table 158: Transition probabilities between micturition levels, without treatment

		Level 1	Level 2	Level 3	Level 4	Level 5
		Severity level at (n+1) months				
Severity level at n months	1	0.063	0.307	0.272	0.195	0.164
	2	0.063	0.307	0.272	0.195	0.164
	3	0.063	0.307	0.272	0.195	0.164
	4	0.063	0.307	0.272	0.195	0.164
	5	0.063	0.307	0.272	0.195	0.164

Table 159: Transition probabilities between incontinence levels, on mirabegron 50 mg

		Level 1	Level 2	Level 3	Level 4	Level 5
		Severity level at 1 month				
Severity level at baseline	1	0.879	0.100	0.012	0.005	0.005
	2	0.518	0.364	0.078	0.022	0.018
	3	0.348	0.354	0.184	0.076	0.037
	4	0.209	0.290	0.219	0.158	0.125
	5	0.123	0.134	0.135	0.144	0.463
		Severity level at 2 months				
Severity level at 1 month	1	0.866	0.105	0.015	0.007	0.007
	2	0.484	0.361	0.096	0.033	0.026
	3	0.305	0.329	0.212	0.105	0.050
	4	0.168	0.247	0.231	0.199	0.154
	5	0.089	0.103	0.129	0.164	0.515
		Severity level at 3 months				
Severity level at 2 months	1	0.850	0.120	0.015	0.008	0.008
	2	0.454	0.394	0.091	0.034	0.026
	3	0.284	0.357	0.201	0.109	0.050
	4	0.156	0.267	0.218	0.206	0.152
	5	0.083	0.112	0.122	0.170	0.512

Table 160: Transition probabilities between incontinence levels, on tolterodine 4 mg ER

		Level 1	Level 2	Level 3	Level 4	Level 5
		Severity level at 1 month				
Severity level at baseline	1	0.884	0.094	0.011	0.005	0.006
	2	0.532	0.349	0.074	0.022	0.023
	3	0.359	0.341	0.175	0.077	0.048
	4	0.211	0.273	0.203	0.157	0.157
	5	0.113	0.115	0.114	0.130	0.528
		Severity level at 2 months				
Severity level at 1 month	1	0.871	0.098	0.014	0.007	0.009
	2	0.497	0.346	0.091	0.033	0.033
	3	0.313	0.316	0.201	0.106	0.064
	4	0.168	0.231	0.213	0.196	0.192
	5	0.080	0.087	0.107	0.146	0.580
		Severity level at 3 months				
Severity level at 2 months	1	0.856	0.113	0.014	0.008	0.010
	2	0.467	0.379	0.086	0.035	0.033
	3	0.293	0.343	0.190	0.110	0.064
	4	0.156	0.250	0.201	0.203	0.190
	5	0.052	0.070	0.093	0.167	0.618

Table 161: Transition probabilities between incontinence levels, without treatment

		Level 1	Level 2	Level 3	Level 4	Level 5
		Severity level at (n+1) months				
Severity level at n months	1	0.389	0.188	0.146	0.092	0.185
	2	0.389	0.188	0.146	0.092	0.185
	3	0.389	0.188	0.146	0.092	0.185
	4	0.389	0.188	0.146	0.092	0.185
	5	0.389	0.188	0.146	0.092	0.185

10.21 Appendix 21: Transition matrices for the previously treated subgroup

Table 162: Transition probabilities between micturition levels, mirabegron 50 mg

		Level 1	Level 2	Level 3	Level 4	Level 5
		Severity level at 1 month				
Severity level at baseline	1	0.806	0.177	0.016	0.001	0
	2	0.389	0.482	0.116	0.011	0.002
	3	0.177	0.374	0.336	0.08	0.034
	4	0.042	0.207	0.367	0.264	0.12
	5	0.018	0.078	0.126	0.213	0.565
		Severity level at 2 months				
Severity level at 1 month	1	0.77	0.202	0.025	0.003	0
	2	0.326	0.482	0.163	0.025	0.004
	3	0.12	0.302	0.383	0.141	0.055
	4	0.022	0.131	0.329	0.365	0.152
	5	0.008	0.042	0.095	0.25	0.605
		Severity level at 3 months				
Severity level at 2 months	1	0.719	0.248	0.03	0.004	0
	2	0.272	0.528	0.172	0.024	0.004
	3	0.097	0.32	0.391	0.133	0.059
	4	0.018	0.139	0.334	0.344	0.165
	5	0.006	0.042	0.093	0.227	0.631

Table 163: Transition probabilities between micturition levels, tolterodine 4 mg ER

		Level 1	Level 2	Level 3	Level 4	Level 5
		Severity level at 1 month				
Severity level at baseline	1	0.787	0.191	0.02	0.002	0
	2	0.357	0.489	0.137	0.015	0.002
	3	0.15	0.349	0.367	0.096	0.039
	4	0.033	0.178	0.369	0.294	0.126
	5	0.014	0.064	0.122	0.229	0.572
		Severity level at 2 months				
Severity level at 1 month	1	0.748	0.216	0.031	0.005	0
	2	0.294	0.48	0.19	0.032	0.005
	3	0.098	0.272	0.404	0.165	0.06
	4	0.017	0.11	0.322	0.396	0.156
	5	0.006	0.034	0.091	0.264	0.605
		Severity level at 3 months				
Severity level at 2 months	1	0.694	0.264	0.037	0.005	0
	2	0.243	0.522	0.199	0.031	0.005
	3	0.079	0.288	0.412	0.155	0.065
	4	0.014	0.116	0.328	0.374	0.169
	5	0.002	0.018	0.065	0.269	0.647

