NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Vibegron for treating symptoms of overactive bladder [ID6300]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COST COMPARISON APPRAISAL

Vibegron for treating symptoms of overactive bladder [ID6300]

Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Pierre Fabre:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Initial clarification
   b. Additional clarification

3. **NICE medicines optimisation team (MOT) report**

4. **External Assessment Report** prepared by BMJ Technology Assessment Group
   The company stated that they had no comments on the EAR and there is therefore no factual accuracy check document

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Fast track appraisal: cost-comparison case

Vibegron for treating symptoms of overactive bladder ID 6300

Document B

Company evidence submission

April 2024

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ID6300_Vibegron for treating symptoms of overactive bladder_Document B_1.0_CiC_Redacted	1.0	Yes	26.03.2024

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Abbreviations

AE	Adverse event
ANCOVA	Analysis of covariance
B_3-AR	Beta-3 adrenergic receptor
BP	Blood pressure
CFB	Change from baseline
CI	Confidence interval
CMH	Cochran Mantel Haenszel
CrI	Credibility interval
CYCLAMEN	CYCLe AntiMuscarinics in England (study)
DSA	Deterministic sensitivity analysis
ER	Extended release
ERG	Evidence Review Group
EMA	European Medicines Agency
FAS	Full analysis set
FAS-I	Full analysis set in incontinent participants
HRQoL	Health-related quality of life
HRU	Healthcare resource use
HTA	Health technology assessment
ICS	International Continence Society
ITC	Indirect treatment comparison
ITT	Intention to treat
KHQ	King's health questionnaire
LS(M)	Least squares (mean)
MCID	Minimal clinically important difference
MMRM	Mixed model for repeated measures
NA	Not applicable
NICE	National Institute for Health and Care Excellence

NMA	Network meta-analysis
NR	Not reported
OAB	Overactive bladder
OABSS	Overactive bladder symptom score
OAB-q	OAB questionnaire
Odds Ratio	OR
PbR	Payment by results
PSA	Probabilistic sensitivity analysis
PGI	Patient Global Impression
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life-year
QoL	Quality of life
RCT	Randomised controlled trial
SAE	Serious adverse event
SAF	Safety analysis set
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
STA	Single technology appraisal
TEAE	Treatment Emergent Adverse Event
UTI	Urinary tract infection
UUI	Urgency urinary incontinence

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The full decision problem addressed in this submission is summarised in Table 1. Further details on the population, comparator and outcomes are discussed in the following sections.

B.1.1.1 Population

The anticipated market authorisation for vibegron is the "symptomatic treatment of adult patients with overactive bladder (OAB) syndrome" (1), which is fully aligned with population described in the decision problem scope. In practice it is expected that vibegron will be positioned in the NICE pathway at the same place in therapy as mirabegron and consistent with NICE TA290 (2). Therefore, the relevant population is adults with symptoms of OAB in whom antimuscarinic drugs are contraindicated or clinically ineffective, or who have unacceptable side effects. In the UK, it is estimated that around 5 million people have symptoms consistent with OAB (3) with a significant proportion of these being eligible for treatment with vibegron due to poor tolerance of antimuscarinic drugs due to anticholinergic mediated adverse effects (AEs) or a lack of efficacy.

The treatment pathways are discussed in more detail in Section B.1.3.4.

B.1.1.2 Comparator

The comparator to be considered in the decision problem is exclusively mirabegron.

- Mirabegron and vibegron are both β_3-adrenergic agonists, with similar, although not identical, pharmacodynamic profiles (4). This is in marked contrast to the other class of pharmacological treatments used to treat OAB, antimuscarinics, which have a different mechanism of action and AE profile (5, 6).
- Vibegron will be introduced at the same point in the treatment pathway as mirabegron (Section B.1.3). This is consistent with guidance from NICE TA290 (7) (Section B.1.3.4). Consistent with TA290, the evidence base used to inform the efficacy and safety of vibegron will be derived from the population described in the decision problem.

B.1.1.3 Outcomes

The broad relevant outcomes used in the decision problem are listed in Table 1. The key quantitative efficacy outcomes that have been identified are the number of micturition

episodes per day and the number of urgency urinary incontinence (UUI) episodes, which were the co-primary outcomes of the EMPOWUR vibegron trial (8) and trials supporting the use of mirabegron (9). Another outcome commonly reported in trials include the total number of incontinence episodes, which is an umbrella term which captures stress incontinence and UUIs as subsets. Therefore, whilst total incontinence is in some ways a more objective outcome, it lacks the specificity of UUI and “dilutes” the measured efficacy of drugs designed to treat OAB (10, 11). Volume of urine voided is a more objective outcome which is an indirect measure of postvoid residual urine volume. However, the clinical importance of small changes in this volume are not known, with most urologists considering postvoid residual urine volumes of 50 mL to 100 mL to represent significant abnormal bladder function (12).

Table 1. The decision problem addressed by the company submission.

	Final scope issued by NICE	**Decision problem addressed in the company submission**	Rationale if different from scope
Intervention(s)	Vibegron	Vibegron 75 mg once daily.	Clarification of dose based on SmPC (1)
Population(s)	Adults with symptoms of overactive bladder	No change	N/A
Subgroups	If the evidence allows the following subgroups will be considered: • men and women • previously untreated and previously treated overactive bladder	No change	N/A
Comparators	For people who have not had previous treatment for symptoms of overactive bladder: • Bladder training and lifestyle advice For people who have not achieved satisfactory benefit from bladder training and lifestyle advice: • Antimuscarinic treatments, including: o oxybutynin (including modified-release preparations) o tolterodine	Mirabegron	ibegron will be positioned for people in whom antimuscarinic drugs are contraindicated, clinically ineffective, or have unacceptable side effects. Therefore only Mirabegron will considered as the comparator. Antimuscarinic drugs, including all those listed, would be prescribed before mirabegron. Mirabegron is positioned in the treatment pathway as an option for treating the symptoms of overactive bladder only for people in whom antimuscarinic drugs are contraindicated or clinically ineffective or

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from scope
	○ fesoterodine ○ solifenacin ○ trospium ○ darifenacin ○ propiverine For people in whom antimuscarinic drugs are contraindicated, clinically ineffective, or have unacceptable side effects: • Mirabegron		have unacceptable side effects (Section B.1.3.4). The evidence base used to support vibegron in this submission is consistent with that used in TA290 (Section B.2 Key drivers of the cost effectiveness of the comparator(s) with no evidence of difference detected between treatment naïve and prior treatment groups (Section B.3.7.2 Previous treatment
Outcomes	The outcome measures to be considered include: • symptoms of urgency • urinary frequency • frequency of urge urinary incontinence • nocturia • adverse effects of treatment • health-related quality of life.	No Change	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	The economic analysis will be a *de novo* cost comparison in line with NICE fast track methodology. This means that incremental benefits, i.e. quality-adjusted	This is consistent with the FTA programme of NICE.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from scope
	If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. 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 compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	life-years, are not relevant to this submission.	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from scope
Abbreviations: FTA, Fast-track assessment (programme); N/A, not applicable; SmPC, summary of Medicine Product Characteristics			

B.1.2 Description of technology being appraisedh

Summary

- Vibegron is a new generation β_3-agonist intended for the treatment of OAB at the same line of therapy as mirabegron.
- By acting on adrenergic receptors, vibegron avoids many of the Aes associated with antimuscarinic drugs, such as dry mouth and negative cognitive impact.
- Vibegron's high selectivity for β_3-adrenergic receptors means it has no or minimal cardiovascular effects or impact on cognition. The drug has few contraindications, few drug-drug interactions, and is taken daily as a convenient single-dose 75 mg crushable tablet.

Vibegron is a highly selective β_3-agonist with the anticipated indication in the UK for the treatment of OAB (10). The chemical structure is illustrated in Figure 1. The key characteristics of the intervention are summarised in Table 2.

In the sympathetic nervous system, β_1-, β_2-, and β_3-adrenergic receptors are structurally related G-protein coupled receptors with distinct expression patterns and functions (13). In the urinary bladder, β_3-adrenergic receptors (β_3-ARs) account for 94% to 97% of beta receptors as measured through mRNA expression (13, 14). Activation of the β_3-ARs in the detrusor smooth muscle of the bladder increases bladder capacity by relaxing the detrusor during bladder filling (15). Thus, β_3-ARs are a target for small molecule pharmacological drugs intended to treat OAB.

However, β_1- and β_2-ARs are expressed in cardiac tissue, and thus beta-agonists that are not fully selective to β_3 have the potential to have off-target adverse effects. Vibegron has been designed to be highly specific for β_3-ARs (16). Vibegron has demonstrated a higher maximum response on β_3-ARs compared with mirabegron (99.2% vs 80.4%, respectively) (17). Whilst mirabegron is contraindicated in severe uncontrolled hypertension (18), vibegron does not appear to have an appreciable impact on blood pressure (BP) (16). A randomised controlled trial comparing vibegron (75 mg) with placebo in people with OAB (n=197) found no significant difference between treatment arms in terms of BP or heart rate (19).

An additional advantage of vibegron compared with mirabegron is that it does not interact with cytochrome P450 (CYP) isozymes, in particular CYP2D6 which is inhibited by

mirabegron (20). The highly selective nature of vibegron coupled with its low potential for drug-drug interactions make it an important addition to the treatment options for OAB.

Figure 1. Chemical structure of vibegron. Taken from PubChem (21).

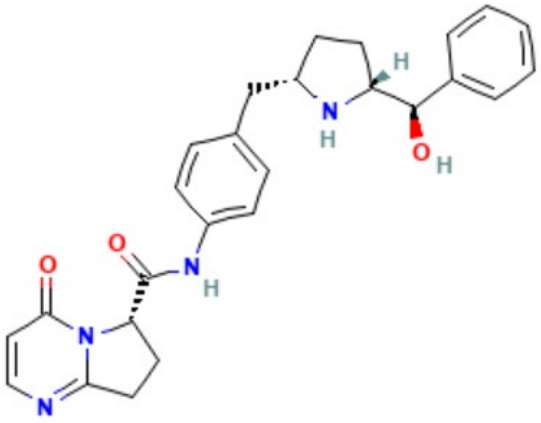


Table 2. Summary of characteristics of vibegron.

UK approved name and brand name	INN: vibegron Brand name: Obgemsa™
Mechanism of action	Vibegron is a highly selective and potent human β_3- AR agonist. B_3- ARs are prototypic G-protein coupled receptors and are widely distributed in humans and are the most prevalent βAR subtype expressed on human detrusor smooth muscle. Activation of the β_3-ARs in the detrusor smooth muscle increases bladder capacity by relaxing the detrusor during bladder filling, providing symptomatic relief of OAB.
Marketing authorisation/CE mark status	Marketing authorisation is scheduled for July 2024.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication for vibegron is for the “symptomatic treatment of adult patients with overactive bladder (OAB) syndrome” (1). No dose adjustments are required for people with renal or hepatic impairment. The only contraindication is hypersensitivity to the ingredient drug or an excipient. Vibegron is not indicated for use in people aged <18 years.
Method of administration and dosage	Vibegron is administered orally, with or without food. It is taken once a day as a 75 mg film-coated tablet. There is no requirement to titrate vibegron.
Additional tests or investigations	No additional tests or investigations are required for people receiving vibegron. It is currently a black triangle drug and is subject to additional pharmacovigilance by regulatory agencies.
List price and average cost of a course of treatment	The UK NHS list price for vibegron is [redacted] per pack of 30.

Patient access scheme (if applicable)	N/A
Abbreviations: β_3-AR, beta-adrenergic receptor; INN, international non-proprietary name; OAB, overactive bladder; N/A, not applicable	

B.1.3 Health condition and position of the technology in the treatment pathway

Summary

- OAB is defined as urinary urgency, with or without urgency incontinence, usually with frequency and nocturia. It is a common condition affecting men and women, and its prevalence increases greatly with older age.
- In the UK, about 12% of the adult population are estimated to be affected by OAB.
- OAB is characterised as wet or dry depending on the presence of incontinence. In all cases, OAB has a large impact on quality-of-life, with wet OAB having a particularly large impact.
- OAB is a diagnosis of exclusion made after conditions including urinary stress incontinence or prostate enlargement have been ruled out.
- In England, first-line treatment consists of lifestyle advice and physical therapies. The second-line treatment for OAB is antimuscarinic drugs.
- Mirabegron is used as a third-line treatment for people in whom antimuscarinic drugs are contraindicated or clinically ineffective or have unacceptable side effects. Vibegron is anticipated for use as an alternative treatment option to mirabegron at the same line of therapy.

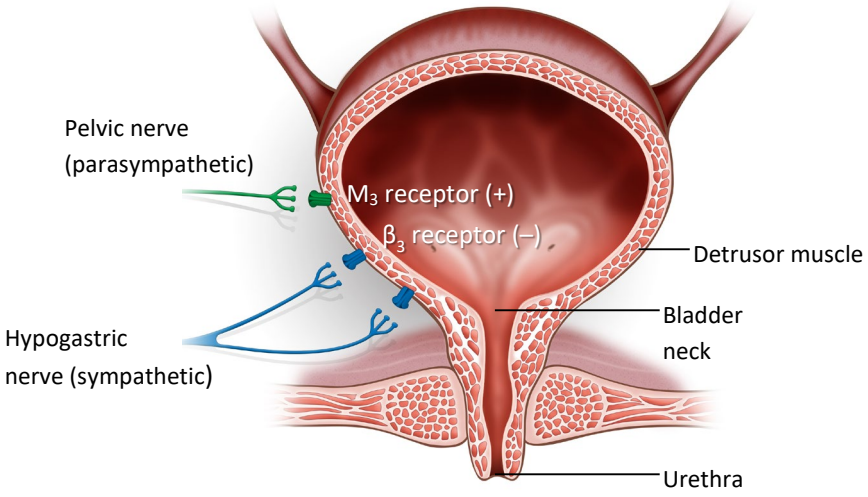
B.1.3.1 Background to the condition

Overactive bladder (OAB) syndrome (or urge syndrome or urgency-frequency syndrome) is a form of lower urinary tract symptoms (LUTS) that has been defined by the International Continence Society (ICS) as urgency, with or without urge incontinence, usually with frequency and nocturia (22). Urgency is defined by the ICS as the “complaint of a sudden, compelling desire to pass urine which is difficult to defer” (22).

The cause of OAB is the dysfunction of the detrusor muscle in the bladder due to neurological (23) or myogenic causes (24). This may be intrinsic, for instance because of detrusor over-activity, or may be secondary to neurological conditions, with several disorders being important risk factors for the development of OAB. For example, patients with spinal cord injury, multiple sclerosis, and stroke have elevated rates of the condition (25, 26). A wide array of other risk factors and diseases are also predictive of OAB, such as smoking, arthritis, depression, heart disease, hypertension, mobility limitations, neurological conditions, recurrent urinary tract infections (UTIs), and prostatitis (27).

Overactive bladder is primarily a disorder concerning the afferent innervation of the bladder (28). From a pharmacological perspective, dysfunction of the detrusor muscle presents two potential targets for treatment (Figure 2). The first of these to be exploited were the efferent muscarinic receptors of the parasympathetic nervous system, which are expressed in the lower urinary tract (29), with the M_3 receptor being primarily involved in OAB (30). The second target, more recently identified, is the β_3-AR of the sympathetic nervous system, which are the most prevalent β-AR subtype expressed in human detrusor smooth muscle, and have been implicated in smooth muscle relaxation in the bladder (15, 31).

Figure 2. Parasympathetic and sympathetic nerves involved in micturition.



B.1.3.2 Burden of illness

B.1.3.2.1 Prevalence

Globally, OAB is one of the most prevalent disease syndromes, with an estimated 455 million people experiencing symptoms of OAB (32), with this number expecting to increase. Approximately 16.5% of adults in the US and Europe are thought to be affected by OAB (33), with the sexes being affected approximately equally (34). This equates to approximately 5.15 million people with OAB in the UK, and nearly one-third of retired people

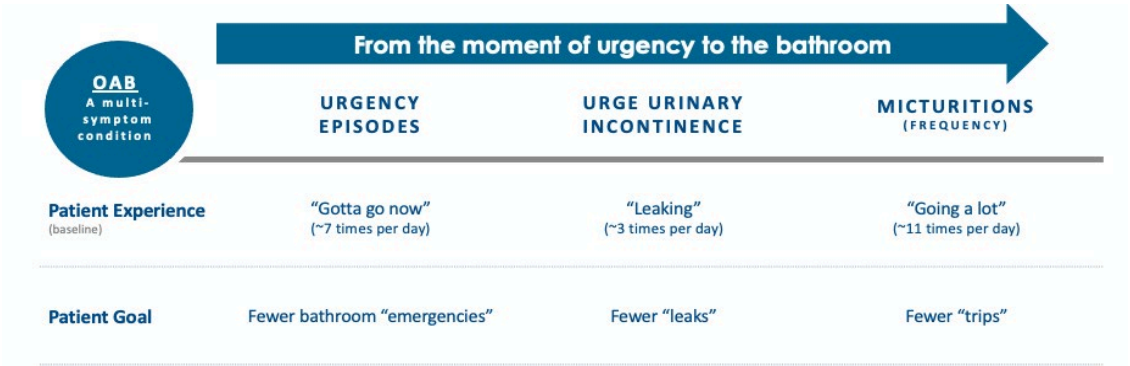
report OAB symptoms. One third of women with OAB symptoms are in the wet category (35).

The largest study of its kind, the EPIC study (n=19,165) was a population-based, cross-sectional telephone survey of adults ≥18 years of age living in Canada, Germany, Italy, Sweden, and the UK (comprising 19.3% of sample) (36). The overall prevalence of OAB was 11.8%; with similar rates in men and women which increased with age. OAB was more prevalent than all types of urinary incontinence combined (9.4%). Consistent with this, in the UK, the prevalence and severity of OAB has been observed to increase with age, becoming problematic after the age of 60 years (37).