Table 164: Transition probabilities between micturition levels, without treatment

		Level 1	Level 2	Level 3	Level 4	Level 5
		Severity level at (n+1) months				
Severity level at n months	1	0.063	0.296	0.262	0.187	0.193
	2	0.063	0.296	0.262	0.187	0.193
	3	0.063	0.296	0.262	0.187	0.193
	4	0.063	0.296	0.262	0.187	0.193
	5	0.063	0.296	0.262	0.187	0.193

Table 165: Transition probabilities between incontinence levels, mirabegron 50 mg

		Level 1	Level 2	Level 3	Level 4	Level 5
		Severity level at 1 month				
Severity level at baseline	1	0.838	0.136	0.014	0.005	0.006
	2	0.42	0.444	0.085	0.032	0.018
	3	0.302	0.393	0.158	0.104	0.043
	4	0.133	0.315	0.187	0.213	0.151
	5	0.077	0.119	0.149	0.152	0.503
		Severity level at 2 months				
Severity level at 1 month	1	0.843	0.124	0.018	0.006	0.009
	2	0.422	0.404	0.109	0.039	0.025
	3	0.29	0.341	0.193	0.12	0.056
	4	0.119	0.255	0.212	0.229	0.186
	5	0.062	0.086	0.152	0.146	0.555
		Severity level at 3 months				
Severity level at 2 months	1	0.807	0.158	0.018	0.007	0.01
	2	0.368	0.469	0.096	0.039	0.027
	3	0.253	0.397	0.17	0.121	0.059
	4	0.102	0.293	0.185	0.227	0.193
	5	0.053	0.098	0.132	0.144	0.574

Table 166: Transition probabilities between incontinence levels, tolterodine 4 mg ER

		Level 1	Level 2	Level 3	Level 4	Level 5
		Severity level at 1 month				
Severity level at baseline	1	0.852	0.12	0.015	0.005	0.008
	2	0.443	0.408	0.093	0.032	0.024
	3	0.315	0.357	0.17	0.102	0.055
	4	0.135	0.278	0.195	0.203	0.19
	5	0.07	0.094	0.14	0.129	0.567
		Severity level at 2 months				
Severity level at 1 month	1	0.855	0.109	0.019	0.006	0.011
	2	0.442	0.368	0.118	0.038	0.033
	3	0.299	0.307	0.205	0.117	0.072
	4	0.118	0.22	0.218	0.214	0.23
	5	0.055	0.067	0.14	0.122	0.616
		Severity level at 3 months				
Severity level at 2 months	1	0.822	0.14	0.019	0.007	0.013
	2	0.389	0.432	0.105	0.039	0.035
	3	0.263	0.36	0.183	0.118	0.077
	4	0.102	0.254	0.191	0.213	0.24
	5	0.036	0.053	0.12	0.112	0.679

Table 167: Transition probabilities between incontinence levels, without treatment

		Level 1	Level 2	Level 3	Level 4	Level 5
		Severity level at (n+1) months				
Severity level at n months	1	0.299	0.187	0.163	0.105	0.247
	2	0.299	0.187	0.163	0.105	0.247
	3	0.299	0.187	0.163	0.105	0.247
	4	0.299	0.187	0.163	0.105	0.247
	5	0.299	0.187	0.163	0.105	0.247

10.22 Appendix 22: Model inputs

Table 168: Inputs parameters for base case model: General OAB population - mirabegron 50 mg vs tolterodine ER 4 mg

Parameter	Base case value	DSA values	PSA	Source
Statistical distributions for proportions of patients by severity level at baseline - General OAB population				
Micturition 1	6.30%	0% - 0%	Dirichlet distribution (α1, α2, α3, α4, α5)=(120,585,518,371,312)	Base case / PSA: SCORPIO based on pooled data from the 3 treatment arms at baseline DSA: assumption
Micturition 2	30.69%	100% - 0%		
Micturition 3	27.18%	0% - 0%		
Micturition 4	19.46%	0% - 0%		
Micturition 5	16.37%	0% - 100%		
Incontinence 1	38.87%	100% - 0%	Dirichlet distribution (α1, α2, α3, α4, α5)=(741,359,279,175 ,352)	
Incontinence 2	18.84%	0% - 0%		
Incontinence 3	14.64%	0% - 0%		
Incontinence 4	9.18%	0% - 0%		
Incontinence 5	18.47%	0% - 100%		
Probabilities of transition between different severity levels, by treatment - for Mirabegron 50 mg, Tolterodine ER 4 mg, Solifenacin 5 mg				
Beta coefficients for Mirabegron 50 mg				
Micturition 1 (5 as reference)	0.6037	0.2239 – 0.9835	Normal distribution (μ , σ)=(0.6037,0.1938)	Base case / PSA: SCORPIO SA: 95% CI assuming normal distribution
Micturition 2 (5 as reference)	0.3803	0.0295 – 0.7311	Normal distribution (μ , σ)=(0.3803,0.1790)	
Micturition 3 (5 as reference)	0.1454	-0.1876 – 0.4784	Normal distribution (μ , σ)=(0.1454,0.1699)	
Micturition 4 (5 as reference)	0.0665	-0.2738 – 0.4068	Normal distribution (μ , σ)=(0.0665,0.1736)	
Incontinence 1 (5 as reference)	0.3617	0.0054 – 0.7180	Normal distribution (μ , σ)=(0.3617,0.1818)	
Incontinence 2 (5 as reference)	0.4634	0.1043 – 0.8225	Normal distribution (μ , σ)=(0.4634,0.1832)	
Incontinence 3 (5 as reference)	-0.0251	-0.4042 – 0.3540	Normal distribution (μ , σ)=(-0.0251,0.1934)	
Incontinence 4 (5 as reference)	0.2040	-0.2119 – 0.6199	Normal distribution (μ , σ)=(0.2040,0.2122)	
Beta coefficients for Tolterodine ER 4 mg				
Micturition 1 (5 as reference)	0.3667	-0.0073 – 0.7407	Normal distribution (μ , σ)=(0.3667,0.1908)	Base case / PSA: SCORPIO DSA: 95% CI assuming normal distribution
Micturition 2 (5 as reference)	0.1826	-0.1610 – 0.5262	Normal distribution (μ , σ)=(0.1826,0.1753)	
Micturition 3 (5 as reference)	-0.0609	-0.3867 – 0.2649	Normal distribution (μ , σ)=(-0.0609,0.1662)	
Micturition 4 (5 as reference)	0.0550	-0.2739 – 0.3839	Normal distribution (μ , σ)=(0.0550,0.1678)	
Incontinence 1 (5 as reference)	0.1431	-0.2028 – 0.4890	Normal distribution (μ , σ)=(0.1431,0.1765)	
Incontinence 2 (5 as reference)	0.1768	-0.1735 – 0.5271	Normal distribution (μ , σ)=(0.1768,0.1787)	
Incontinence 3 (5 as reference)	-0.3271	-0.7009 – 0.0467	Normal distribution (μ , σ)=(-0.3271,0.1907)	