B.1.3.2.2 Presentation

The clinical experience of patients with OAB encompasses urgency episodes followed by UUI in some cases, as well as a high frequency of micturitions (Figure 3). Patients who have both urinary urgency and urgency incontinence are said to have OAB wet; approximately one-third of patients fall into this category (38). The remaining two-thirds of patients who experience symptoms of OAB without incontinence are referred to as having OAB dry. When any of the aforementioned urinary symptoms interrupt sleep, the condition is referred to as nocturia (39). Nocturia polyuria occurs when a patient has increased urine output during sleep.

Figure 3. Clinical experience of patients with OAB.



Abbreviations: OAB, overactive bladder.

B.1.3.2.3 Impact on quality of life

A major concern with OAB is that it can severely impact everyday activities by causing patients to be unwilling to go places where bathroom access may be difficult (39). These issues may in turn result in severe social and psychological consequences and can also impact family and caregivers. Evidence indicates that patients with OAB tend to have higher levels of depression, anxiety, and embarrassment/shame compared with those without the condition (40-42). In a study of individuals who had initiated antimuscarinic therapy, OAB wet

patients had a 33% higher adjusted risk of experiencing depression/anxiety than those without OAB ($p<0.022$) (43).

The unpleasant and troublesome symptoms of OAB pose a significant burden on well-being and quality-of-life (QoL). The EPIC study (36) reported people with OAB had significantly less work productivity and sexual satisfaction, higher rates of depressive symptoms and erectile dysfunction, and lower levels of overall health (44). In a large cross-sectional study set in Korea (n=625), the severity of urinary incontinence was found to be the key factor which reduced health-related quality-of-life (HRQoL) (45), with people who had experienced incontinence reporting significantly lower HRQoL using both disease-specific (Overactive Bladder Questionnaire [OAB-q]) and generic tools (EQ-5D), compared with “dry” people. OAB has also been found to represent a significant burden in terms of annual direct and indirect healthcare expenditures (46-48).

Secondary to OAB itself, inadequate management of OAB may also result in or exacerbate other bothersome and/or serious comorbidities (43), all of which may impact further on HRQoL. In addition to the psychosocial impacts, OAB has been associated with significantly increased rates of UTI, skin infection and irritation, vulvovaginitis, and falls and fractures compared with controls (all $p< 0.0001$) (41). Following diagnosis of OAB, the number of services received for these conditions decreased by up to 60% and was associated with significant material cost savings (49).

B.1.3.3 Diagnosis of OAB

OAB is a diagnosis of exclusion (50). On presentation of a person with LUTS consistent with OAB, a full medical history should be taken (for relevant comorbidities and prescriptions) alongside a physical examination and urinalysis. Additionally, a measurement of post-void residue and the implementation of a bladder diary should be considered (51). Urgency incontinence present in OAB needs to be distinguished from stress urinary incontinence, which is the involuntary loss of urine on effort or physical exertion (e.g., sporting activities), or on sneezing or coughing. Some patients may have both OAB and urinary stress incontinence symptoms and are diagnosed as having mixed urinary symptoms (33). Diagnosis of OAB is considered in the absence of UTI, metabolic disorders (affecting urination), or urinary stress incontinence (generated by effort or overexertion) (33)

Diagnosis of OAB in men should be made with consideration to the possible presence of an enlarged prostate causing obstruction and outflow complications (52). This should include examination of the abdomen, external genitalia and a digital rectal examination (DRE). Optional actions include performing prostate-specific antigen (PSA) testing, flow rate measurement, and a serum creatinine test (if renal impairment is suspected). In women, a

full medical history should be taken including history of childbirth and prior surgery. Physical examination should include an assessment of the pelvic floor, examination for vaginal atrophy, and assessment of prolapse (51). The cause of urinary incontinence should be categorised as stress urinary incontinence, mixed urinary incontinence or urgency urinary incontinence/OAB at the initial clinical assessment (53). If OAB, is suspected, treatment should be started immediately on this basis, and in mixed urinary incontinence, treatment should be directed towards the predominant symptom.

B.1.3.4 Treatment pathways

There are no UK-based specific guidelines on the management of OAB in males or females. There are NICE clinical guidelines providing relevant information on *Urinary incontinence and pelvic organ prolapse in women: management* (NG123) (53) and *Lower urinary tract symptoms in men: management* (CG97) (52). Additionally, there are guidelines published by the *American Urological Association* on non-neurogenic OAB in adults (50) and *European Association of Urology Guidelines* (EAU) on non-neurogenic OAB in females (54), and non-neurogenic male lower urinary tract symptoms in men (55). In practice in the UK, many treating clinicians will be guided by EAU guidelines in addition to NICE guidance (11).

For women with urinary incontinence, NICE NG123 recommends lifestyle modification and physical therapies as the initial management strategies for the condition (53). For women who require pharmacological management, a full medical review should be performed before antimuscarinic drugs are prescribed as first-line drug treatment. This should take into account the woman's coexisting conditions (such as poor bladder emptying, cognitive impairment or dementia); the current use of other medicines that affect total anticholinergic load, and the risk of adverse effects, including cognitive impairment (53).

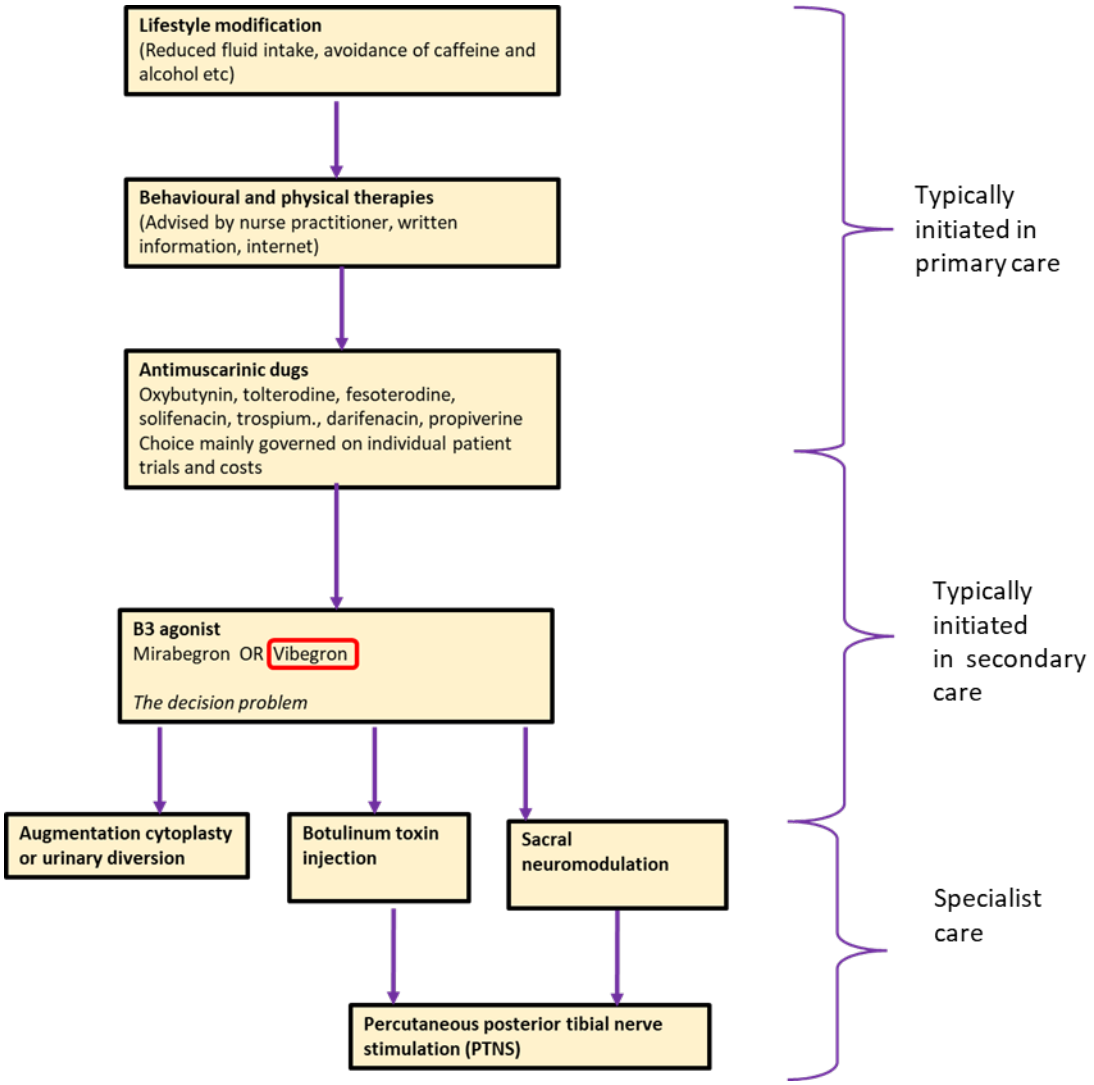
For the prescribing of mirabegron, the guideline recommends this should be done in accordance with TA290 (2), namely, mirabegron should be offered as an option for treating the symptoms of OAB only for people in whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects. For most women, this will mean mirabegron being used instead of antimuscarinic treatment, not in addition to it. However notably, EAU guidelines position mirabegron at the same line of treatment as anti-muscarinic drugs in women (54). Although mirabegron is an option available in primary care, in practice in England, treatment with mirabegron is usually initiated in secondary care (10, 11).

Management options subsequent to treatment with mirabegron are currently limited to surgery, botulinum toxin injections, or nerve stimulation. There are NICE interventional procedures guidance on *Laparoscopic augmentation cystoplasty (including clam cystoplasty)* (IPG326) (56) and *Percutaneous posterior tibial nerve stimulation for overactive bladder*

syndrome (2010) (57), and medical technologies guidance on *Axonics sacral neuromodulation system for treating refractory overactive bladder* (58). However, as these are performed downstream of the proposed position of vibegron in the patient pathway, they are not relevant to the decision problem. The treatment pathway for OAB is summarised in Figure 4.

For men, the position of mirabegron in the pathway is less clear, because TA290 is not referenced in CG97. However, it can be inferred from TA290 (2) that, as with the management of women with OAB, vibegron would be positioned following unsuccessful treatment with other drugs, including alpha blockers, 5-alpha reductase inhibitors, or antimuscarinic drugs, or when these drugs are not suitable or effective. Whilst international guidelines are not specific as to the order of initiation of drug treatment for OAB, β_3-AR agonists are recommended as a treatment option (8, 50).

Figure 4. Proposed position of vibegron in treatment pathway. Based on NICE guideline NG123 and input from clinical experts.



B.1.3.5 Treatment options

As shown in Figure 4, once diagnosed, management of OAB currently consists of four lines of treatment, namely non-pharmacological therapies; antimuscarinic drugs; mirabegron; and procedural and surgical interventions.

B.1.3.5.1 Lifestyle changes and physical therapies

Prior to management of OAB, people should be assessed for comorbidities which could contribute to the condition, as OAB has been independently predicted by poor general health (59). Known comorbidities associated with OAB include advanced age, diabetes mellitus, obesity and recurrent UTIs (49). Lifestyle advice that may help address OABs and associated comorbidities include improved diet, fluid intake, bowel and weight management; and smoking cessation (60). The patient may also be advised to use a bladder diary to urinate at fixed intervals to avoid urgency symptoms.

Physical therapies that may be considered in the management of OAB include urgency control techniques, bladder training, multicomponent behavioural training, pelvic floor muscle training (in women), and delayed voiding (60). A systematic review found these interventions to be effective, with the most evidence available for bladder training (61). However, these therapies are not always successful and pharmacological interventions are often required. Physical therapies may require several sessions with specialist nurses or physiotherapists through NHS continence services, and accessibility may be an issue in some areas (11).

B.1.3.5.2 Antimuscarinic drugs

For decades, antimuscarinic drugs have been the mainstay of pharmacological management for OAB and are regarded as second-line treatment. Options available on the NHS include oxybutynin, tolterodine, fesoterodine, solifenacin, trospium, darifenacin, and propiverine (62). These drugs all work through blockade of the M_2 and M_3 receptors in the detrusor muscle in the bladder. They affect the efferent control on detrusor contraction, causing symptomatic relief of OAB. As antimuscarinic drugs have variable selectivity for M_2 and M_3 receptors, they have subtle differences in their efficacy (63). Additionally, differences in pharmacokinetic profile can impact on the effectiveness of these drugs, with some evidence suggesting extended release (ER) formulations are better tolerated (63). In England, the choice of anti-muscarinic drug is largely guided by cost or on an individual trial basis (“what works”) (10, 11), although other factor may be considered.

A Cochrane review of 101 studies incorporating 47,106 participants found that antimuscarinic drugs, both individually and as a class, were effective at improving some symptoms associated with OAB (63). However, these improvements were generally modest.

The authors reported that at the end of the treatment period, compared with placebo, anticholinergics may slightly increase condition-specific QoL using tools such as the overactive bladder questionnaire short form (OAB-Q-SF) or King's Health Questionnaire (KHQ), but this result was associated with low certainty using GRADE analysis (64). Antimuscarinic drugs were also associated with improved patient perception of symptoms. More objectively, the mean number of urgency episodes per 24-hour period (mean difference [MD] was 0.85 lower in active intervention groups (95% CI 1.03 to 0.67); there was a modest degree of certainty in this result. The mean number of micturitions per day was also reduced by an MD 0.85 (95% CI 0.98 to 0.73, moderate-certainty evidence).

However, antimuscarinic treatment was also associated with bothersome adverse effects, in particular dry mouth, which was increased by a relative risk (RR) of 3.50, 95% CI 3.26 to 3.75). Patients taking antimuscarinics were more likely to withdraw from studies due to Aes (RR 1.37, 95% CI 1.21 to 1.56). Tolerance, adherence and persistence with therapy is a major issue with antimuscarinic drugs and contributes to the unmet need in people with OAB (Section B.1.3.6). One review found that the proportion of adherent patients varied between 1% and 36% after 1 year in clinical trials that reported this outcome (65). Rates of discontinuation of antimuscarinic drugs at 12 weeks have been reported as ranging from 4% to 31% in clinical trials and 43% to 83% in medical claims databases (66). In England, the CYCLe AntiMuscarinics in England (CYCLAMEN) study was a retrospective observational analyses that linked primary care records from the Clinical Practice Research Datalink (CPRD) database linked to Hospital Episode Statistics secondary care data to estimate healthcare resource use (HRU) associated with antimuscarinic drugs for OAB. The median duration of the first antimuscarinic treatment episode was 57 days and after 18 months <20% were still receiving antimuscarinic treatment (67).

Several studies have reported an association between the use of antimuscarinics and an increased risk of cognitive impairment and dementia (68-70), especially among older patients (71, 72). The risk of dementia has been shown to increase with higher cumulative doses and long-term use of antimuscarinic drugs (73), including among patients with LUTS (74). Thus, the use of antimuscarinic drugs to treat OAB in the elderly requires clinical caution.

B.1.3.5.3 Mirabegron

NICE TA290 recommends mirabegron as follows: "Mirabegron is recommended as an option for treating the symptoms of OAB only for people in whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects" (2). It is a first-generation β_3-AR agonist that relaxes the detrusor during bladder filling, causing

symptomatic relief of OAB. Mirabegron was shown to be effective in the treatment of OAB by three Phase 3 randomised controlled trials (RCTs), namely the SCORPIO trial (75), the ARIES trial (76) and the CAPRICORN trial (77).

Mirabegron is associated with some limitations. Whilst mirabegron is associated with higher adherence and persistence rates than antimuscarinic drugs (78), treatment adherence is influenced extensively by a multitude of patient and drug characteristics. In a retrospective real-world study (79), adherence with mirabegron (44%) was higher than adherence to antimuscarinic agents (31%) over a 12-month follow-up period, but was still low. Treatment failure and discontinuation rates of mirabegron over the follow-up period were 81% and 67%, respectively. In a recent retrospective analysis of a US pharmacy claims database which matched baseline characteristics, real-world adherence and persistence was reported to be higher in patients initiating vibegron compared with patients initiating mirabegron or antimuscarinic drugs (80).

In *in vitro* studies, whilst vibegron has demonstrated no measurable β_1 and low β_2 activity, mirabegron has exhibited low β_1 and some β_2 activity. And, whilst both drugs have shown considerable selectivity at β_3-ARSs, vibegron has demonstrated near-exclusive β_3 activity and a higher maximum β_3 response (81). Mirabegron should be used with caution in people with hypertension and is contraindicated in people with severe hypertension (18).

Mirabegron is known to inhibit CYP2D6, a member of the cytochrome P450 superfamily of enzymes that are primarily expressed in the liver and has the potential to cause drug-drug interactions (82). Therefore, when mirabegron and other medications that are also CYP2D6 substrates are used concomitantly, monitoring is necessary to detect and manage these interactions, particularly among elderly patients who are often on multiple medications (83). Mirabegron may require dose adjustments, based on efficacy and tolerability. The dose should not exceed 25 mg once daily in patients with severe renal impairment or moderate hepatic impairment (18).

Finally, a potential disadvantage of mirabegron is that it must be swallowed whole and cannot be crushed. This may make administration challenging for geriatric and care populations, as 40% to 60% of long-term nursing home residents have difficulty swallowing (84).

B.1.3.5.4 Surgery and procedures

Surgical and procedural interventions will normally only be considered once pharmacological treatment has failed and will be provided in specialist care by a multi-disciplinary team. Options available on the NHS include botulinum toxin A injections; sacral nerve stimulation;

posterior tibial nerve stimulation (PTNS); augmentation cystoplasty; and, as a last resort, urinary diversion surgery (85).