Parameter	Base case value	DSA values	PSA	Source
Incontinence 4 (5 as reference)	-0.0298	-0.4385 – 0.3789	Normal distribution (μ , σ)=(-0.0298,0.2085)	
Beta coefficients for Solifenacin 5 mg				
Micturition 1 (5 as reference)	0,9977	0,6237 – 1.3717	Normal distribution (μ , σ)=(0,9977,0,1908)	MTC based on SCORPIO and calibration method (calibration following the seven-step approach defined by Vanni, 2011) (97) Initial betas for the calibration were those for mirabegron 50 mg
Micturition 2 (5 as reference)	0,4933	0,1497 – 0.8639	Normal distribution (μ , σ)=(0,4933,0,1753)	
Micturition 3 (5 as reference)	0,0384	0,3641 - -0.2874	Normal distribution (μ , σ)=(0,0384,0,1662)	
Micturition 4 (5 as reference)	-0,0729	0,2560 - -0.4017	Normal distribution (μ , σ)=(-0,0729,0,1678)	
Incontinence 1 (5 as reference)	1,1403	0,7944 – 1.4863	Normal distribution (μ , σ)=(1,1403,0,1765)	
Incontinence 2 (5 as reference)	0,7343	0,3840 – 1.0845	Normal distribution (μ , σ)=(0,7343,0,1787)	
Incontinence 3 (5 as reference)	0,0347	0,4084 - -0.3391	Normal distribution (μ , σ)=(0,0347,0,1907)	
Incontinence 4 (5 as reference)	0,1136	0,5223 - -0.2950	Normal distribution (μ , σ)=(0,1136,0,2085)	
Probability of having a dry mouth AE				
Mirabegron 50 mg	2.80%	2.1% - 3.5%	Beta distribution (α,ß)=(47.60,1652.40)	Base case / PSA: SCORPIO DSA: 95% CI
Tolterodine 4 mg	10.10%	8.7% - 11.5%	Beta distribution (α,ß)=(113.12,1006.86)	
No treatment	0%	NA	NA	Assumption
Probability of having a constipation AE				
Mirabegron 50 mg	1.60%	1% - 2.20%	NA	Base case / PSA: SCORPIO DSA: 95% CI
Tolterodine 4 mg	2%	1.40% - 2.60%	NA	
No treatment	0%	NA	NA	Assumption
Probability of success of botulinum toxin (all patients)				
	79%	60% - 92%	NA	Wu et al, 2009 (102)
Utilities according to symptom severity – EQ-5D (coefficients of regression equation)				
Micturition 1 (5 as reference)	0.0632	0.0453 – 0.0811	Normal distribution (μ , σ)=(0.0632,0.0091)	Base case/PSA: SCORPIO DSA: 95% CI assuming normal distribution
Micturition 2 (5 as reference)	0.0422	0.0258 – 0.0587	Normal distribution (μ , σ)=(0.0422,0.0084)	
Micturition 3 (5 as reference)	0.0204	0.0045 – 0.0363	Normal distribution (μ , σ)=(0.0204,0.0081)	
Micturition 4 (5 as reference)	0.0104	-0.0054 – 0.0262	Normal distribution (μ , σ)=(0.0104,0.0081)	
Incontinence 1 (5 as reference)	0.0586	0.0422 – 0.0749	Normal distribution (μ , σ)=(0.0586,0.0083)	
Incontinence 2 (5 as reference)	0.0437	0.0271 – 0.0602	Normal distribution (μ , σ)=(0.0437,0.0084)	
Incontinence 3 (5 as reference)	0.0314	0.0142 – 0.0486	Normal distribution (μ , σ)=(0.0314,0.0088)	
Incontinence 4 (5 as reference)	0.0128	-0.0056 – 0.0313	Normal distribution (μ , σ)=(0.0128,0.0094)	
Utilities according to symptom severity – OAB-5D (coefficients of regression equation)				
Micturition 1 (5 as reference)	0.0988	0.0919 – 0.1057	Normal distribution (μ , σ)=(0.0988,0.0035)	Base case/PSA: SCORPIO

Parameter	Base case value	DSA values	PSA	Source
Micturition 2 (5 as reference)	0.0620	0.0556 – 0.0683	Normal distribution (μ , σ)=(0.0620,0.0033)	DSA: 95% CI assuming normal distribution
Micturition 3 (5 as reference)	0.0353	0.0292 – 0.0415	Normal distribution (μ , σ)=(0.0353,0.0031)	
Micturition 4 (5 as reference)	0.0185	0.0123 – 0.0246	Normal distribution (μ , σ)=(0.0185,0.0031)	
Incontinence 1 (5 as reference)	0.0777	0.0714 – 0.0840	Normal distribution (μ , σ)=(0.0777,0.0032)	
Incontinence 2 (5 as reference)	0.0511	0.0447 – 0.0575	Normal distribution (μ , σ)=(0.0511,0.0033)	
Incontinence 3 (5 as reference)	0.0246	0.0179 – 0.0313	Normal distribution (μ , σ)=(0.0246,0.0034)	
Incontinence 4 (5 as reference)	0.0094	0.0022 – 0.0166	Normal distribution (μ , σ)=(0.0094,0.0037)	
Utility decrement associated with AE				
All AE	-0.0357	0 - -0.1	NA	Base case: SCORPIO SA: Assumption
Pad use per day by level of incontinence (coefficients of linear regression equation)				
Incontinence 1	0.17	0.150 – 0.198	NA	Base case: SCORPIO SA: 95% CI assuming normal distribution
Incontinence 2	0.75	0.687 – 0.817	NA	
Incontinence 3	1.38	1.282 – 1.486	NA	
Incontinence 4	1.89	1.745 – 2.039	NA	
Incontinence 5	3.34	3.167 – 3.511	NA	
Mean percentage work time missed (base case)				
Incontinence severity levels 1/2 (≤1 episodes/24H)	0%	1.68%	NA	SA: SCORPIO
Incontinence severity levels 3/4/5 (>1 episodes/24H)	0%	3.87%	NA	
Monthly probability of discontinuation of OAB therapy				
Without AEs	6.40%	0% - 14.5%	NA	Base case: 28.2% of patients on tolterodine ER persistent at 12 months (Wagg et al. 2012) (22), N=1,758; 24% of discontinuations are due to AEs (Castro-Diaz 2001) (98) SA: Estimate based on mean duration of treatment with tolterodine (156.7 days) instead of persistence rate at 12 months (Wagg et al, 2012) (22) SA: Assumption
With AEs	90%	50% - 100%	Beta distribution (α,ß)=(6.92,0.77)	Base case and SA: Assumption

Parameter	Base case value	DSA values	PSA	Source
Monthly probability of switch after discontinuation of OAB therapy				
Probability of switch, among all patients discontinuing OAB treatment	26.06%	15.32% - 50%	Beta distribution	Base case: Odeyemi et al, 2006 (100)
				SA: D'Souza et al, 2008(101) / Assumption
Monthly probabilities of restarting OAB therapy among patients without treatment				
Monthly probability of restarting treatment	10%	0.05% - 20%	Beta distribution (α,ß)=(1.74,15.63)	Base case and SA: Assumption
Split between different medications, for general OAB population*				
- Initial treatment (mirabegron or tolterodine)	33.33%	0% - 50%	NA	Base case and SA: Assumption
- Next line A	33.33%	0% - 50%	NA	Base case and SA: Assumption
- Next line B	33.33%	0% - 50%	NA	Base case and SA: Assumption
Monthly probability of transition to botulinum toxin				
Monthly probability of having botulinum toxin injection in the general OAB population	0.01%	0% - 0.05%	Beta distribution (α,ß)= (0.70,834.78)	Base case and SA: Assumption
Resource utilisation (physician visits and botulinum toxin reinjections)				
Number of GP consultations	1 visit at the start and at every switch	0 - 2	Lognormal distribution (μ , σ)=(1,0.20)	Base case: Cardozo 2010 (87) SA: Assumption
Number of specialist consultations	1.5 visits at the start and at every switch	1 - 3	Lognormal distribution (μ , σ)=(1.5,0.95)	Base case: Cardozo 2010 (87) SA: Assumption
Number of Botulinum toxin reinjections, following success of first injection	0.17 per month	0	NA	Base case: Expert opinion (Once every 6 months) SA: Assumption
Model inputs: Monthly OAB medication costs				
Mirabegron 50 mg	£28.00	NA	NA	Mirabegron: Astellas
Tolterodine 4 mg ER	£28.01	£8.4	NA	Tolterodine: British National Formulary 2011: Tolterodine ER: Detrusitol® XL (Pharmacia) Capsules, blue, m/r, tolterodine tartrate 4 mg, net price 28-cap pack = £25.78. DSA: price
Model inputs: unit costs of health care resources				