B.1.3.6 Unmet needs

Despite the currently available treatments for OAB, there remains an unmet need in the management of OAB in both men and women. The principal issue is that current first-line pharmacological interventions, which consist of a number of licensed antimuscarinic drugs, are associated with anticholinergic related adverse effects (63). Antimuscarinic drugs (Section B.1.3.5.2) may impair secretion by exocrine glands, resulting in a dry mouth and sore throat. Antimuscarinic blockade of receptors may cause tachycardia, whilst their effects on smooth muscle can cause constipation due to decreased smooth muscle motility and tone in the gastrointestinal tract. Blockade of the receptors in the ciliary muscle may cause blurred vision and light sensitivity (86). Some antimuscarinics may also cause mood changes, hallucinations, confusion, or disorientation. Finally, antimuscarinic drugs are known to increase the risk of dementia risk and cognitive impairment, making them unsuitable for some people at risk (87).

A consequence of the poor tolerability profile of antimuscarinic drugs is that many patients may discontinue medication within months of starting treatment. Real-world evidence suggests that discontinuation rates are significantly higher than reported in clinical trials (63). In a survey of 5,392 patients reporting use of prescribed antimuscarinic drugs for OAB, patient-reported reasons for discontinuing therapy included unmet treatment expectations, a switch to a new medication, learning to get by without medication, and/or side effects (88). Real-world discontinuation rates for tolterodine have been reported to be 49% at 6 months follow up (89). The CYCLAMEN study in England reported the use of multiple drugs, a high incidence of switching between anti-muscarinic drugs (including 10% of patients involved in sequential cycling), and an overall poor adherence rate leading to very high level of drug discontinuation (67). Although the study was not designed to ascertain the nature of these events, overall the results strongly suggest that anti-muscarinic drug therapy is suboptimal in primary care in England.

In England, following discontinuation of antimuscarinic treatment, most patients will have the option of switching to mirabegron (2). However, this drug has some issues with contraindications, adverse effects, dosing titration, discontinuation, and ease of administration in elderly patients (18) (Section B.1.3.5.3). For these reasons, vibegron may be preferred for some patients with OAB, and will provide an additional option to mirabegron for the treatment of their condition.

B.1.4 Equality considerations

There are no equality considerations anticipated with the introduction of vibegron into the NHS.

B.2 Key drivers of the cost effectiveness of the comparator(s)

Summary

- Mirabegron was given a positive recommendation by NICE in June 2013 in TA290 as second-line pharmacological treatment to anti-muscarinic drugs.
- The manufacturer of mirabegron (Astellas) submitted a Markov decision analytic model to support the cost effectiveness of mirabegron, informed by a mixed-treatment comparison for the key trials on mirabegron and its comparators (antimuscarinic drugs).
- The key efficacy inputs that informed the model were the number of daily micturitions and number of urinary urge incontinence episodes. Additionally, discontinuation rates associated with the adverse effects of dry mouth and constipation were used in the model.
- The model was sensitive to the key efficacy assumptions, but mirabegron remained cost-effective using all plausible estimates and in all scenarios, with an ERG base case ICER estimate of £5272 associated with mirabegron compared with tolterodine tartrate. The model was not sensitive to alternate estimates of costs.

B.2.1 Clinical outcomes and measures

B.2.1.1 Description of the *de novo* model used in TA290

The cost-effectiveness of the comparator, mirabegron, was assessed against antimuscarinic drugs using a *de novo* Markov model developed by Astellas, the manufacturer of mirabegron. The key documents reporting, critiquing and interpreting this model are the company submission (90), the Evidence Review Group (ERG) report (91), and the technology assessment (TA) guidance recommendations from NICE (7).

The overall model structure is illustrated in Figure 5. The model was designed to simulate the therapeutic management, the course of the condition, and complications in hypothetical cohorts of patients with OAB to estimate costs and quality-adjusted life years (QALYs) over 5 years. The model simulated patients with OAB requiring first-line pharmacological interventions, with them being allocated mirabegron or an antimuscarinic drug at the start of the model. The cycle length was one month and the time horizon was five years, with utilities and costs discounted at 3.5% (90). Upon entry to the model, at the end of each monthly cycle patients can remain on the same medication, switch medication or stop all medication. For patients who stop their current medication, the next line of therapy is considered to have the cost, efficacy and safety equivalent to solifenacin succinate 5 mg. Once two drugs have failed, or one drug has failed followed by a cycle off any drug, botulinum toxin is available as a final treatment option.

The model simultaneously simulated two key symptoms of OAB and these were used to assess severity level, and subsequently key parameters such as utilities and probability of discontinuation. These symptoms were *frequency of micturition* and *incontinence*. Each symptom was categorised into five severity levels, resulting in a matrix of 25 possible combinations of micturition and incontinence (Figure 6A). The categories represented the quintiles of frequency of micturition and incontinence observed in a pooled analysis of the three pivotal mirabegron trials, namely the ARIES (76), SCORPIO (75) and CAPRICORN (77) trials. At model entry, patients were distributed across the 25 severity profiles and assigned to treatment with either mirabegron or a comparator antimuscarinic. Then, in monthly cycles, patients could simultaneously transition through the five severity levels of micturition and the five severity levels of incontinence; i.e. a patient's severity profile was reassessed each month according to improvement, deterioration or stabilisation of the individual symptoms of micturition frequency and incontinence. At the end of each month, a person's symptoms could stay the same, improve or deteriorate (Figure 6B). The categorisation of micturition and incontinence severity levels are reported in Figure 6C.

For patients receiving mirabegron, the transitions between symptom severity states were determined by multinomial logistic regression using patient-level data from the SCORPIO trial (75) and defined as a function of treatment, symptom severity in previous month, age and sex. For each symptom (micturition and incontinence), three transmission probability matrices were produced depending on the patient's duration in treatment (transition between baseline and month 1; transition between month 1 and month 2; and transition between month 2 and month 3 and onwards). For patients remaining on treatment beyond 3 months, the third matrix was applied until discontinuation. For patients receiving antimuscarinic drugs, transition matrices were calibrated directly from trial evidence in the case of

tolterodine (as RCT data were available) or data from a mixed-treatment comparison (MTC) for other antimuscarinic drugs (as no direct comparative data were available).

The model incorporated two AEs; namely *dry mouth* and *constipation*, both recognised antimuscarinic side effects that occur with this drug class. Monthly probabilities of Aes were obtained from SCORPIO trial (75) for mirabegron and tolterodine tartrate modified release (MR) 4 mg and from the MTC for the other antimuscarinic drugs (90). It was assumed that people who were on no treatment experienced no AEs.

An important element of the model was the rate of discontinuation of treatment, which was incorporated as a combination of background persistence with OAB antimuscarinic medication and the occurrence of AEs. This is described in Section B.2.1.3.

The manufacturer performed deterministic and probabilistic sensitivity analyses on assumptions and parameter estimates in the model. It also performed subgroup analyses of the base case for men and women, and treatment and previous treatment groups. For the latter analyses, no was found there was no significant difference between groups (see Section B.4.5 Subgroup analysis It was found that mirabegron remained cost-effective using all plausible estimates and in all scenarios, with an ERG base case incremental cost-effectiveness ratio (ICER) estimate of £5272 of mirabegron compared with tolterodine tartrate (7).

Figure 5. Model structure used in TA290. From ERG report (91).

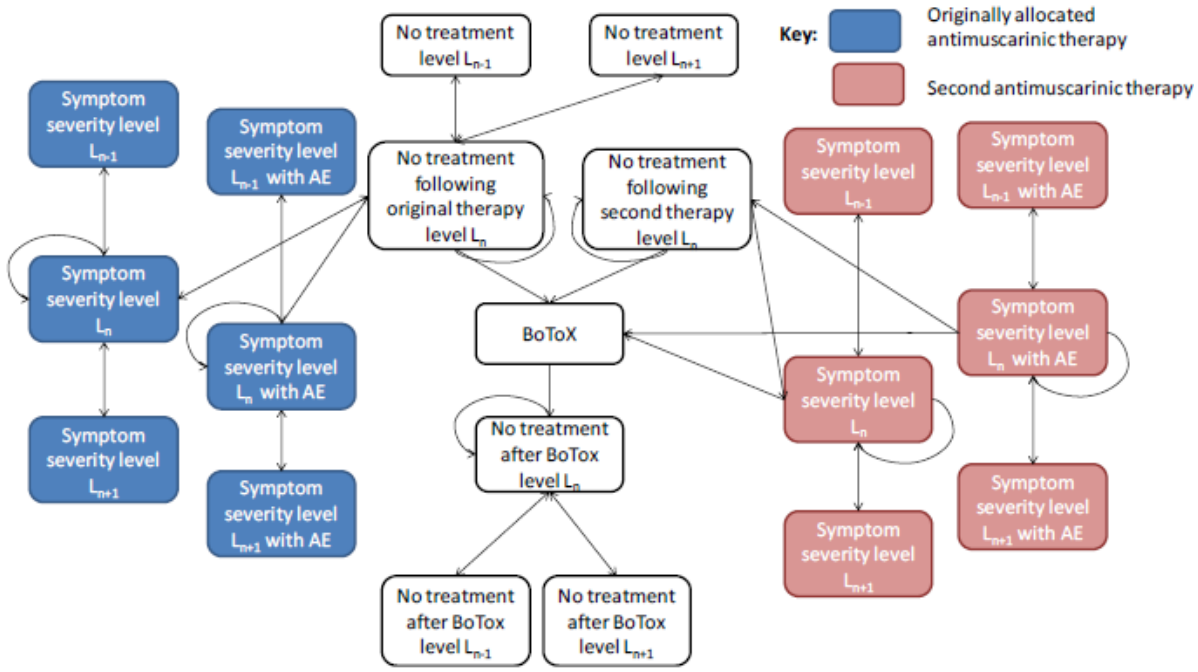
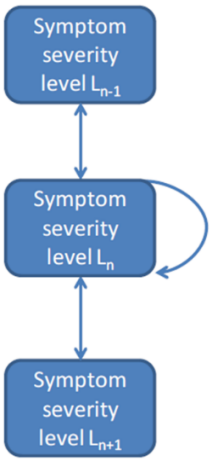


Figure 6. Symptom severity and movement between severity states in the model. From ERG report (91).

A

Incontinence level	Micturition level				
	1	2	3	4	5
1	A	B	C	D	E
2	F	G	H	I	J
3	K	L	M	N	O
4	P	Q	R	S	T
5	U	V	W	X	Y
For example, patients in severity level N would experience 12 to 14 micturitions per day and 1 or 2 episodes of incontinence					

B



C

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

Legend: A: Each patient resides in one of 25 severity-related health states each month. These determine utility levels. B: Patients can transition up or down in severity (or stay the same) in each symptom dimension. C: Micturition and incontinence severity categories.

B.2.1.2 Efficacy

B.2.1.2.1 Key efficacy inputs

The key efficacy inputs in the model were based on the frequency of daily episodes of micturition and frequency of daily episodes of incontinence. These were the co-primary outcomes of all three pivotal Phase 3 trials for mirabegron, with the change from baseline (CFB) measured at 12 weeks (75-77). These are patient reported outcome measures (PROMs) recorded with the aid of a urination diary. Frequency of micturition and incontinence are appropriate outcomes to assess drug efficacy as they are defining symptoms of OAB syndrome (22) (Section B.1.3.1). Both the ERG (91) and the Appraisal Committee (7) agreed these were the correct outcomes to inform the economic model.

Two additional symptoms that inform the ICS definition of OAB are urgency and nocturia. When questioned by the ERG on the omission of these symptoms in their model, the manufacturer of mirabegron responded (91):

- "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".

Following advice from clinical experts, this was accepted by both the ERG (91) and the Committee (7).

B.2.1.2.2 Sensitivity of the model to efficacy outcomes

As described in Section B.2.1.1, the frequency of daily episodes of micturition and incontinence, divided by quintiles, were used to inform the treatment-specific transition probabilities between micturition and urination levels in the matrix respectively. The company tested the impact of varying these parameters using univariate deterministic sensitivity analysis (DSA), using "the limits of confidence intervals around each parameter or other fixed values" (90). This is illustrated in Appendix D.3 (Figure 21).

The ICERs were sensitive to lower estimates of the number of episodes of incontinence and higher estimates to the number of episodes of micturition, with these resulting in higher ICERs. However, in neither case did the ICER exceed the willingness-to-pay (WTP) threshold of £20,000 per QALY, with the ERG noting "most of the analyses returned ICER estimates of less than £17,000 per QALY gained" (91). Additionally, it is noted that the value of the incremental QALYs (measure of health benefit) reported in the model were relatively small. For instance, the incremental gain in QALYs of mirabegron compared with tolterodine was 0.0005. Finally, it should be noted that the key uncertainties in trial efficacy did not relate to mirabegron, which has an extensive evidence base including several high-quality RCTs; rather, uncertainty arises from the MTC in the comparison of mirabegron with antimuscarinic drugs (91). This is not relevant for the current submission, which is a comparison with mirabegron, not antimuscarinic drugs.

B.2.1.3 Safety

B.2.1.3.1 Key safety outcomes

In the cost-effectiveness model used in TA290, the informative safety outcomes used were *dry mouth* and *constipation* (90). The company stated these were used on the basis of expert opinion in that these adverse effects were most relevant to patients, and were likely to drive treatment discontinuation, a key parameter used in the model.

Discontinuation of treatment was incorporated into the model as a combination of background persistence with OAB medication and the occurrence of AEs. The background persistence rate for the base case was taken from a published study by Wagg *et al.* (2012) (92), which was an analysis of antimuscarinic prescription data taken from a UK-based patient database. For mirabegron, the data used to inform the AEs were from the SCORPIO trial (75).

The company estimated that 54.7% of patients *without* an AE would discontinue treatment by 12 months. Discontinuation due to AEs was based on expert opinion and was set at 90%. The company did not identify any literature on treatment re-initiation rates following treatment discontinuation. The company assumed that 50% of patients who had stopped treatment with mirabegron or tolterodine tartrate (in the base-case model) would restart treatment annually (5.6% per month), either with the original drug or switching to the next line of therapy.

The ERG criticised several aspects of the implementation of the adverse effects and drug discontinuation (7, 91). These included the assumption of variable other-cause discontinuation for mirabegron patients; the assumption that immediate (that is, within the same cycle) discontinuation as a result of an AE would be equivalent to the rate of other cause discontinuation; the possibility of infinite treatment discontinuation and re-initiation, a feature of the 'lack of memory' associated with the Markov model; and the use of AE rates from SCORPIO rather than the manufacturer's safety study (TAURUS) (93). However, the ERG did not correct the base case inputs using their own preferred values. Instead, they relied on the DSA performed by the company to test the model's assumptions (91).

B.2.1.3.2 Sensitivity of safety outcomes

The impact of AEs in the model were manifested indirectly through discontinuation rates (90). Changing the estimates of adverse effects and associated parameters had minimal impact on the ICERs overall. This is illustrated in Appendix D.3 (Figure 22).

B.2.2 Resource use assumptions

The model used in TA290 included direct costs associated with the unit costs of the drugs (the key driver of costs), GP appointments, and the costs of incontinence pads. There were no costs associated with health states or directly from management of AEs.

The monthly acquisition cost of antimuscarinic drugs were taken from the list price in the British National Formulary (BNF) (94). Antimuscarinic costs were calculated assuming that patients used one tablet a day per month. The acquisition cost of mirabegron was provided

by the company: it is currently listed as £29.00 for a pack size of 30 tablets (25 mg or 50 mg) in the BNF (95), the same value used in the original assessment.

The company assumed there would be one GP consultation at treatment initiation and treatment switch, and one and a half specialist consultations at treatment initiation and treatment switch based on a previous UK cost-effectiveness analysis of antimuscarinic drugs (96). Costs for these were derived from Unit Costs of Health and Social Care and Payment by Results (PbR) tariffs respectively. The number of incontinence pads used was related to the severity of incontinence, based on data reported from the SCORPIO trial (75). The ERG accepted these costing assumptions (91).

The ERG summarised the costs by stating “the costs associated with each treatment arm were primarily comprised of medication and incontinence pad costs. Treatments that reduced the severity of incontinence accrued less costs as patients required fewer incontinence pads. Treatments that were associated with higher levels of discontinuation or AEs implicitly accrued higher costs as a result of treatment switching” (91).

The unit cost data did not differ between arms and rates were ultimately derived from efficacy (Section B.2.1.2) and safety (Section B.2.1.3) data.

B.2.3 Summary of key drivers of cost-effectiveness

The key drivers influencing the cost-effectiveness of mirabegron in TA290 are summarised in Table 3. Note: no other single technology appraisals (STAs) are relevant to this submission.

Table 3. Summary of drivers of cost-effectiveness used in TA290.