Parameter	Base case value	DSA values		PSA	Source
GP consultation	£36	NA		NA	PSSRU 2011
Specialist visit: Follow-up visit	£96	NA		NA	NHS Payment 2010-2011
Botulinum toxin injection: Initial / Reinjections	£ 1158 / £964	NA		NA	http://www.nottinghamurologygroup.co.uk/treatments/bladder-botulinum toxin-injections
Incontinence pad (per pad)	£0.16	NA		NA	Age UK incontinence
Model inputs: cost of absenteeism					
Proportion of workers	NA	46.28%		NA	OECD Stats 2011
Labour cost per month	NA	£2,923		NA	OECD Stats / Average annual wages 2010
Discount rates					
Costs Outcomes (QALYs)	3.5% 3.5%	3.5% 0%	6% 6%	NA NA	NICE guidelines

SA: Sensitivity Analyses

Table 169: Inputs parameters for subgroups: mirabegron 50 mg vs tolterodine ER 4 mg

Parameter	Base case value	DSA values	PSA	Source
Statistical distributions for proportions of patients by severity level at baseline - Previously treated				
Micturition 1	6.25%	NA	NA	SCORPIO based on pooled data from the 3 treatment arms at baseline / No SA was performed for subgroups
Micturition 2	29.61%	NA	NA	
Micturition 3	26.23%	NA	NA	
Micturition 4	18.65%	NA	NA	
Micturition 5	19.26%	NA	NA	
Incontinence 1	29.92%	NA	NA	
Incontinence 2	18.65%	NA	NA	
Incontinence 3	16.29%	NA	NA	
Incontinence 4	10.45%	NA	NA	
Incontinence 5	24.69%	NA	NA	
Statistical distributions for proportions of patients by severity level at baseline – Treatment-naive				
Micturition 1	6.50%	NA	NA	SCORPIO based on pooled data from the 3 treatment arms at baseline / No SA was performed for subgroups
Micturition 2	31.90%	NA	NA	
Micturition 3	28.00%	NA	NA	
Micturition 4	19.90%	NA	NA	
Micturition 5	13.70%	NA	NA	
Incontinence 1	47.10%	NA	NA	
Incontinence 2	19.80%	NA	NA	
Incontinence 3	12.80%	NA	NA	
Incontinence 4	7.90%	NA	NA	
Incontinence 5	12.40%	NA	NA	
Statistical distributions for proportions of patients by severity level at baseline – Females				
Micturition 1	6.03%	NA	NA	SCORPIO based on pooled data from the 3 treatment arms at baseline baseline / No SA was performed for subgroups
Micturition 2	30.34%	NA	NA	
Micturition 3	27.96%	NA	NA	
Micturition 4	19.62%	NA	NA	
Micturition 5	16.05%	NA	NA	
Incontinence 1	28.87%	NA	NA	
Incontinence 2	19.69%	NA	NA	
Incontinence 3	16.26%	NA	NA	
Incontinence 4	11.77%	NA	NA	
Incontinence 5	23.41%	NA	NA	
Statistical distributions for proportions of patients by severity level at baseline – Males				
Micturition 1	6.50%	NA	NA	SCORPIO based on pooled data from the 3 treatment arms at baseline baseline / No SA was performed for subgroups
Micturition 2	31.90%	NA	NA	
Micturition 3	28.00%	NA	NA	
Micturition 4	19.90%	NA	NA	
Micturition 5	13.70%	NA	NA	
Incontinence 1	47.10%	NA	NA	
Incontinence 2	19.80%	NA	NA	
Incontinence 3	12.80%	NA	NA	
Incontinence 4	7.90%	NA	NA	
Incontinence 5	12.40%	NA	NA	
Monthly probability of having botulinum toxin injection				
Previously treated population	0.04%	0% - 0.1%	NA	Base case: Assumption
Treatment naive patients	0.01%	0% - 0.05%	NA	
Female patients	0.01%	0% - 0.05%	NA	
Male patients	0.01%	0% - 0.05%	NA	
Probabilities of transition between different severity levels, by treatment – Previously treated				