	Outcome	Measurement scale	Used in CE model?	Impact on ICER	Committee's preferred assumptions	Uncertainties
Efficacy parameters	Mean number of micturition (per day)	Episodes measured in urination diary	Yes	Yes, indirectly. Lower transition probabilities associated with greater ICERs (but remained within WTP).	Company values used in base case. Effect on ICERs explored in DSA.	Main uncertainty arises from MTC (comparative efficacy of antimuscarinic drugs)
	Mean number of incontinence episodes (per day)	Episodes measured in urination diary	Yes	Yes, indirectly. Higher transition probabilities associated with greater ICERs (but remained within WTP).	Company values used in base case. Effect on ICERs explored in DSA	Main uncertainty arises from MTC (comparative efficacy of antimuscarinic drugs)
	Mean volume voided per micturition	mL	No	N/A	N/A	N/A
	Mean number of nocturia episodes (per day)	Episodes measured in urination diary	No	N/A	N/A	N/A
	Mean number of urge urinary episodes g¾e 3/4 (per day)	Episodes measured in urination diary	No	N/A	N/A	N/A
	Mean level of urgency	Episodes measured in urination diary	No	N/A	N/A	N/A
	Mean number of urge incontinence episodes (per day)	Episodes measured in urination diary	No	N/A	N/A	N/A
	Mean number in urinary pads used (per day)	Episodes measured in urination diary	No	N/A	N/A	N/A
HRQoL	Disease specific HRQoL: OAB-q	Questionnaire	Yes (sensitivity analysis)	N/A	N/A	N/A
	Generic HRQoL: EQ-5D	Questionnaire VAS	Yes	Minimal impact on ICERs ICERs remain within WTP in DSA	Company values used in base case.	Data from SCORPIO trial (75) and adjusted with multivariate

	Outcome	Measurement scale	Used in CE model?	Impact on ICER	Committee's preferred assumptions	Uncertainties
						analysis. Low uncertainty.
Safety/AEs	Frequency of dry mouth symptoms	Trial measurement	Yes	Minimal impact on ICERs ICERs remain within WTP in DSA	Company values used in base case.	Discontinuation data derived from patient database (92) and assumption, High uncertainty.
	Frequency of constipation symptoms	Trial measurement	Yes	Minimal impact on ICERs ICERs remain within WTP in DSA	Company values used in base case.	Discontinuation data derived from patient database (92) and assumption, High uncertainty.
	Other AEs	Trial measurement	No	N/A	N/A	N/A
Costs	Unit cost of drugs	GBP	Yes	Minimal impact on ICERs ICERs remain within WTP in DSA	Company values used in base case.	Unit costs antimuscarinics derived from BNF (94). No uncertainty.
	Cost of GP and specialist appointments	GBP	Yes	Minimal impact on ICERs ICERs remain within WTP in DSA	Company values used in base case.	PSSRU and PbR tariffs. Minimal uncertainty.
	Incontinence pads	GBP	Yes	Minimal impact on ICERs ICERs remain within WTP	Company values used in base case.	

Abbreviations: AE, adverse event; BNF, British National Formulary; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; MTC, mixed treatment comparison; N/A, not applicable; OABq, overactive bladder questionnaire; PbR, payment by results; PSSRU, Personal Social Services Research Unit; WTP, willingness-to-pay [threshold].

B.3 Clinical effectiveness

B.3.1 Identification and selection of relevant studies

Summary

A systematic literature review was undertaken to identify all relevant Phase 2 and above RCTs on the pharmacological treatment of OAB. Eight studies were identified as being in scope.

- The pivotal study of interest was the EMPOWUR trial (NCT03492281), which was an RCT comparing vibegron, placebo, and tolterodine (active comparator) in patients with OAB. The co-primary outcomes were number of daily micturitions and episodes of UUI at 12 weeks. This study was judged to be at low risk of bias. An extension study, EMPOWUR-EXT (NCT03583372), followed up patients to 1 year.
- Three additional placebo-controlled trial were identified. The Phase 3 trial by Yoshida *et al.* (2018) included the active comparator imidafenacin, and the Phase 2b trial by Mitcheson *et al.* (2019) included the active comparator tolterodine alone and in combination with vibegron. Shin *et al.* (2023) compared vibegron with placebo but had a relatively small sample size. None of these studies used vibegron at the anticipated UK dose of 75 mg, and all had some concerns regarding the potential for bias.
- Two head-to head studies were identified which compared vibegron (50 mg) directly with mirabegron (50 mg). However, these were small studies, were assessed to be at high risk of bias, and neither administered the anticipated UK dose of vibegron of 75 mg.
- A study by Wada et al. (2023) was a cross-over trial comparing vibegron with mirabegron but had a relatively small sample size and was published as an abstract only.

B.3.1.1 Search strategy

A systematic literature review (SLR) was conducted to identify all relevant clinical evidence from the published literature reporting the clinical efficacy, safety, and tolerability of vibegron and relevant comparator therapies for the treatment of OAB syndrome (97). The SLR was

conducted in compliance with published guidelines issued by the Cochrane Collaboration (98), the Centre for Reviews & Dissemination (CRD) (99), the National Institute for Health and Care Excellence (NICE) (100), and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (101).

The original search was conducted to include results from database inception up until March 2023. An updated search was then performed in November 2023.

Full details of the searches used, and results of these searches are provided in Appendix D.1.1.

B.3.1.2 Study selection

In the SLR, study selection was consistent with the decision problem (Table 1) for all domains except intervention, which was broadened to include all relevant technologies for the treatment of OAB syndrome. However, for the purposes of this submission, only those technologies reporting on the use of vibegron and the relevant comparator mirabegron were included. Additionally, due to the volume of studies that have been published for this condition, only RCTs (Phase 2, 3 or 4) were included.

For vibegron, attention is drawn to the Phase 3 randomised controlled trial (RCT) EMPOWUR used in the indirect treatment comparison (ITC), which was employed to show equivalence between vibegron and mirabegron. For mirabegron, attention is drawn to those studies used in the original mixed treatment-comparison (MTC) and cost-effectiveness analysis used in TA290 (90, 91).

The results of the study selection process for the original and updated searches are shown in Figure 7 and Figure 8.

Figure 7. PRISMA diagram illustrating progressive exclusion of studies identified in the original search.

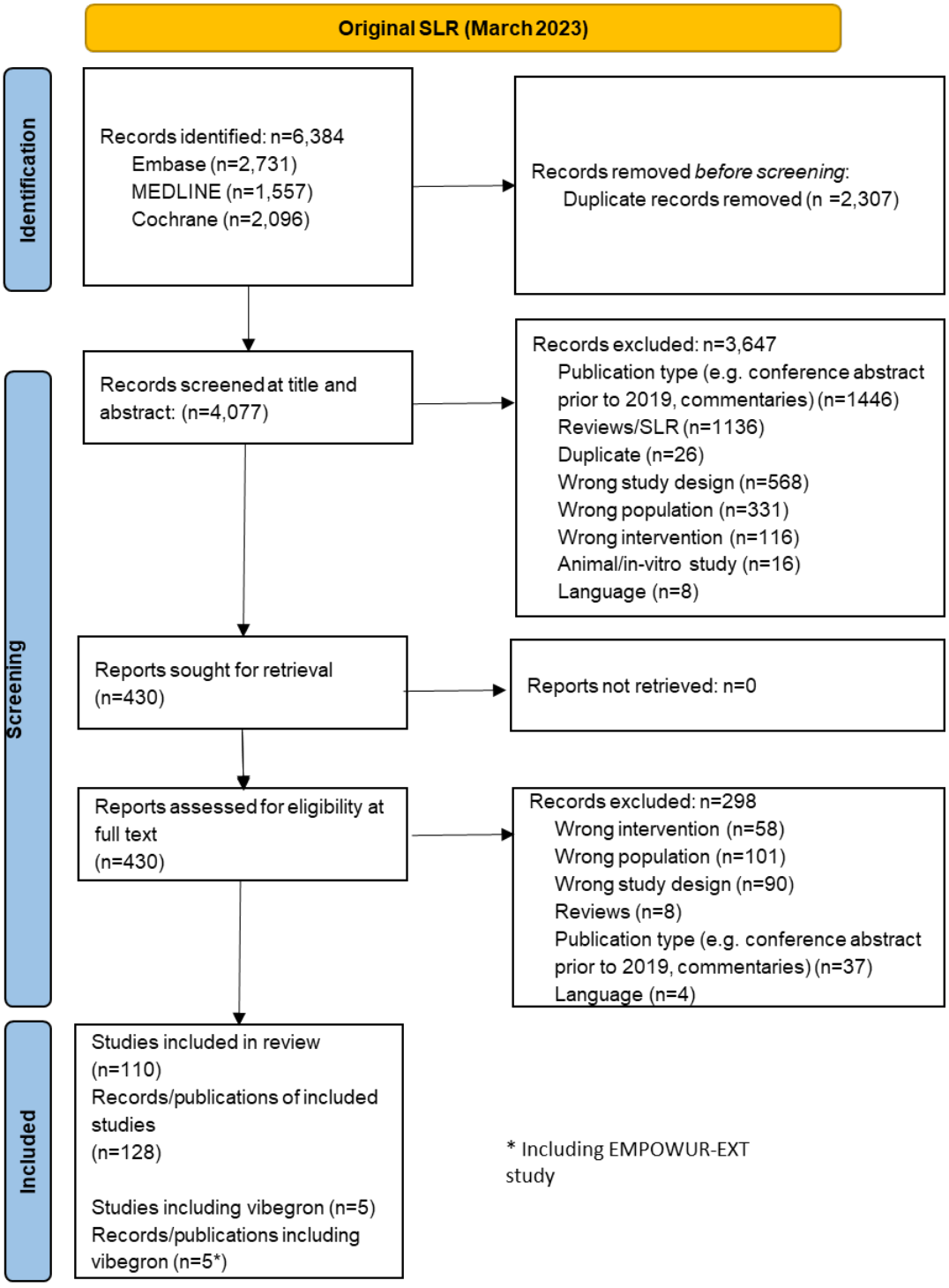
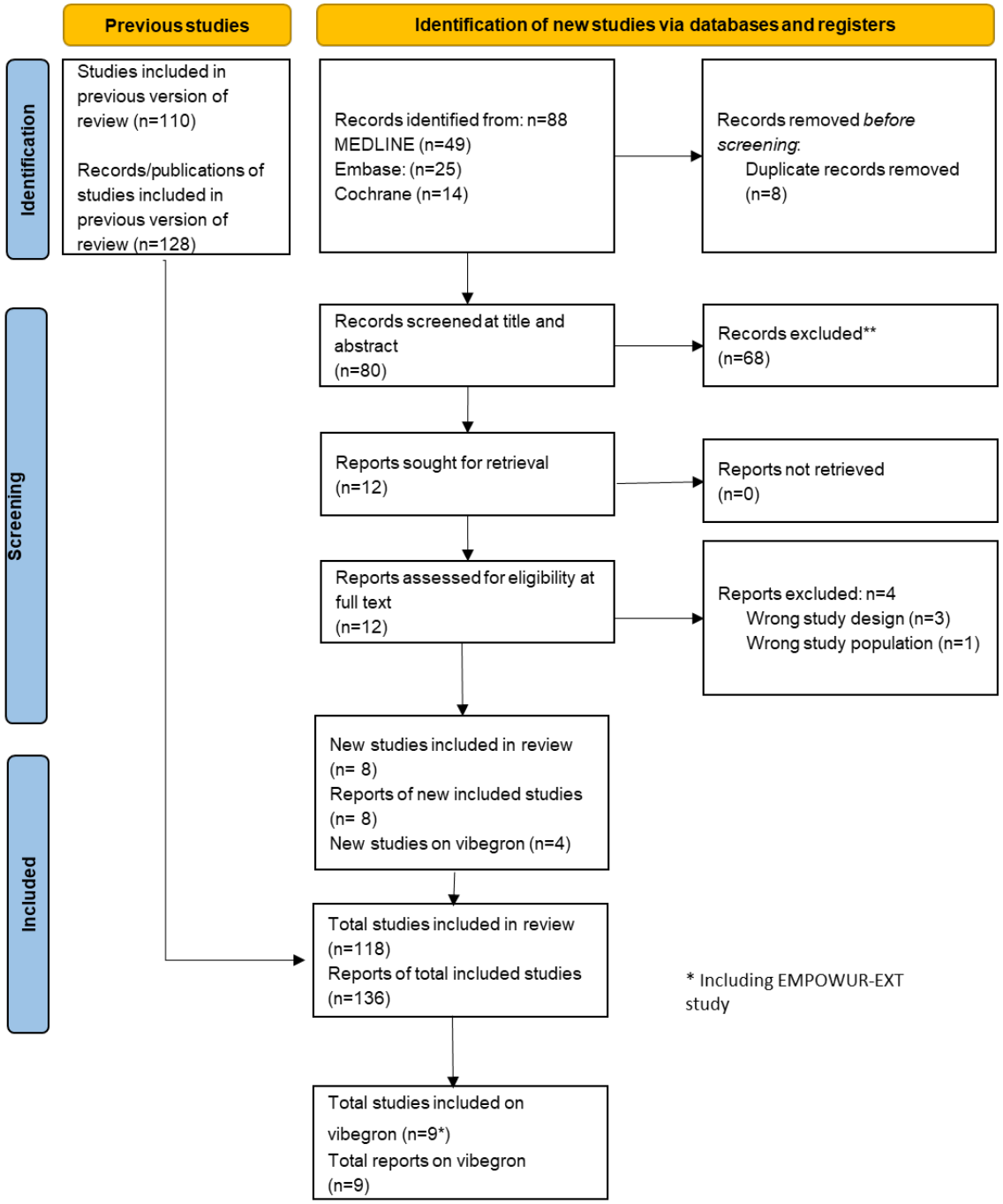


Figure 8. PRISMA diagram illustrating progressive exclusion of studies identified in the combined searches (original search plus update).



B.3.2 List of relevant clinical effectiveness evidence

The SLR identified seven studies enrolling unique patients reporting on vibegron (8, 102-107), and an extension study featuring additional randomisation of patients from the EMPOWUR study (108) The comparators used in the studies are reported in Table 4. The principal study that informs this submission is the EMPOWUR trial, which was the main study used in the ITC (Section B.3.9) and used to show equivalence of vibegron compared with mirabegron in the relevant outcomes used in the cost-effectiveness of TA290. The other studies were excluded from the ITC on the following basis:

- The study by Yoshida *et al.* (2018) (104) was a Phase 3 double-blind RCT with a relatively large sample size (n=1224, full analysis set [FAS]). However, vibegron was prescribed at a dose of 50 mg or 100 mg, which is not consistent with the anticipated UK market authorisation.
- The study by Mitcheson *et al.* (2019) (103) was a Phase 2 RCT. This study was partly designed to establish the optimal dose of vibegron, which was administered at a dose of 3, 15, 50, or 100 mg, none of which reflect the anticipated dose used in the UK.
- The EMPOWUR extension trial (EMPOWUR-EXT) (108) was a long-term study whose participants had immediately prior contributed to the EMPOWUR RCT (8). It also did not report data at 12 weeks (the time of the primary outcome of interest). However, data from EMPOWUR-EXT was used in the ITC to compare the longer-term safety profiles of vibegron and mirabegron (Section B.3.9).
- The RCT by Kinjo *et al.* (2023) (102) was relatively small (n=213) and reported on the use of vibegron 50 mg (not the anticipated UK licensed dose) only in women with OAB. As this trial provided direct comparative evidence with mirabegron it was of particular interest to the decision problem.
- The RCT by Sato *et al.* (2023) (105) was relatively small (n=104) and reported on the use of vibegron 50 mg (not the UK licensed dose) in post-menopausal women with OAB. Nevertheless, as with Kinjo *et al.* (2018), this trial provided the only direct comparative evidence with mirabegron and therefore was of particular interest to the decision problem.
- The study by Shin *et al.* (2023) (106) is a recently identified RCT identified in the SLR update. It compared placebo with vibegron in people with OAB from Korea; however, the dose of vibegron used was 50 mg making it unsuitable for inclusion in the ITC.

- The study by Wada *et al.* (2023) (107), identified in the SLR update, was a cross-over trial that compared mirabegron with vibegron in women with OAB. However, this study was published as a conference abstract only, meaning it was not possible to appraise the methodology or fully interpret the results.

For these reasons, particular attention is focussed on the EMPOWUR study in the current submission, although the other studies are also briefly described and results reported, where relevant to the decision problem.

Table 4. Comparators in identified studies

References of trial	Vibegron (dose*)	Mirabegron	Tolterodine	Placebo
Yoshida et al. (2018)† (104)	✓ (50 or 100 mg)	×	×	✓
Mitcheson et al. (2019) (103)	✓ (Variable dose)	×	×	✓
EMPOWUR trial (2020) (8)	✓ (75 mg)	×	✓	✓
EMPOWUR-EXT(2021) (108)	✓ (75 mg)	×	✓	×
Kinjo *et al.* (2023) (102)	✓ (50 mg)	✓	×	×
Sato *et al.* (2023) (102)	✓ (50 mg)	✓	×	×
Shin *et al.* (2023) (106)	✓ (50 mg)	✓	×	✓
Wada *et al.* (2023) (107)	✓ (50 mg)	✓	×	×

* Whilst the scope included all globally licensed doses of vibegron, in the UK the sole authorised dose is 75 mg. Only studies using this dosing regimen were used to inform the indirect treatment comparison (Section B.3.9 Indirect and mixed treatment comparisons

† Included imidafenacin (0.1 mg twice daily) as an active comparator. This anticholinergic drug is not available in the UK.

The characteristics of the included studies are listed in Table 5.

Table 5. Characteristics of included studies (ordered by date of publication).