Parameter	Base case value	DSA values	PSA	Source
Beta coefficients for Mirabegron 50 mg				
Micturition 1 (5 as reference)	0.6037	NA	NA	Base case: SCORPIO
Micturition 2 (5 as reference)	0.3803	NA	NA	
Micturition 3 (5 as reference)	0.1454	NA	NA	
Micturition 4 (5 as reference)	0.0665	NA	NA	
Incontinence 1 (5 as reference)	0.3617	NA	NA	
Incontinence 2 (5 as reference)	0.4634	NA	NA	
Incontinence 3 (5 as reference)	-0.0251	NA	NA	
Incontinence 4 (5 as reference)	0.204	NA	NA	
Beta coefficients for Tolterodine ER 4 mg				
Micturition 1 (5 as reference)	0.422	NA	NA	Base case: SCORPIO
Micturition 2 (5 as reference)	0.251	NA	NA	
Micturition 3 (5 as reference)	0.037	NA	NA	
Micturition 4 (5 as reference)	0.1658	NA	NA	
Incontinence 1 (5 as reference)	0.1913	NA	NA	
Incontinence 2 (5 as reference)	0.1102	NA	NA	
Incontinence 3 (5 as reference)	-0.1607	NA	NA	
Incontinence 4 (5 as reference)	-0.1879	NA	NA	
Probabilities of transition between different severity levels, by treatment – Treatment-naïve				
Beta coefficients for Mirabegron 50 mg				
Micturition 1 (5 as reference)	0.5362	NA	NA	Base case: SCORPIO
Micturition 2 (5 as reference)	0.3406	NA	NA	
Micturition 3 (5 as reference)	0.2418	NA	NA	
Micturition 4 (5 as reference)	0.0445	NA	NA	
Incontinence 1 (5 as reference)	0.2984	NA	NA	
Incontinence 2 (5 as reference)	0.4427	NA	NA	
Incontinence 3 (5 as reference)	-0.1171	NA	NA	
Incontinence 4 (5 as reference)	0.4632	NA	NA	
Beta coefficients for Tolterodine ER 4 mg				
Micturition 1 (5 as reference)	0.3053	NA	NA	Base case: SCORPIO
Micturition 2 (5 as reference)	0.1023	NA	NA	
Micturition 3 (5 as reference)	-0.1663	NA	NA	
Micturition 4 (5 as reference)	-0.0769	NA	NA	
Incontinence 1 (5 as reference)	-0.0114	NA	NA	
Incontinence 2 (5 as reference)	0.1572	NA	NA	
Incontinence 3 (5 as reference)	-0.6564	NA	NA	
Incontinence 4 (5 as reference)	0.2059	NA	NA	
Probabilities of transition between different severity levels, by treatment – Females				
Beta coefficients for Mirabegron 50 mg				
Micturition 1 (5 as reference)	0.7373	NA	NA	Base case: SCORPIO
Micturition 2 (5 as reference)	0.3943	NA	NA	
Micturition 3 (5 as reference)	0.1413	NA	NA	
Micturition 4 (5 as reference)	0.1699	NA	NA	
Incontinence 1 (5 as reference)	0.2648	NA	NA	
Incontinence 2 (5 as reference)	0.3825	NA	NA	
Incontinence 3 (5 as reference)	-0.0894	NA	NA	
Incontinence 4 (5 as reference)	0.1965	NA	NA	
Beta coefficients for Tolterodine ER 4 mg				
Micturition 1 (5 as reference)	0.3146	NA	NA	Base case: SCORPIO
Micturition 2 (5 as reference)	0.2135	NA	NA	

Parameter	Base case value	DSA values	PSA	Source
Micturition 3 (5 as reference)	-0.0353	NA	NA	
Micturition 4 (5 as reference)	0.1152	NA	NA	
Incontinence 1 (5 as reference)	0.1614	NA	NA	
Incontinence 2 (5 as reference)	0.1165	NA	NA	
Incontinence 3 (5 as reference)	-0.3291	NA	NA	
Incontinence 4 (5 as reference)	-0.0507	NA	NA	
Probabilities of transition between different severity levels, by treatment – Males				
Beta coefficients for Mirabegron 50 mg				
Micturition 1 (5 as reference)	0.2525	NA	NA	Base case: SCORPIO
Micturition 2 (5 as reference)	0.4071	NA	NA	
Micturition 3 (5 as reference)	0.1627	NA	NA	
Micturition 4 (5 as reference)	-0.1555	NA	NA	
Incontinence 1 (5 as reference)	1.1201	NA	NA	
Incontinence 2 (5 as reference)	1.2508	NA	NA	
Incontinence 3 (5 as reference)	0.6975	NA	NA	
Incontinence 4 (5 as reference)	0.3484	NA	NA	
Beta coefficients for Tolterodine ER 4 mg				
Micturition 1 (5 as reference)	0.5291	NA	NA	Base case: SCORPIO
Micturition 2 (5 as reference)	0.1005	NA	NA	
Micturition 3 (5 as reference)	-0.1078	NA	NA	
Micturition 4 (5 as reference)	-0.0703	NA	NA	
Incontinence 1 (5 as reference)	0.1802	NA	NA	
Incontinence 2 (5 as reference)	0.5307	NA	NA	
Incontinence 3 (5 as reference)	-0.3022	NA	NA	
Incontinence 4 (5 as reference)	0.1655	NA	NA	
Utilities according to symptom severity – EQ5D – Previously treated				
Micturition 1 (5 as reference)	0.062	NA	NA	Base case: SCORPIO
Micturition 2 (5 as reference)	0.050	NA	NA	
Micturition 3 (5 as reference)	0.029	NA	NA	
Micturition 4 (5 as reference)	0.026	NA	NA	
Incontinence 1 (5 as reference)	0.048	NA	NA	
Incontinence 2 (5 as reference)	0.041	NA	NA	
Incontinence 3 (5 as reference)	0.023	NA	NA	
Incontinence 4 (5 as reference)	0.009	NA	NA	
Utilities according to symptom severity – EQ5D – Treatment-naïve				
Micturition 1 (5 as reference)	0.059	NA	NA	Base case: SCORPIO
Micturition 2 (5 as reference)	0.031	NA	NA	
Micturition 3 (5 as reference)	0.009	NA	NA	
Micturition 4 (5 as reference)	-0.008	NA	NA	
Incontinence 1 (5 as reference)	0.069	NA	NA	
Incontinence 2 (5 as reference)	0.049	NA	NA	
Incontinence 3 (5 as reference)	0.043	NA	NA	
Incontinence 4 (5 as reference)	0.019	NA	NA	
Utilities according to symptom severity – EQ5D – Females				
Micturition 1 (5 as reference)	0.070	NA	NA	Base case: SCORPIO
Micturition 2 (5 as reference)	0.046	NA	NA	
Micturition 3 (5 as reference)	0.022	NA	NA	
Micturition 4 (5 as reference)	0.010	NA	NA	
Incontinence 1 (5 as reference)	0.061	NA	NA	
Incontinence 2 (5 as reference)	0.050	NA	NA	
Incontinence 3 (5 as reference)	0.030	NA	NA	