Study	Yoshida *et al.* (2018) (104)	Mitcheson *et al.* (2019) (103) [Part 2]	EMPOWUR trial (2020) (8) (NCT03492281)	EMPOWUR EXT (2021) (108) (NCT03583372)	Kinjo *et al.* (2023) (102)	Sato *et al.* (2023) (105)	Shin *et al.* (2023) (106) (NCT04917315)	Wada *et al.* (2023) (107)
Study design	Multicentre, randomised, four-arm, parallel-group, placebo controlled Phase 3 study with active anticholinergic reference (imidafenacin)	International, Phase 2b, randomised, double blind, placebo and active comparator controlled, two-part superiority trial	International, Phase 3, randomised, double-blind, placebo- and active-controlled multicentre trial	Phase 3, randomised, double-blind, active-controlled, parallel-group study	Prospective randomised controlled trial.	Prospective randomised controlled trial.	Prospective, multicentre, parallel, placebo controlled randomised trial.	Multicentre, prospective, randomised, cross-over trial.
Population (key inclusion criteria)	Age ≥20 years old Symptoms of OAB for ≥6 months Willing and able to complete the micturition diary and accompanying study questionnaires correctly Able to go to the bathroom without support and could	Clinical history of OAB for at least 3 months Able to read, understand and complete questionnaires and voiding diaries Ambulatory and in good general physical and mental health No clinically significant or laboratory abnormality Sexually abstinent or sing contraception	History of OAB for at least 3 months prior to the Screening Visit Meets either OAB wet or OAB dry criteria OAB wet: mean of ≥8 micturitions and ≥1.0 UUI episodes per day OAB dry: mean of ≥8 micturitions, ≥3.0 urgency episodes, and <1.0 UUI episodes per day	Completed participation in Study RVT 901 3003 (EMPOWUR) Demonstrated 80% compliance with self administration of study treatment in Study RVT 901 3003 (EMPOWUR)	Post-menopausal women with OAB who are naïve of pharmacological treatment.	Post-menopausal women with OAB who are naïve of pharmacological treatment.	Adults with OAB who were symptomatic of OAB for ≥6 months.	Women ≥50 year diagnosed with OAB. Participants were naïve to pharmacological treatment.
Intervention(s)	Vibegron 50 or 100 mg once daily.	Vibegron 100 mg once daily	Vibegron 75 mg once daily	Vibegron 75 mg once daily	Vibegron 50 mg once daily	Vibegron 50 mg once daily	Vibegron 50 mg once daily	Vibegron 50 mg once daily
Comparator(s)	Placebo Imidafenacin 0.1 mg twice daily,	Placebo Tolrerodine MR Vibegron + tolterodine	Placebo Tolrerodine MR	Tolrerodine MR	Mirabegron 50 mg once daily	Mirabegron 50 mg once daily	Matching placebo	Mirabegron 50 mg once daily

Study	Yoshida *et al.* (2018) (104)	Mitcheson *et al.* (2019) (103) [Part 2]	EMPOWUR trial (2020) (8) (NCT03492281)	EMPOWUR EXT (2021) (108) (NCT03583372)	Kinjo *et al.* (2023) (102)	Sato *et al.* (2023) (105)	Shin *et al.* (2023) (106) (NCT04917315)	Wada *et al.* (2023) (107)
Indicate if trial supports application for marketing authorisation	Yes	Yes	Yes	No	No	No	No	
Included in ITC? (reasons)	No Incorrect dose	No Incorrect dose	Yes	No Study length	No Population, incorrect dose	No Population, incorrect dose	No Incorrect dose	No Incorrect dose Reported as abstract only
Primary outcome	Average daily number of micturitions compared with placebo (12 weeks)*	Average daily number of micturitions compared with placebo (12 weeks)*	Coprimary outcomes: 1) Average daily number of micturitions compared with placebo (12 weeks)** 2) Average daily number of UUI episodes (OAB wet patients) in the vibegron group compared with the placebo group *	AEs and SAEs Up to 52 weeks * Proportion and frequency of TEAEs * Discontinuation	OABSS QoL index Voided urine volumes	OABSS	Change in mean daily number of micturitions compared with placebo (12 weeks)*	Change in OABSS from baseline.
Secondary outcome	Improvement in average daily number of: • UUI episodes* • Urgency episodes* • Incontinence episodes* • Nocturia episodes*	Improvement in average daily number of: • UUI episodes* • Urgency episodes* • Incontinence episodes* • Nocturia episodes*	Improvement in average daily number of: • UUI episodes* • Urgency episodes* • Incontinence episodes* • Nocturia episodes*	Improvement in average daily number of: • UUI episodes* • Urgency episodes* • Incontinence episodes* • Nocturia episodes*	Improvement in average daily number of: • UUI episodes* • Urgency episodes* • Incontinence episodes* • Nocturia episodes*	OABSS sub-domains: Daytime frequency • Nocturia* • Urgency* • UUI* • IPSS • IPSS-S • IPPS-V • SIPSS-QoL	Daily episodes of: • Nocturia • UUI • Total incontinence • Average volume voided per micturition* OABSS	AEs PVR OABSS subdomains Maximum voided urine Patient satisfaction

Study	Yoshida *et al.* (2018) (104)	Mitcheson *et al.* (2019) (103) [Part 2]	EMPOWUR trial (2020) (8) (NCT03492281)	EMPOWUR EXT (2021) (108) (NCT03583372)	Kinjo *et al.* (2023) (102)	Sato *et al.* (2023) (105)	Shin *et al.* (2023) (106) (NCT04917315)	Wada *et al.* (2023) (107)
	• Average volume voided per micturition* • AEs*	• Average volume voided per micturition* • AEs*	• Average volume voided per micturition* • OABq score* • EQ-5D score* • AEs*	• Average volume voided per micturition*	• Average volume voided per micturition* • AEs *	• KHQ • BP • AEs*	OABSS subdomains QoL Patient satisfaction	

Abbreviations: AEs, adverse events; BP, blood pressure; ECG electrocardiogram; EQ-5D, Euroqol 5 dimensions;' IPSS, International Prostrate Symptom Score; KHQ,'King's Health Questionnaire; MR. modified release; OAB, overactive bladder [syndrome); OABq, overactive bladder syndrome questionnaire; OABSS, overactive bladder symptom score; PVR, postvoid residual volume; QoL, quality of life; SAE, serious adverse events; TEAEs, treatment emergent adverse events; UUI, urinary urge incontinence.
* Outcome specified in the scope, or related to outcome specified in the scope.
† Mitcheson also featured a part 1 stage which was used to determine optimal dosage of vibegron in part 2.

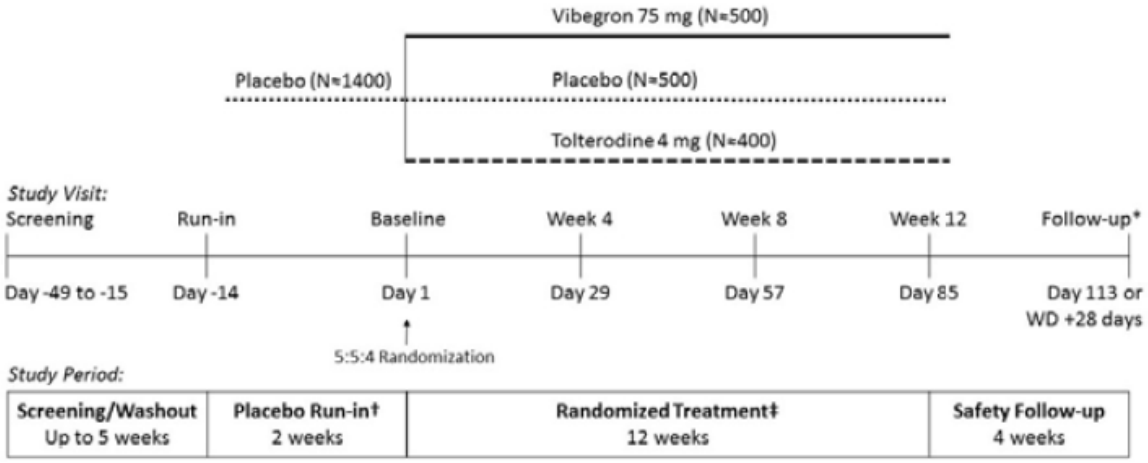
B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

B.3.3.1 EMPOWUR trial (pivotal)

EMPOWUR was a Phase 3, multicentre, randomised, double-blind, placebo- and active-controlled study (8). The objective of the study was to prospectively assess the efficacy and safety of vibegron in treating symptoms of OAB compared to placebo. The study consisted of a 1 to 5 week screening period (including a 28 day washout); a 2 week single-blind, placebo run-in period; a 12 week double-blind, randomised treatment period; and a 4-week follow-up period for safety evaluation (8). Patients who met eligibility criteria were randomised in a 5:5:4 ratio to receive an orally administered, once-daily dose of vibegron 75 mg with a placebo to match tolterodine ER 4 mg (active control); a placebo to match vibegron and placebo to match tolterodine, or tolterodine with a placebo to match vibegron. Randomisation was stratified by sex and by OAB type (wet versus dry).

Patients filled out the voiding diary for seven days prior to the run-in, baseline, week 2, week 4, week 8, and week 12 visits (time of primary outcome). The volume portion of the diary was filled out for 1 day of the 7 diary days completed prior to each visit. Patient visits occurred at baseline and at weeks 4, 8, and 12 of the treatment period. Patients who completed the full 12-week treatment period were eligible for an optional 40-week extension study initiated under a distinct protocol (see Section B.3.3.1.1). Those who did not enrol in the extension study entered a four-week safety period after their last dose of study treatment and had a visit at week 16. Patients who discontinued the study early also had a follow-up visit 4 weeks after treatment withdrawal. Unscheduled study visits were available as needed for patients with suspected safety concerns. A schematic of the trial design is reported in Figure 9. Full eligibility criteria, interventions used, and outcomes are detailed in Table 6.

Figure 9. Trial design of EMPOWUR study



*The Follow-up visit occurred at Day 113 for subjects who completed the Week 12 visit but did not enroll in the optional 40-week extension study (RVT-901-3004) or at 28 days after withdrawal (WD) for subjects who withdraw early from the study; †Single-blind (subjects did not know they were receiving placebo); ‡Double-blind.

B.3.3.1.1 EMPOWUR extension study

The EMPOWUR extension study (EMPOWUR-EXT) was an international, Phase 3, double-blind, active controlled, multicentre extension study that evaluated the long-term safety and efficacy of vibegron in patients with symptoms of OAB (108). The objective of the study was to prospectively assess the safety and efficacy of vibegron in treating the symptoms of OAB as compared to an active control (tolterodine) over a long-term follow-up period of 40 additional weeks beyond the EMPOWUR treatment period, for a total of 52 weeks. Patients completed the same voiding diary that they were trained to use during the EMPOWUR trial and completed the diary for 7 days before the Week 16, 24, 44, and 52 visits. The emphasis on the outcomes of the extension study was the safety and tolerability of vibegron, with primary outcome being the incidence of treatment emergent adverse events (TEAEs). Safety measures also included extent of exposure, treatment compliance, clinical laboratory evaluations, vital signs, physical examinations, electrocardiograms and post-void residual urine volume measured via ultrasound.

Table 6. Details of the EMPOWUR trial.

Trial name and number	**EMPOWUR** trial, NCT03492281. Staskin *et al.* (2020) (8) Associated references: Frankel *et al.* (2020) (109); Varano *et al.* (2021) (110); Frankel *et al.* (2021) (111)
Trial design	EMPOWUR was an international, Phase 3, randomised, double-blind, placebo-controlled with active control (tolterodine), parallel-group, multicentre study in men and women with overactive bladder, conducted in conformance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice.
Objectives	Primary: To evaluate the efficacy of vibegron compared to placebo in subjects with symptoms of OAB, specifically the frequency of micturitions and frequency of urge urinary incontinence episodes. Secondary: To evaluate the overall efficacy of vibegron compared to placebo in subjects with symptoms of OAB.
Eligibility criteria for participants	**Inclusion criteria** 1. Willing and able to provide written informed consent. 2. Males or females ≥ 18 years of age. Note: Up to 15% of subjects could be male. 3. Had a history of OAB (as diagnosed by a physician) for at least 3 months prior to the screening visit. Note: OAB was defined as urgency, with or without UUI, usually associated with frequency and nocturia. Urodynamic evaluation was not required. 4. Met either the OAB Wet or OAB Dry criteria described below, based on the patient voiding diary returned both at the run-in visit and baseline visit (all complete diary days must have been used in determining eligibility). A minimum of 5 complete diary days [not necessarily consecutive] were required for the diary returned at the run-in visit, and 4 complete diary days were required for the diary returned at the baseline visit. Averages should not have been rounded up to the whole number: 5. OAB Wet criteria: • An average of ≥ 8.0 micturitions per Diary Day; and • An average of ≥ 1.0 UUI episodes per Diary Day; and • If stress urinary incontinence was present, the total number of UUI episodes must have been greater than the total number of stress urinary incontinence episodes from the previous visit diary. OAB Dry criteria: • An average of ≥ 8.0 micturitions per Diary Day; and, • An average of ≥ 3.0 urgency episodes per Diary Day; and

Trial name and number	**EMPOWUR** trial, NCT03492281. Staskin *et al.* (2020) (8) Associated references: Frankel *et al.* (2020) (109); Varano *et al.* (2021) (110); Frankel *et al.* (2021) (111)
	• An average of < 1.0 UUI episodes per diary day; and • If stress urinary incontinence was present, the total number of UUI episodes must have been greater than the total number of stress urinary incontinence episodes from the previous visit diary. Note: Up to 25% of subjects that met OAB Dry criteria may have been enrolled. 6. For females of reproductive potential: Agreed to remain abstinent or use (or have their male partner use) an acceptable method of birth control) each time the subject had intercourse from the screening visit until completion of the follow-up visit. 7. For females of reproductive potential: • Agreed not to donate ova (eggs) until at least 1 month after the last dose of study treatment. • Had demonstrated ≥ 80% compliance with self-administration of study treatment during the run-in period. 8. Was ambulatory and in good general physical and mental health as determined by the investigator. In the opinion of the investigator, was able and willing to comply with the requirements of the protocol, including completing electronic versions of questionnaires, the patient voiding diary, and the urine volume diary (will require ability to collect, measure, and record voided volume by herself/himself using a graduated urine collection and measurement container [provided by the sponsor, if needed]). **Exclusion criteria (urological)** 1. Subject had a history of 24-hour urine volume greater than 3,000 mL in the past 6 months, or a urine volume diary day measurement greater than 3,000 mL during the run-in period. 2. Had lower urinary tract pathology that could, in the opinion of the investigator, be responsible for urgency, frequency, or incontinence; including, but not limited to, urolithiasis, interstitial cystitis, prostate cancer, GI cancer, tuberculosis, stone disease, urothelial tumour, prostatitis, and clinically relevant BPH or bladder outlet obstruction, as judged by the investigator. Note: Male subjects with mild to moderate BPH without evidence of bladder obstruction as determined by the investigator may have been included as long as they had been taking a medication for the treatment of BPH for at a least 1 year prior to Screening, with no change in dose of herbal medications, alpha antagonist medications or other symptomatic treatments or medications within 3 months prior to Screening, and no change in dose of alpha reductase inhibitors within 6 months of Screening. 3. Had a history of surgery to correct stress urinary incontinence, pelvic organ prolapse, or procedural treatments for BPH within 6 months of Screening. 4. Had current history or evidence of Stage 2 or greater pelvic organ prolapse (prolapse extended beyond the hymenal ring).

Trial name and number	**EMPOWUR** trial, NCT03492281. Staskin *et al.* (2020) (8) Associated references: Frankel *et al.* (2020) (109); Varano *et al.* (2021) (110); Frankel *et al.* (2021) (111)
	5. Subject was currently using a pessary for the treatment of pelvic organ prolapse. 6. Had a known history of elevated post-void residual volume defined as greater than 150 mL. 7. Had undergone bladder training or electrostimulation within 28 days prior to Screening or planned to initiate either during the study. 8. Had an active or recurrent (> 3 episodes per year) urinary tract infection by clinical symptoms or laboratory criteria (≥ 5 white blood cells WBC or a positive urine culture, defined as ≥ 105 colony forming units CFU/mL in 1 specimen). Subjects diagnosed with a UTI at the Screening Visit may have been treated and rescreened once the infection had resolved. 9. Had a requirement for an indwelling catheter or intermittent catheterization. 10. Had received an intradetrusor injection of botulinum toxin within 9 months prior to Screening. **Note:** other exclusion criteria applied based on general medical, laboratory and procedure history.
Settings and locations where the data were collected	199 study locations, mainly in United States (89.4% of participants) but also Poland (6.3%), Hungary (1.7%), Canada (1.7%), Latvia (0.7%) and Lithuania (0.2%). See www.auajournals.org.
Trial drugs	**Intervention:** Vibegron 75 mg tablet + placebo capsule to match tolterodine ER 4 mg capsule **Comparator 1** (dummy): Placebo tablet to match vibegron 75 mg tablet + placebo capsule to match tolterodine ER 4 mg capsule. **Comparator 2** (active): Tolterodine ER 4 mg capsule + placebo tablet to match vibegron 75 mg tablet
Co-Primary efficacy outcomes	• CFB at Week 12 in average number of micturitions per 24 hours in all OAB subjects • CFB at Week 12 in average number of UUI episodes per 24 hours in OAB Wet subjects.
Secondary efficacy outcomes	• CFB at Week 12 in average number of urgency episodes (need to urinate immediately) over 24 hours in all OAB subjects • Percent of OAB Wet subjects with at least a 75% reduction from baseline in UUI episodes per 24 hours at Week 12 • Percent of OAB Wet subjects with a 100% reduction from baseline in UUI episodes per 24 hours at Week 12

Trial name and number	**EMPOWUR** trial, NCT03492281. Staskin *et al.* (2020) (8) Associated references: Frankel *et al.* (2020) (109); Varano *et al.* (2021) (110); Frankel *et al.* (2021) (111)
	• Percent of all OAB subjects with at least a 50% reduction from baseline in urgency episodes (need to urinate immediately) per 24 hours at week 12 • CFB at week 12 in average number of total incontinence episodes over 24 hours in OAB Wet subjects • CFB at week 12 in Coping Score from the Overactive Bladder Questionnaire Long Form (OAB-q LF, 1-week recall) in all OAB subjects • CFB at week 12 in average volume voided per micturition in all OAB subjects.
HRQoL outcomes	• CFB at week 12 in HRQL Total Score from the OAB-q LF (1-week recall) in all OAB subjects • CFB at week 12 in Symptom Bother Score from the OAB-q LF (1-week recall) in all OAB subjects • Percent of all OAB subjects with average number of micturitions < 8 per 24 hours at week 12 • Percent of OAB Wet subjects with at least a 50% reduction from baseline in total incontinence episodes per 24 hours at week 12 • CFB at week 12 in overall bladder symptoms based on PGI-Severity in all OAB subjects • CFB at week 12 in overall control over bladder symptoms based on PGI-Control in all OAB subjects.
Safety outcomes	• Incidence of AEs • Clinical laboratory assessments • Vital signs and physical examinations • Post-void residual (PVR) urine volume (measured via ultrasound). TEAEs were coded to preferred term and system organ class using MEDRA version 20.1. AEs of special interest were: • Potential MACCE; these events were adjudicated by an independent external expert clinical adjudication committee. • Hypertension • AEs consistent with orthostatic hypotension as confirmed by orthostatic vital signs • AEs suggestive of cystitis or urinary tract infection • Elevated laboratory value requiring that study drug be temporarily withheld or permanently discontinued.
Pre-planned subgroups	The following subgroups were analysed a priori: • Region (US vs non-US)

Trial name and number	**EMPOWUR** trial, NCT03492281. Staskin *et al.* (2020) (8) Associated references: Frankel *et al.* (2020) (109); Varano *et al.* (2021) (110); Frankel *et al.* (2021) (111)
	• Age category 1 (< 40, ≥ 40 to < 55, ≥ 55 to < 65, ≥ 65 to < 75, ≥ 75 years) • Age category 2 (< 65, ≥ 65 years) • Age category 3 (< 65, ≥ 65 to < 85, ≥ 85 years) • Race (white vs other) • Sex (female vs male) • Males with BPH vs males without BPH • Prior anticholinergic use in the last 12 months (yes vs no) • Prior beta-3 agonist use in the last 12 months (yes vs no) • OAB type (Wet vs Dry) • OAB-d type (Wet, Dry, or Missing)
Abbreviations: AE, adverse events; ALT, alanine transferase; AST, aspartame transferase; BPH, benign prostatic hyperplasia, CFU, colony forming unit; CFB, change from baseline; HRQoL, health-related quality of life; MedDRA, Medical Dictionary for Regulatory Activities ; OAB; overactive bladder; OABq LF, overactive bladder questionnaire long-form; PGI, patient impression of change; MACCE, major adverse cardiac and cerebrovascular events; TEAE, treatment-emergent adverse event; UTI, urinary tract infection; UUI, urinary urgency incontinence; WBC, white blood cell.	

B.3.3.2 Other studies

B.3.3.2.1 Yoshida et al. (2018)

The study by Yoshida *et al.* (2018) (104) was a multicentre, randomised, four-arm, parallel-group, placebo-controlled Phase 3 study with an active anticholinergic reference (imidafenacin). The objective of the study was to prospectively assess the safety and efficacy of vibegron (dosed at 50 or 100 mg) in treating the symptoms of OAB in a population of Japanese patients. Patients aged ≥20 years with symptoms of OAB for ≥6 months were included.

The study consisted of a single-blind, placebo run-in phase and a double-blind treatment phase. Patients who met the eligibility criteria entered a two-week placebo run-in phase, during which they received vibegron-matching placebo once daily and imidafenacin-matching placebo twice daily. Eligible patients entered a 12-week double-blind treatment phase and were randomly assigned (in a 3:3.3:1 ratio) to receive vibegron 50 mg once daily, vibegron 100 mg once daily, imidafenacin 0.1 mg twice daily, or placebo.

Efficacy endpoints were assessed using a three-day micturition diary that patients completed before each visit (104). The primary endpoint was CFB to Week 12 in average daily number of micturitions. Secondary endpoints included changes from baseline to each visit in average daily number of micturitions, UUI episodes, urgency episodes, incontinence episodes, nocturia episodes, and voided volume per micturition. HRQoL was assessed using the King's Health Questionnaire (KHQ) and patient satisfaction was assessed using the patient global impression (PGI) scale questionnaire. Safety assessments included evaluation of AEs, post-voided residuals, clinical tests, vital signs, and ECG. In addition to the main analysis, two post-hoc analyses were conducted to evaluate the impact of vibegron on nocturia (112) and outcomes among patients with UUI at baseline (113).

B.3.3.3.2 Mitcheson et al. (2019)

Mitcheson *et al.* (2019) was an international, Phase 2b, randomised, double-blind, placebo- and active-controlled, two-part superiority trial conducted in patients with wet or dry OAB aged 18 to 75 years (103). The objective of the study was to evaluate the safety and efficacy of once-daily vibegron (100 mg) for patients with OAB regardless of UUI. In addition, the safety, tolerability, and efficacy of vibegron in combination with tolterodine were evaluated. Patients were required to have OAB for ≥3 months prior to screening, meet predefined OAB wet or OAB dry criteria, have a greater number of urge episodes than UUI episodes, and have no clinically significant laboratory or electrocardiogram (ECG) abnormalities.

The study was run in two parts, with Part 1 informing the doses of Part 2, and patients who participated in Part 1 of the study not participating in Part 2 (103). For each part of the study, patients were stratified as OAB wet or OAB dry at randomisation and the investigators/study staff, patients, and the sponsor were all blinded to treatment assignments. In Part 1, patients were equally randomised into one of seven groups, including different doses of once-daily oral vibegron monotherapy, tolterodine ER 4 mg, or placebo for 8 weeks, or a combination of drugs for 4 weeks followed by monotherapy for 4 weeks. In Part 2, patients were randomised 2:2:2:1 to receive once-daily vibegron (100 mg), tolteridone, combination, or placebo for 4 weeks. Dose selection for Part 2 was based on the interim results from Part 1.

In the study, patients completed seven-day voiding diaries before each visit for use in efficacy measures. The primary endpoint was vibegron dose-related reductions from baseline in Least Squares (LS) mean daily number of micturitions at week 8, specific to Part 1 of the study (103). Secondary endpoints included: CFB to week 4 in LS mean daily number of micturitions (Part 2); changes from baseline to week 8 (Part 1) and week 4 (Part 2) in LS mean daily number of total incontinence and UUI episodes (OAB wet patients only); and CFB to week 8 (Part 1) and week 4 (Part 2) in LS mean daily number of urgency episodes. Safety and tolerability assessments included evaluation of AEs, vital signs, ECG, and laboratory tests.

B.3.3.3.3 Kinjo et al. (2023)

Kinjo *et al.* (2023) reported on a randomised, prospective, parallel-group study comparing the efficacy and safety of mirabegron versus vibegron monotherapy in postmenopausal women with treatment-naïve OAB (102). This was a single centre study set in Japan, where vibegron is licensed only at a dose of 50 mg and is contraindicated in women of childbearing age. Women were randomised in 1:1 ratio to receive vibegron (50 mg) or mirabegron (50 mg). The primary outcomes of the study was the OAB symptom score (OABSS), measured at 12 weeks. OABSS is a validated scoring system used to assess the severity of OAB (114). A urination diary was also used to assess secondary outcomes including quality of life (QoL) index, number of micturitions per day, number of urgency episodes per day, and the number of UUIs per day. Mean volume of urine and AEs were also measured.

B.3.3.3.4 Sato et al. (2023)

Sato *et al.* (2023) reported on a prospective, randomised, open-label, parallel-group trial designed to compare the safety and efficacy of mirabegron and vibegron in postmenopausal women with treatment-naïve OAB (105). As with the study by Kinjo et al (2023), women were randomised in 1:1 ratio to receive vibegron (50 mg) or mirabegron (50 mg), with the primary outcome of the study being OABSS (total score), measured at 12 weeks. Secondary

outcomes reported included the four domains of the OABSS, the international prostrate symptom score (IPSS), which has utility in women as well as men (115), and the'King's Health Questionnaire (KHQ).

B.3.3.3.5 Shin et al. (2023)

Shin *et a*l. (2023) reported on a multicentre, parallel-group RCT in adult patients with OAB in Korea (106). Screened patients were randomly assigned to either the placebo or the vibegron (50 mg) group in a 1:1 ratio with adjustment for sex, baseline mean daily micturition, and presence of urgency incontinence. The respective drugs (vibegron or mirabegron) were administered once daily for 12 weeks, and follow-up visits were scheduled at 4, 8, and 12 weeks (primary outcome) after the start of the treatment phase, which followed a 2-week placebo run-in phase. The primary outcome was the change in mean daily micturitions, which was recorded using a 3-day diary. Secondary outcomes included episodes of UUI, episodes of incontinence, volume of urine voided, the OABSS and its subdomains, the KHQ, and the PGI was used to gauge patient preference.

B.3.3.3.6 Wada et al. (2023)

Wada et al. (2023) reported on a randomised cross-over trial that compared vibegron (50 mg) with mirabegron (50 mg) (107). Enrolled women with OAB were randomised to receive either drug for 8 weeks, before crossing over to receive the other drug for 8 weeks. There no wash-out period. The primary outcome was the change in the number of daily micturitions, with post void residual (PVR) urine volume, maximum recorded urine volume, and patient preference also being reported. This study was reported as a conference abstract.

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.3.4.1 EMPOWUR trial

The EMPOWUR study had two primary outcomes (Section B.3.3.1) which were assumed to be independent for the purpose of analyses. The co-primary alternative hypotheses were:

- In subjects with OAB, vibegron 75 mg will have a different mean CFB in the average number of daily micturitions compared with placebo at week 12.
- In subjects with wet OAB, vibegron 75 mg will have a different mean CFB in the average number of daily UUI episodes compared with placebo at week 12.

EMPOWUR planned to randomise approximately 500 patients to each of the vibegron and placebo groups, and 400 patients to the tolterodine group (8). These sample sizes were selected based on a power calculation with the assumption that 10% of patients would discontinue vibegron during treatment, leaving 450 patients, of whom 75% would have wet OAB. The resultant estimated samples sizes would have approximately 98% power to detect significant between-group differences in the co-primary endpoints using a two-sided significance level of 0.05. The between-group treatment differences were 0.6 and 0.51 for number of daily micturitions and episodes of UUI, respectively (see Section B.3.9.5 Uncertainties in the indirect and mixed treatment comparisons To control overall Type-1 error rate at α = 0.05 level (rejecting the null hypothesis wh'n it's actually true), co-primary and key secondary endpoints were tested in a predefined hierarchical order at week 12 and would stop when p<0.05 was reported. The formal efficacy analysis compared vibegron with placebo. Comparisons between tolterodine and placebo were given nominal p values.

Efficacy was analysed in either the FAS or the FAS for incontinence (FAS-I) (8). The FAS included all unique randomised patients with at least one measurement for CFB in average daily number of micturitions. The FAS-I included all unique randomised patients with OAB wet who had one or more measurements for CFB in average daily number of UUI episodes. The safety analysis set (SAF) included all patients who received at least one dose of double-blind medication after randomisation. A mixed model for repeated measures (MMRM) with restricted maximum likelihood estimation was used for endpoint analysis. Responder endpoints were analysed using the Cochran Mantel Haenszel (CMH) risk difference estimate stratified by sex and OAB type (for the FAS only).

The flow of participants in EMPOWUR is reported in Appendix D.1.2.1.

B.3.4.1.1 EMPOWUR extension study

The planned enrolment for EMPOWER-EXT was the approximately 500 patients who had completed the EMPOWUR study (8). The safety set extension dataset was comprised of all patients who received at least one dose of treatment during the extension study. The full analysis set extension dataset of the study included all randomised patients who received at least one dose of study treatment and had at least one evaluable CFB micturition measurement during the extension 40 week study period. Changes from baseline in efficacy endpoints were analysed using a MMRM with restricted maximum likelihood estimation. Safety assessments were summarised by treatment group; no inferential statistical testing was carried out on the safety data and no imputation was performed for missing safety data.

The flow of participants in EMPOWUR-EXT is reported in Appendix D.1.2.1.

B.3.4.2 Other studies

B.3.4.2.1 Yoshida et al. (2018)

The sample size for part 2 of the study (comparison of vibegron, tolterodine and placebo) was established based on the results of the mean and the standard deviation (SD) of the change in the mean micturitions per day in the first phase of the study. A sample size of 192 patients per arm provided 90% power to demonstrate the superiority of vibegron over placebo with a two-sided significance level of 5%. Similarly, with respect to changes in the secondary endpoints, the number of patients required per group to demonstrate the superiority over placebo in terms of urgency and urgency incontinence were 284 and 170, respectively. Therefore, part 2 of the study planned to enrol 330 patients per group, taking into account patient dropout. The number of patients in the imidafenacin group was set to 100 as an active reference, without statistical testing for noninferiority of efficacy and safety.

Analyses were conducted on the FAS or the SAF, which consisted of randomised patients who took >1 dose of the study drug and had a safety measurement. The FAS was included in the SAF patients, who had at least an efficacy measurement after the first treatment. The per protocol (PP) dataset was defined as the subset of patients in the FAS who met all the eligibility criteria without prohibited concomitant drugs/therapies, whose exposure duration of the study drug was 242 days, and who took ≥75% of the scheduled study drugs.

The LSM and two-sided 95% confidence interval of changes in the efficacy variables from baseline to time of assessment in each group were calculated using a constrained longitudinal data analysis model including the adjustment factors except baseline mean micturitions (117). For superiority of vibegron over placebo, differences in the primary and secondary efficacy variables on comparison of the vibegron and placebo groups were compared using the constrained longitudinal data analysis model. The flow of participants in the Yoshida study is reported in Appendix D.1.2.2.

B.3.4.2.2 Mitcheson et al. (2019)

To evaluate the primary and secondary endpoints, the FAS (all randomised patients receiving at least one dose of the study medication) was used (103). The PP dataset was used for supportive analyses of primary and secondary endpoints. The safety population included all patients who received at least one dose of the study medication, and safety data were descriptively summarised. Primary and secondary endpoints were analysed using a constrained longitudinal data analysis model. The baseline score was entered as the dependent variable in the model with adjustments for treatment, time, region, and interaction of time with treatment. Type-I error rate over multiple treatment dose comparisons for the

primary endpoint was controlled by a step-down trend test at week 8 in Part 1 of the study. The flow of participants is reported in Appendix D.1.2.3.

B.3.4.2.3 Kinjo et al. (2023)

Efficacy was evaluated in the FAS which included all patients who took mirabegron or vibegron and underwent at least one post-treatment efficacy measurement. Safety was analysed in the SAF, which included patients who took at least one dose of mirabegron or vibegron and underwent a safety evaluation. The patients' baseline characteristics were compared between treatment arms using Student's t-test. Repeated-measures analysis of variance were used to compare data before and after the commencement of each medication. The Fisher's exact test was used to compare AEs between the 2 groups.

The sample size was calculated using an effect size set of 0.2 (α) of 0.05, and power (1-β) of 0.80. On the basis of these parameters, a sample of 42 or 52 patients per group was needed. However, the authors did not specify the outcome used for this power calculation or what the minimally important difference (MID) was. It is also unclear if the authors were attempting to prove superiority of one drug or non-inferiority. The flow of participants is reported in Appendix D.1.2.4.

B.3.4.2.4 Sato et al. (2023)

Safety analysis was performed on patients in the SAF, and efficacy analysis was performed primarily on the FAS. The LSM and two-sided 95% CIs of changes in the primary and secondary efficacy outcome measures from baseline to end of treatment in the mirabegron and vibegron groups were calculated using an analysis of covariance (ANCOVA) model adjusting for the treatment group, age, and baseline value. The percentage change in OABSS and KHQ score from baseline to end of treatment achieving minimal clinically important change (MCIC) and the percentage of OAB dry and wet at end of treatment were calculated using a logistic regression model including the same factors as the ANCOVA models, with odds ratios (ORs) and 95% CIs comparing the treatment effects between the mirabegron and vibegron groups. Multiple imputations were used for all missing data. All tests were two-sided, and significance was set at $p<0.05$. No formal statistical sample-size calculations were conducted.

B.3.4.2.5 Sato et al. (2023)

The study reported data on randomised, FAS, SAF, and *per protocol* sets. Baseline characteristics and demographics of the study population were assessed in a randomised set, involving all patients who were allotted to the treatment phase. Safety was analysed in the SAF and included all patients who took the study drug least once during the treatment

phase. Efficacy analysis was performed primarily in the FAS and secondarily *per protocol*. A power calculation was undertaken informed by the study by Yoshida *et al*. (2018) (104). Continuous outcomes were measured using LSM with 95% CIs. Categorical variables were compared with a chi-square test or Fisher exact test. The significance level of p=0.05 was used; no adjustments for multiple comparisons were made.

B.3.4.2.5 Wada et al. (2023)

The study by Wada et al. (2023) was reported as an abstract and did not report information on the statistical analysis methods employed.

B.3.5 Quality assessment of the relevant clinical effectiveness evidence

The EMPOWUR study (8) was assessed using the risk of bias (RoB) 2 tool (118), consistent with Cochrane methodology (119). The study was assessed to be at low risk of bias in each domain and at low risk of bias overall (Appendix D.1.3). In terms of generalisability, the trial was conducted with a suitable wash out period and is applicable to the population described in the scope of the decision problem in England. However, approximately 85% of those enrolled into the trial were women. This is discussed further in Section B.3.7.1.

The main limitation of the EMPOWUR study was its 12-week treatment period. This was partly addressed through EMPOWUR-EXT (108), an extension study reporting long-term follow-up data on a period of 40 additional weeks, for a total of 52 weeks. However, interpretation of these data is limited by potential selection bias, as, although the trial continued the blinding protocols, patients voluntarily opted into the study. Only a small proportion (<40%) of patients who completed the 12-week Phase 3 study completed EMPOWUR-EXT. This may limit the generalisability of the extension safety and efficacy findings.