Parameter	Base case value	DSA values	PSA	Source
Incontinence 4 (5 as reference)	0.014	NA	NA	
Utilities according to symptom severity – EQ5D – Males				
Micturition 1 (5 as reference)	0.045	NA	NA	Base case: SCORPIO
Micturition 2 (5 as reference)	0.032	NA	NA	
Micturition 3 (5 as reference)	0.018	NA	NA	
Micturition 4 (5 as reference)	0.011	NA	NA	
Incontinence 1 (5 as reference)	0.019	NA	NA	
Incontinence 2 (5 as reference)	-0.010	NA	NA	
Incontinence 3 (5 as reference)	0.018	NA	NA	
Incontinence 4 (5 as reference)	-0.004	NA	NA	

Table 170: Inputs parameters for other antimuscarinics comparators

Parameter	Base case value	DSA value	PSA	Source
Probabilities of transition between different severity levels, by treatment				
Beta coefficients for Solifenacin 5 mg				
Micturition 1 (5 as reference)	0.7175	NA	NA	MTC based on SCORPIO and calibration method (calibration following the seven-step approach defined by Vanni et al. 2011) (97) Initial betas for the calibration were those for mirabegron 50 mg
Micturition 2 (5 as reference)	0.4063	NA	NA	
Micturition 3 (5 as reference)	0.1178	NA	NA	
Micturition 4 (5 as reference)	0.0309	NA	NA	
Incontinence 1 (5 as reference)	0.4191	NA	NA	
Incontinence 2 (5 as reference)	0.5053	NA	NA	
Incontinence 3 (5 as reference)	0.0253	NA	NA	
Incontinence 4 (5 as reference)	0.2224	NA	NA	
Beta coefficients for Fesoterodine 4 mg				
Micturition 1 (5 as reference)	0.3576	NA	NA	MTC based on SCORPIO and calibration method (calibration following the seven-step approach defined by Vanni et al. 2011) (97) Initial betas for the calibration were those for mirabegron 50 mg
Micturition 2 (5 as reference)	0.3134	NA	NA	
Micturition 3 (5 as reference)	0.2176	NA	NA	
Micturition 4 (5 as reference)	0.1603	NA	NA	
Incontinence 1 (5 as reference)	-0.2793	NA	NA	
Incontinence 2 (5 as reference)	0.3811	NA	NA	
Incontinence 3 (5 as reference)	0.0164	NA	NA	
Incontinence 4 (5 as reference)	0.2750	NA	NA	
Beta coefficients for Oxybutynin 10 mg IR				
Micturition 1 (5 as reference)	0.3544	NA	NA	MTC based on SCORPIO and calibration method (calibration following the seven-step approach defined by Vanni et al. 2011) (97) Initial betas for the calibration were those for mirabegron 50 mg
Micturition 2 (5 as reference)	0.3139	NA	NA	
Micturition 3 (5 as reference)	0.2169	NA	NA	
Micturition 4 (5 as reference)	0.1594	NA	NA	
Incontinence 1 (5 as reference)	-0.3630	NA	NA	
Incontinence 2 (5 as reference)	0.3902	NA	NA	
Incontinence 3 (5 as reference)	0.0150	NA	NA	
Incontinence 4 (5 as reference)	0.2676	NA	NA	
Beta coefficients for Trospium chloride 60 mg				
Micturition 1 (5 as reference)	0.6048	NA	NA	MTC based on SCORPIO trial and calibration method (calibration following the seven-step approach defined by Vanni et al. 2011) (97) Initial betas for the calibration were those for mirabegron 50 mg
Micturition 2 (5 as reference)	0.3805	NA	NA	
Micturition 3 (5 as reference)	0.1451	NA	NA	
Micturition 4 (5 as reference)	0.0662	NA	NA	
Incontinence 1 (5 as reference)	0.1114	NA	NA	
Incontinence 2 (5 as reference)	0.4395	NA	NA	
Incontinence 3 (5 as reference)	0.0221	NA	NA	

Parameter	Base case value	DSA value	PSA	Source
Incontinence 4 (5 as reference)	0.2528	NA	NA	
Probability of dry mouth for other antimuscarinics				
Oxybutynin 10 mg ER	16.37%	NA	NA	For other treatments, log odds ratios of each treatment versus mirabegron 50 mg for each AE were obtained from an MTC reported separately.
Solifenacin 5 mg	10.86%	NA	NA	
Fesoterodine 4 mg	11.33%	NA	NA	
Trospium chloride 60 mg	11.43%	NA	NA	
Probability of constipation for other antimuscarinics				
Oxybutynin 10 mg ER	1.63%	NA	NA	For other treatments, log odds ratios of each treatment versus mirabegron 50 mg for each AE were obtained from an MTC reported separately.
Solifenacin 5 mg	3.91%	NA	NA	For other treatments, log odds ratios of each treatment versus mirabegron 50 mg for each AE were obtained from an MTC reported separately.
Fesoterodine 4 mg	1.70%	NA	NA	For other treatments, log odds ratios of each treatment versus mirabegron 50 mg for each AE were obtained from an MTC reported separately.
Trospium chloride 60 mg	11.0%	NA	NA	For other treatments, log odds ratios of each treatment versus mirabegron 50 mg for each AE were obtained from an MTC reported separately.
Model inputs: Monthly OAB medication costs (BNF 63)				
Solifenacin 5mg	£28.00	NA	NA	Vesicare® (Astellas) Tablets, f/c, solifenacin succinate 5 mg (yellow), net price 30-tab pack = £27.62; 10 mg (pink), 30-tab pack = £35.91.
Solifenacin 10 mg	£36.41	NA	NA	Vesicare® (Astellas) Tablets, f/c, solifenacin succinate 5 mg (yellow), net price 30-tab pack = £27.62; 10 mg (pink), 30-tab pack = £35.91.
Trospium chloride 60 mg	£25.04	NA	NA	Regurin® XL (Speciality European) Capsules, orange/white, m/r, trospium chloride 60 mg, net price 28-cap pack = £23.05.
Fesoterodine 4 mg and 8 mg	£28.01	NA	NA	Toviaz® (Pfizer) Tablets, m/r, f/c, fesoterodine fumarate 4 mg (light blue), net price 28-tab pack = £25.78; 8 mg (blue), 28-tab pack = £25.78.
Oxybutynin 10 mg ER	£27.92	NA	NA	Lyrinel® XL (Janssen) Prescription only medicine Tablets, m/r, oxybutynin hydrochloride 5 mg (yellow), net price 30-tab pack = £13.77; 10 mg (pink), 30-tab pack = £27.54.
Oxybutynin 10 mg IR	£ 8.40	NA	NA	Oxybutynin Hydrochloride (Non-proprietary) Tablets, oxybutynin hydrochloride 2.5 mg, net price 56-tab pack = £5.86; 3

Parameter	Base case value	DSA value	PSA	Source
				mg, 56-tab pack = £14.00; 5 mg, 56-tab pack = £6.11, 84-tab pack = £11.60.

Table 171: Inputs parameters on utilities according to symptom severity – OAB-5D

Parameter	Base case value	DSA values	PSA	Source
Utilities according to symptom severity – OAB-5D – General OAB population				
Micturition 1 (5 as reference)	0.0988	0.0919 – 0.1057	Normal distribution (μ , σ)=(0.0988,0.0035)	Base case/PSA: SCORPIO DSA: 95% CI assuming normal distribution
Micturition 2 (5 as reference)	0.0620	0.0556 – 0.0683	Normal distribution (μ , σ)=(0.0620,0.0033)	
Micturition 3 (5 as reference)	0.0353	0.0292 – 0.0415	Normal distribution (μ , σ)=(0.0353,0.0031)	
Micturition 4 (5 as reference)	0.0185	0.0123 – 0.0246	Normal distribution (μ , σ)=(0.0185,0.0031)	
Incontinence 1 (5 as reference)	0.0777	0.0714 – 0.0840	Normal distribution (μ , σ)=(0.0777,0.0032)	
Incontinence 2 (5 as reference)	0.0511	0.0447 – 0.0575	Normal distribution (μ , σ)=(0.0511,0.0033)	
Incontinence 3 (5 as reference)	0.0246	0.0179 – 0.0313	Normal distribution (μ , σ)=(0.0246,0.0034)	
Incontinence 4 (5 as reference)	0.0094	0.0022 – 0.0166	Normal distribution (μ , σ)=(0.0094,0.0037)	
Utilities according to symptom severity – OAB-5D – Previously treated				
Micturition 1 (5 as reference)	0.089	NA	NA	Base case: SCORPIO
Micturition 2 (5 as reference)	0.054	NA	NA	
Micturition 3 (5 as reference)	0.033	NA	NA	
Micturition 4 (5 as reference)	0.016	NA	NA	
Incontinence 1 (5 as reference)	0.072	NA	NA	
Incontinence 2 (5 as reference)	0.046	NA	NA	
Incontinence 3 (5 as reference)	0.023	NA	NA	
Incontinence 4 (5 as reference)	0.006	NA	NA	
Utilities according to symptom severity – OAB-5D – Treatment-naïve				
Micturition 1 (5 as reference)	0.106	NA	NA	Base case: SCORPIO
Micturition 2 (5 as reference)	0.069	NA	NA	
Micturition 3 (5 as reference)	0.038	NA	NA	
Micturition 4 (5 as reference)	0.022	NA	NA	
Incontinence 1 (5 as reference)	0.085	NA	NA	
Incontinence 2 (5 as reference)	0.059	NA	NA	
Incontinence 3 (5 as reference)	0.028	NA	NA	
Incontinence 4 (5 as reference)	0.016	NA	NA	

Parameter	Base case value	DSA values	PSA	Source
Utilities according to symptom severity – OAB-5D – Females				
Micturition 1 (5 as reference)	0.104	NA	NA	Base case: SCORPIO
Micturition 2 (5 as reference)	0.066	NA	NA	
Micturition 3 (5 as reference)	0.037	NA	NA	
Micturition 4 (5 as reference)	0.020	NA	NA	
Incontinence 1 (5 as reference)	0.083	NA	NA	
Incontinence 2 (5 as reference)	0.053	NA	NA	
Incontinence 3 (5 as reference)	0.025	NA	NA	
Incontinence 4 (5 as reference)	0.010	NA	NA	
Utilities according to symptom severity – OAB-5D – Males				
Micturition 1 (5 as reference)	0.084	NA	NA	Base case: SCORPIO
Micturition 2 (5 as reference)	0.051	NA	NA	
Micturition 3 (5 as reference)	0.032	NA	NA	
Micturition 4 (5 as reference)	0.014	NA	NA	
Incontinence 1 (5 as reference)	0.046	NA	NA	
Incontinence 2 (5 as reference)	0.026	NA	NA	
Incontinence 3 (5 as reference)	0.014	NA	NA	
Incontinence 4 (5 as reference)	0.005	NA	NA	