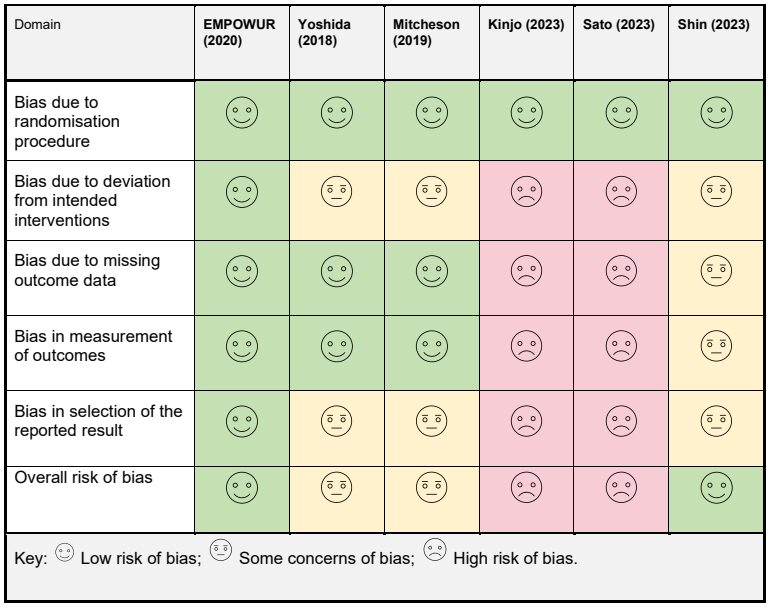
Of the remaining studies, the study by Yoshida *et al.* (2018) (104) was considered to be at low risk of bias, whilst the study by Mitcheson *et al.* (2019) (103) had some concerns regarding potential bias using the RoB2 tool (Appendix D.1.3).This was mainly due to the complex nature of the Phase 2 study, lack of a published protocol, and insufficient reporting. Both these studies lacked generalisability to the decision problem because they utilised doses of vibegron not available in the UK (50 or 100 mg). The study by Shin et al. (2023) (106) had some concerns overall mainly due to a lack of detail on how masking was implemented and maintained and inadequate reporting of patient attrition.

The head-to-head trials reported by Kinjo *et al.* (2023) (102) and Sato *et al.* (2023) were both assessed as being at high risk of bias (Appendix D.1.3). This was mainly because, although the trials were randomised, they were not blinded, with patients and assessors aware of the treatment allocation. Furthermore, both were conducted in a single centre, lacked a placebo control, and did not have an accessible published protocol. The authors did not declare any potential conflicts of interest. Wada et al. (2023) reported direct comparative data between vibegron and mirabegron but could not be appraised due to it being available in conference abstract form only (120)

A summary of the internal validity of the identified trials is reported in Figure 10. In terms of individual domains, all the studies reported adequate randomisation processes, but the two head-to-head studies were considered to be at high risk of bias in all the other domains.

In terms of external validity (generalisability), all the trials with the exception of EMPOWUR used doses of vibegron (50 or 100 mg) that are not anticipated to be licensed in the UK (75 mg). Thus, results reported by these studies should be considered with this context in mind.

Figure 10. Pictorial table summarising the individual risk of bias in the included studies.



B.3.6 Clinical effectiveness results of the relevant trials

Summary

The focus of results is placed on the pivotal Phase 3 EMPOWUR study and its extension, as these were the only studies relevant to the UK licensed indication that administered the anticipated UK dosage of vibegron (75 mg) and included in the ITC.

- The baseline characteristics of patients were well-balanced across arms in EMPOWUR trial.
    - The trial reported statistical superiority over placebo at 12 weeks in the coprimary endpoints of daily micturitions (-0.5, 95% CI -0.8 to -0.2, p< 0.001) and episodes of–UI --0.6 (95% CI -0.9 to -0.3, p<0.0001). Vibegron was numerically, but not statistically, superior to tolterodine. The benefits of vibegron were observed after 2 weeks and persisted for at least 52 weeks.
    - Vibegron was statistically superior compared with placebo in terms of the secondary outcome of urgency episodes, total incontinence episodes, and volume voided. Vibegron was non-statistically numerically superior compared with tolterodine in these outcomes.
    - Vibegron significantly improved HRQoL compared with placebo when measured using the OABq and patient global impression instrument after 12 weeks of treatment.
    - The EMPOWUR-EXT study reported continued efficacy against OAB symptoms up to at least 52 weeks. Forty one percent of patients treated with vibegron were effectively ‘dry’ at week 52 (i.e. had zero incontinence episodes over seven days) as evidenced by a 100% reduction in average daily number of UUI episodes,
- The studies by Yoshida *et al.* (2018) and Mitcheson *et al.* (2019) both reported statistical superiority of vibegron 50 mg over placebo in their primary outcome (daily micturitions) as well as their secondary outcomes. This was also observed in the study by Shin *et al.* (2023).
- The head-to-head studies of Kinjo *et al.* (2023) and Sato *et al.* (2023) did not report any significant or meaningful differences in efficacy between vibegron and mirabegron. Wada *et al*. (2023) reported a patient preference in favour of vibegron compared with mirabegron.

B.3.6.1. EMPOWUR trial

B.3.6.1.1 Baseline characteristics

A total of 1,518 patients were randomised in the EMPOWUR trial, 1,373 (90.4%) of whom completed the 12-week treatment period and 1,463 (96.4%) of whom comprised the FAS (8). Among patients in the FAS, 1,127 patients with wet OAB were included in the FAS-I. Baseline patient characteristics were well balanced across the study groups. The mean age ranged from 59.8 years to 60.8 years across treatment groups and the proportion of females ranged from 84.4 to 85.6%. The proportion of patients aged 65 years or older was 46.0% in the vibegron group, 42.3% in the placebo group, and 39.8% in the tolterodine group. The proportion of patients with wet OAB ranged from 76.5% to 77.9% across groups. The mean number of UUI episodes per day among patients in the FAS-I ranged from 3.42 to 3.49. The mean baseline number of micturitions per day ranged from 11.31 to 11.75; the mean number of urgency episodes per day ranged from 7.92 to 8.13; and the mean volume voided per micturition ranged from 147.0 to 155.4 mL. The baseline characteristics of participant randomised in the EMPOWUR are reported in Table 7.

Table 7. Baseline characteristics of participants in the EMPOWUR trial.

Characteristic		Placebo (n=520)	Vibegron (n=526)	Tolterodine (n=417)
Age	Median (IQR) (years)	61.0 (16.0)	63.0 (18.0)	61.0 (17.0)
	≥65 n (%)	220 (42.3)	242 (46.0)	166 (39.8)
	≥75 n (%)	57 (11.0)	75 (14.3)	47 (11.3)
Sex n (%)	Female	445 (85.6)	449 (85.4)	352 (84.4)
	Male	75 (14.4)	77 (14.6)	65 (15.6)
Region n (%)	US	463 (89.0)	472 (89.7)	376 (90.2)
	Non-US	57 (11.0)	54 (10.3)	41 (9.8)
Previous drug use	Anticholinergic n (%)	85 (16.3)	77 (14.6)	51 (12.2)
	Mirabegron n (%)	27 (5.2)	21 (4.0)	32 (7.7)
OAB category	Wet* n (%)	405 (77.9)	403 (76.6)	319 (76.5)
	Median UUI/day (IQR)	2.00 (2.57)	2.00 (2.85)	2.00 (2.57)
	Dry n (%)	115 (22.1)	123 (23.4)	98 (23.5)
Median micturitions/day (IQR)		10.43 (3.99)	10.43 (3.57)	10.67 (3.73)
Median urgency episodes/day (IQR)		8.00 (5.91)	7.75 (6.21)	8.00 (5.47)
Median voided (mL) (IQR)		141.7 (76.8)†	150.0 (80.6)‡	143.3 (73.5)⁑

Abbreviations: FAS, full analysis set; FAS-I full analysis set (in wet patients); IQR, inter-quartile range; US, United States; UUI, urge urinary incontinence (episodes)
* Defined as an average of 8.0 or more micturitions and 1.0 or more UUI episodes per day, based on voiding diaries submitted at the beginning of run-in and the beginning of study drug treatment in FAS-I population
† (n=514) ‡ (n=524) ⁑ (n=415)

B.3.6.1.2 Co-primary outcomes

Vibegron provided statistically significant reductions in the co-primary endpoints (micturitions and UUI episodes) compared with placebo (8, 121). At week 12 (primary endpoint), vibegron was associated with significantly greater reductions from baseline compared with placebo in average daily number of:

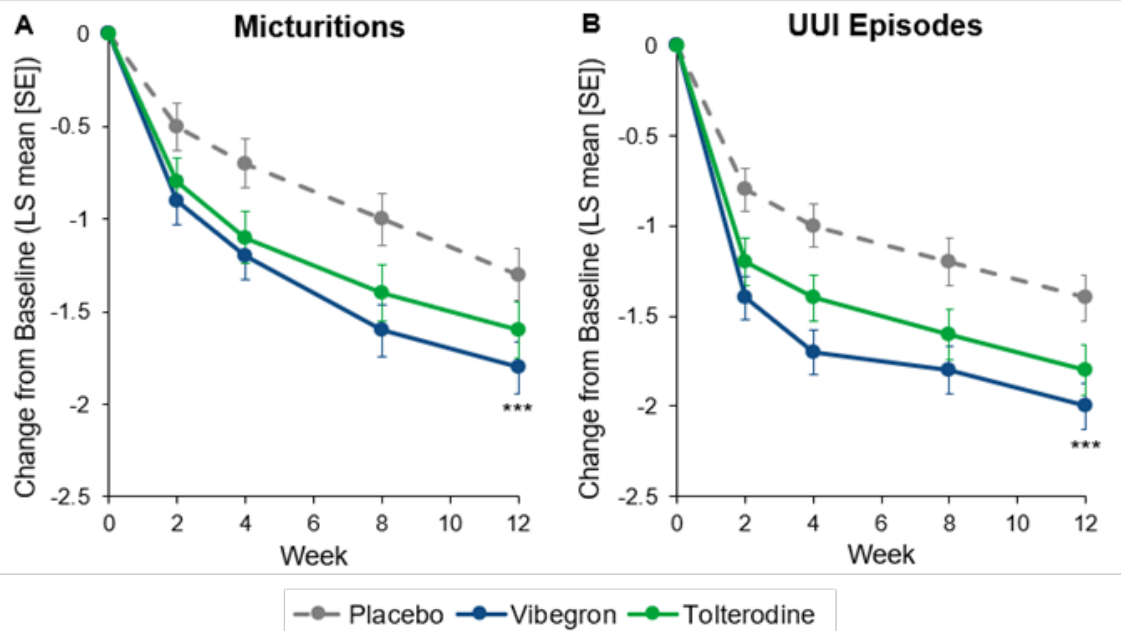
- Micturitions: LSM difference from baseline of -1.8 for vibegron (n=492) compared with -1.3 for placebo (n=475), with a LSM difference between interventions of -0.5 (95% confidence interval [CI] -0.8 to -0.2, p< 0.001).
- UUI episodes: LSM difference from baseline of -2.0 for vibegron (n=383) compared with -1.4 for placebo (n=372), with a LSM difference between interventions of -0.6 (95% CI -0.9 to -0.3, p<0.0001).

A statistically significant decrease in adjusted mean change for vibegron vs placebo was rapidly achieved by week 2 (the first observation time point, prespecified exploratory end point), and was maintained at all subsequent exploratory time points (Figure 11).

In comparison, tolterodine (n=378) was associated with a LSM 12-week reduction in daily micturition of-1.6 compared with baseline, and a LSM difference of -0.3 from placebo (95% CI -0.6 to 0.1, p=0.0988). For episodes of UUI, the corresponding figures were for tolterodine (n=286) were an LSM reduction at 12-weeks of 1.8, and a LSM difference of -0.4 compared with placebo (95% CI -0.7 to -0.1, p=0.0123).

The co-primary outcomes reported in the EMPOWUR study were used to demonstrate that vibegron was at least as safe and effective compared with mirabegron in the ITC (Section B.3.9).

Figure 11. Least squares mean change from baseline in average daily number of (A) micturitions (FAS), (B) UUI episodes (FAS-I).



Abbreviations: FAS = full analysis set; FAS-I = full analysis set for incontinence; LS = least squares; SE = standard error; UUI = urge urinary incontinence.

Note: *** denotes p<0.001 for vibegron vs. placebo using a mixed model for repeated measures.

Source: Staskin (2020) (8), Clinical Study Report (121)

B.3.6.1.3 Secondary efficacy outcomes

Vibegron was associated with statistically significant improvements in all seven key secondary endpoints compared with placebo at week 12, reported in Table 8. At week 12, vibegron was also associated with a statistically significant CFB in:

- Reduction in the average daily number of urinary urge episodes (LSM -0.7, 95% CI -1.1 to -0.2, p=0.002)
- Reduction in total incontinence episodes (LSM -0.7, 95% CI -1.0 to -0.4, p< 0.0001);
- Increase from baseline in average volume voided per micturition (LSM 21.2 mL, 95% CI 14.3 to28.1, p<0.0001) (Figure 12) (8, 121).

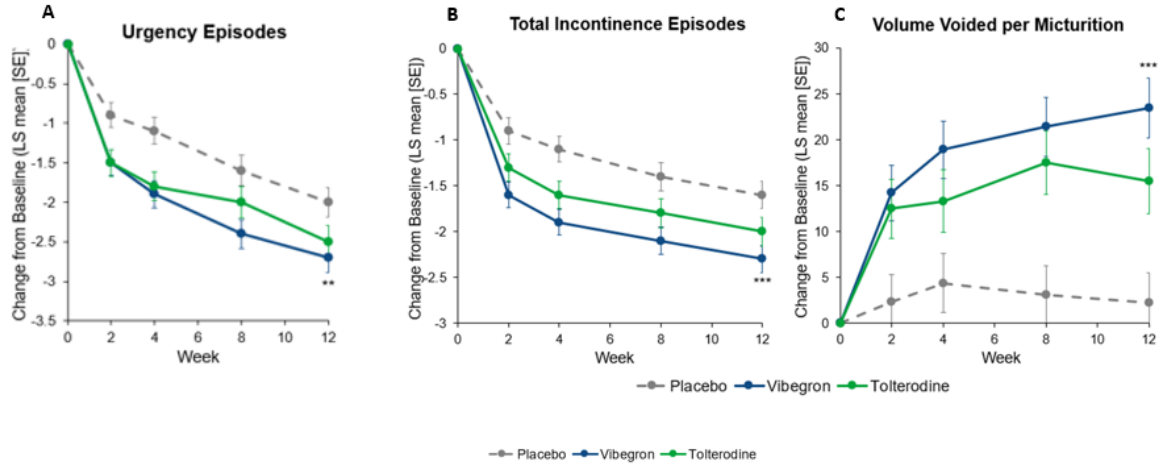
In addition, the proportion of wet OAB patients with 75% or greater reduction from baseline to week 12 in average daily number of UUI episodes was significantly higher in the vibegron group compared with the placebo group (52.4% vs. 36.8%, <0.0001) (Figure 12). The proportion of wet OAB patients with a 100% reduction from baseline in average daily number of UUI episodes and the proportion of all patients with a 50% or greater reduction from baseline to week 12 in average daily number of urgency episodes were also significantly higher in the vibegron group compared with the placebo group (Figure 13).

Table 8. Placebo-adjusted outcomes at Week 12 for the co-primary and key secondary endpoints from the EMPOWUR study (vibegron and placebo).

Endpoint	Vibegron	n	*P*-Value	Tolterodine	n	p-Value
Placebo-adjusted LS Mean Change from Baseline						
Micturitions[a,b,c]	-0.5	492	<0.001	-0.3	378	0.0988
UUI Episodes[a,b,d]	-0.6	383	<0.0001	-0.4	286	0.0123
Urgency Episodes[b,c,e]	-0.7	492	0.0020	-0.4	378	0.0648
Total Incontinence Episodes[b,d,e]	-0.7	383	<0.0001	-0.5	286	0.0074
Volume Voided[c,e], mL	21.2	490	<0.0001	13.3	375	<0.001
OAB-q Coping Score[c,e]	3.6	512	0.0039	3.1	400	0.0210
Placebo-adjusted CMH Difference						
Proportion of OAB wet patients with a ≥75% reduction in UUI episodes[d,e]	16.5	403	<0.0001	9.4	319	0.0120
Proportion of OAB wet patients with 100% reduction in UUI episodes[d,e]	6.3	403	0.0360	1.9	319	0.5447
Proportion of all patients with a ≥50% reduction in urgency episodes[c,e]	6.8	526	0.0235	3.7	417	0.2400

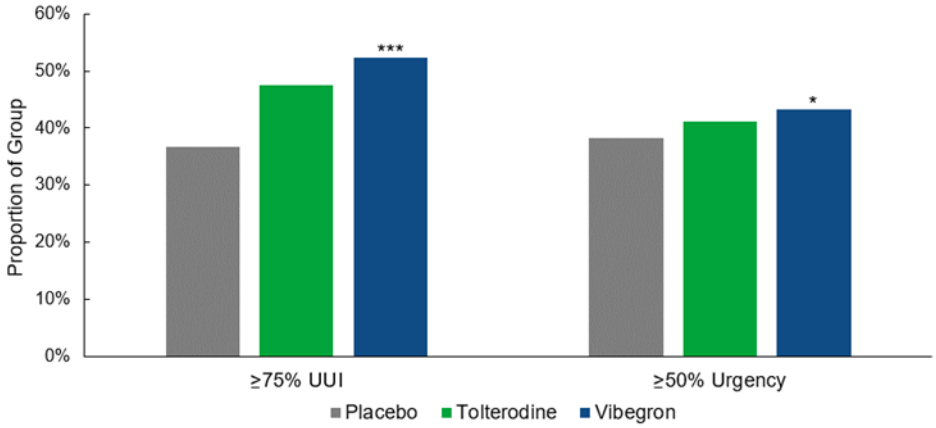
Abbreviations: CMH = Cochran-Mantel-Haenszel; FAS = full analysis set; FAS-I = full analysis set for incontinence; LS = least squares; OAB = overactive bladder; OAB-q = overactive bladder questionnaire; UUI = urge urinary incontinence.
[a] Co-primary endpoint. [b] Change from baseline in average daily number of episodes. [c] Assessed in the FAS. [d] Assessed in the FAS-I (OAB wet patients only). [e] Key secondary endpoint.
Source: Staskin (2020) (8), Clinical Study Report (121)

Figure 12. LS mean change from baseline in (A) average daily number of total urgency episodes (B) incontinence episodes (FAS-I) and (C) average volume voided per micturition (FAS) over 12 Weeks, EMPOWUR study



Abbreviations: FAS = full analysis set; FAS-I = full analysis set for incontinence; LS = least squares; SE = standard error.
Note: ** denotes p<0.01, *** denotes p<0.001 for vibegron vs. placebo using a mixed model for repeated measures
Source: adapted from Staskin (2020) (8) and Frankel (2020) (109)

Figure 13. Proportion of OAB wet patients who had a ≥75% reduction in average daily number of UUI episodes (FAS-I) and proportion of patients who had a ≥50% reduction in average daily number of urgency episodes (FAS) at Week 12, EMPOWUR study.

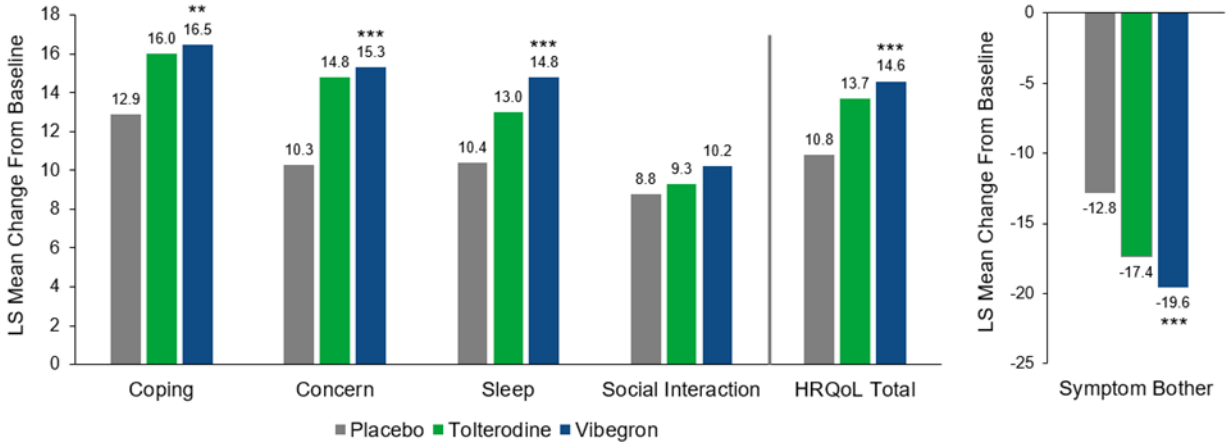


Abbreviations: CMH = Cochran-Mantel-Haenszel; FAS = full analysis set; FAS-I = full analysis set for incontinence; OAB = overactive bladder; SE = standard error; UUI = urge urinary incontinence.
Note: * denotes p<0.05 and *** denotes p<0.001 for vibegron vs. placebo using the CMH risk difference estimate.
Source: Staskin (2020) (8), Clinical Study Report (121).

B.3.6.1.3 HRQoL and utility outcomes

The EMPOWUR trial used PROMs to assess QoL and response rates. At week 12 of treatment, vibegron was associated with significantly greater improvements from baseline compared with placebo in OAB-q subscores of coping, concern, sleep, HRQoL, and symptom bother (all p<0.01) (Figure 14) (111). In addition, a *post hoc* analysis showed that a greater proportion of patients in the vibegron group compared with the placebo group achieved the best response score on all patient global impression (PGI) endpoints after 12 weeks of treatment (p<0.05) (Figure 15).

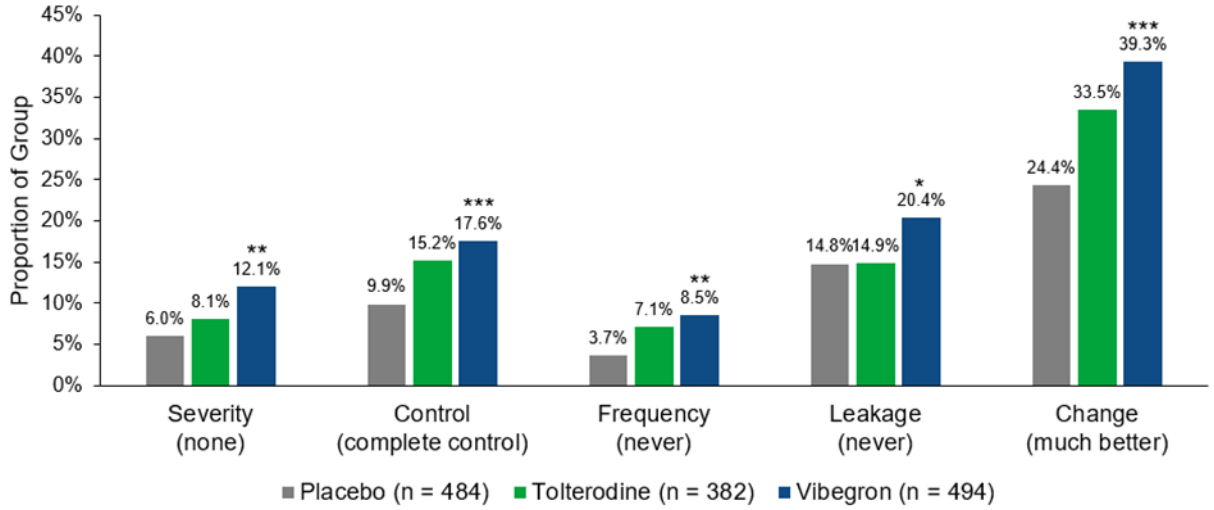
Figure 14. LS mean change from baseline to Week 12 in OAB-q scores for coping, concern, sleep, social interaction, HRQoL total, and symptom bother, EMPOWUR study (FAS).



Abbreviations: FAS = full analysis set; HRQoL = health-related quality of life; LS = least squares; OAB = overactive bladder; OAB-q = overactive bladder questionnaire.
Note: OAB-q domains other than coping were exploratory endpoints that were prespecified but were not adjusted for multiplicity; these endpoints were assigned supportive p-values. ** denotes p<0.01 and *** denotes p<0.001 for vibegron vs. placebo. For coping, concern, sleep, social interaction and HRQoL total, increases indicate improvement; for symptom bother, decreases indicate improvement.
Source: adapted from Frankel, Varano (111).

The EMPOWUR study reported changes in EQ-5D scores from baseline compared with 12 weeks. This was exploratory in nature and reported as descriptive analyses. Data from the five domains of the EQ-5D were reported alongside visual analogue scale (VAS) scores ranging from 0 mm (worst health) to 100 mm (best health) and a single index utility score (Table 9). There were only small changes to EQ-5D over the course of the study, and there were no notable differences between the intervention groups. Generic HRQoL measures such as EQ-5D are known to be relatively insensitive to changes in OAB (122).

Figure 15. Post-hoc analysis of proportion of patients reporting the best response for each PGI measure at Week 12, EMPOWUR study (FAS).



Abbreviations: FAS = full analysis set; PGI = patient global impression.
Note: * denotes *P* < 0.05, ** denotes *P* < 0.01, and *** denotes *P* < 0.001 for vibegron vs. placebo. Percentages were calculated based on the number of patients included in the regression model, where each patient had values at baseline and at Week 12.
Source: adapted from Frankel, Varano (111).

Table 9. Change in EQ-5D VAS and index score between baseline and 12 weeks in EMPOWUR trial.

	EQ-5D parameter	Placebo	Vibegron	Tolterodine
Index score	Mean (SD)	0.0162 (0.12756)	0.0300 (0.11950)	0.0312 (0.11379)
	Median (IQR)	0.000 (-0.034, 0.073)	0.000 (-0.005, 0.090)	0.000 (-0.012, 0.095)
VAS (mm)	Mean (SD)	1.7 (14.20)	3.4 (13.28)	2.4 (12.67)
	Median (IQR)	0.0 (-5, 10)	0.0 (-5, 10)	0.0 (-5, 10)
Abbreviations: IQR, interquartile range; SD, standard deviation; VAS, visual analogue scale				

Staskin *et al*. (2023) reported on a *post hoc* subgroup analyses on patients enrolled in the EMPOWUR trial (123). Patients were stratified according to three levels of continence, namely dry (0 UUI episodes), episodic continence (between 0 and 1 daily episodes of UUI) and incontinent (≥1 daily episode of continence). The authors reported that, whilst all the patient subgroups reported significant benefits in terms of OAB-q and PGI, those with fewer baseline episodes of incontinence tended to experience the greatest benefits.

B.3.6.1.1. EMPOWUR extension study

Overall, 506 patients were randomised, 505 (99.8%) received ≥1 dose of study treatment, and 430 (85.0%) completed the study (108). Of those who received ≥1 dose of study treatment, 273 were treated with vibegron and 232 received tolterodine. Baseline characteristics were similar between groups. The mean age was 61.1 years and 46.5% of patients were aged ≥65 years. Most patients were female (78.2%) and met criteria for wet OAB (78.2%).

Once daily vibegron demonstrated favourable safety and tolerability in patients with OAB consistent with the results of the 12-week study. Patients treated with vibegron also had sustained efficacy over 52 weeks. The primary efficacy endpoints from EMPOWUR (micturitions and UUI), urgency episodes, and total incontinence episodes CFB at 52 weeks are reported in Table 10. The primary outcomes are illustrated in Figure 16. Vibegron was associated with statistically superior improvements compared with placebo and numerically superior improvements compared with tolterodine. Of note, 41% of patients treated with vibegron were effectively 'dry' at week 52 (i.e. had zero incontinence episodes over 7 days), as evidenced by a 100% reduction in average daily number of UUI episodes.

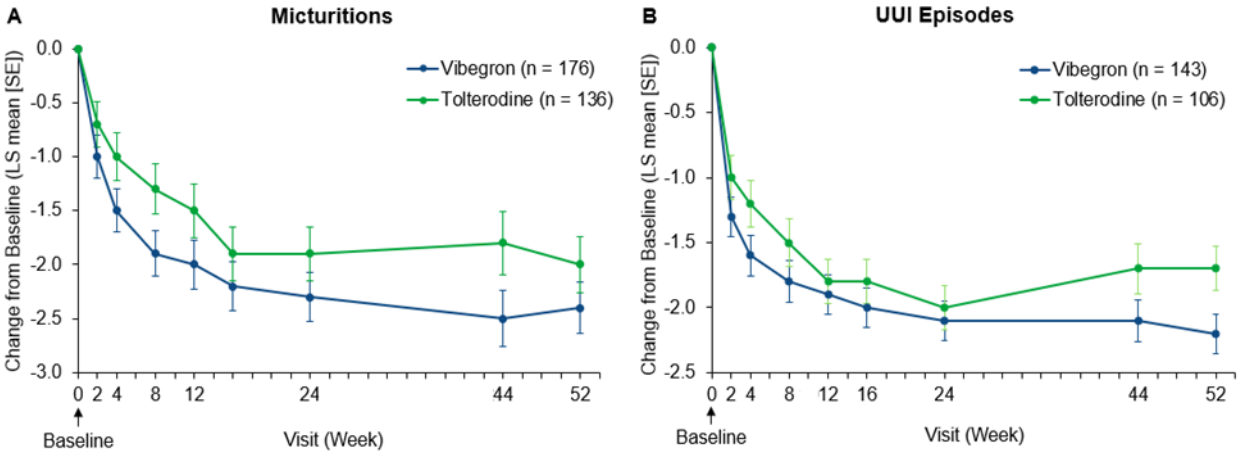
Table 10. LS mean change from baseline to Week 52 for efficacy endpoints among patients receiving either vibegron or tolterodine, EMPOWUR-EXT (FAS-Ext or FAS-I-Ext datasets).

Endpoint	Vibegron	n	95% CI	Tolterodine	n	95% CI
Micturitions[a]	-2.4	152	-2.9, -2.0	-2.0	120	-2.5, -1.5
UUI Episodes[b]	-2.2	125	-2.5, -1.9	-1.7	91	-2.0, -1.3
Urgency Episodes[a]	-3.4	152	-4.0, -2.7	-3.2	120	-4.0, -2.5
Total Incontinence Episodes[b]	-2.5	125	-2.8, -2.2	-1.9	91	-2.3, -1.6

Abbreviations: CI = confidence interval; FAS-Ext = full analysis set extension; FAS-I-Ext = full analysis set extension for incontinence; LS = least squares; OAB = overactive bladder; UUI = urge urinary incontinence.
Source: Staskin, Frankel (124).
- Note: all outcomes represent change in average daily number of episodes.

a Assessed in FAS-Ext. b Assessed in FAS-I-Ext (OAB wet patients only).
Source: Staskin (2021) (108)

Figure 16. LS mean change from baseline in average daily number of (A) micturitions (FAS-Ext) and (B) UUI episodes (FAS-I-Ext) over 52 weeks, EMPOWUR-EXT study.



Abbreviations: FAS-Ext = full analysis set extension; FAS-I-Ext = full analysis set for incontinence extension; LS = least squares; SE = standard error; UUI = urge urinary incontinence.
Source: adapted from Staskin (2021) (108).

B.3.6.2 Other studies

B.3.6.2.1 Yoshida et al. (2018)

A total of 1,232 patients were randomised, 1,224 of whom were included in the FAS (104). The baseline characteristics were well balanced across study groups, with mean patient age ranging from 58.0 to 59.7 years across groups and the proportion of females ranging from 89.7% to 90.3%. The proportion of patients with wet OAB ranged from 77.2% to 79.5% across groups and the mean duration of OAB symptoms ranged from 56.4 months to 69.8 months. Most patients had not received OAB therapy within the last year.

Treatment with vibegron was associated with significant improvements on the primary endpoint and all secondary endpoints compared with placebo (104) (Table 11). These improvements were observed across all endpoints by the first visit after initiating study treatment (i.e., by week 4) and were sustained throughout the study. In addition, the proportions of patients with normalisation of micturition and resolution of urgency, episodes of UUI and incontinence were significantly higher in the vibegron groups compared with the placebo group. Treatment with vibegron was associated with significantly greater improvements in QoL and patient satisfaction compared with placebo. Vibegron was also associated with significantly greater improvements from baseline to week 12 compared with placebo in the frequency of nocturnal voiding, change in volume per nocturnal void, change in volume of the first nocturnal voiding, and hours of undisturbed sleep (112).

Table 11. Efficacy results on the primary and secondary endpoints, placebo-adjusted LS mean change from baseline to Week 12, Yoshida *et al.* (2018, full analysis set).

Endpoint (placebo-adjusted LS mean change from baseline [95% CI])[a]	Vibegron 50 mg	n	*p*-Value	Vibegron 100 mg	n	*p*-Value
Primary Endpoint						
Micturitions	-0.86 (-1.12, -0.60)	370	<0.001	-0.81 (-1.07, -0.55)	368	<0.001
Secondary Endpoints						
UUI Episodes	-0.27 (-0.44, -0.10)	329	0.001	-0.39 (-0.55, -0.22)	327	<0.001
Urgency Episodes	-0.51 (-0.76, -0.25)	370	<0.001	-0.67 (-0.93, -0.42)	368	<0.001
Incontinence Episodes	-0.30 (-0.49, -0.12)	329	0.001	-0.43 (-0.61, -0.24)	327	<0.001
Nocturia Episodes	-0.11 (-0.21, -0.02)	312	0.016	-0.16 (-0.25, -0.06)	304	0.001
Voided Volume per Micturition, mL	25.76 (20.05, 31.46)	370	<0.001	22.16 (16.44, 27.89)	368	<0.001

Abbreviations: CI = confidence interval; LS = least squares; UUI = urge urinary incontinence.
Note: Statistical analyses were not conducted to compare imidafenacin with either placebo or vibegron; therefore, imidafenacin is not included in this table. All outcomes except voided volume are average daily number of episodes.
[a] Estimated difference in LS mean between the vibegron and placebo groups.

B.3.6.2.2 Mitcheson et al. (2019)

In the study by Mitcheson, 1,395 patients were randomised, 1,393 (99.9%) received study medications, and 1,324 (94.9%) completed the trial (103). Baseline patient characteristics were generally well balanced across study groups. Mean patient age ranged from 55.5 to 60.3 years across study groups and 86.0% to 93.3% of patients were female (103). Patients with wet OAB comprised 78.2% to 83.4% of study groups and 31.2% to 42.0% of patients had previously received anticholinergic therapy for OAB.

The most relevant phase of this trial was Part 2 of the study. Vibegron, at a dose of 100 mg, was associated with a significantly greater reduction from baseline to week 4 compared with placebo in average daily number of micturitions (LS mean difference: -0.79; p=0.009). Additionally, the combination of vibegron with tolterodine was associated with significantly greater reductions from baseline to Week 4 compared with tolterodine alone in terms of daily number of micturitions (LS mean difference: -0.91; p<0.001), urgency episodes (LS mean difference: -1.27; p<0.001), UUI episodes (LS mean difference: -0.53; p=0.027), and total incontinence episodes (LS mean difference: -0.51; p=0.038).

B.3.6.2.3 Kinjo et al. (2023)

In the study by Kinjo *et al.* (2023), 211 patients were eligible for the study, and of these 199 of these patients were randomised to either the mirabegron group (n=97) or vibegron group (n=102). In total, 82 and 83 patients in each arm were eligible for the 12-week analysis (see Appendix D.1.2.4). The study was completed by 84.5% of the original patient population in the mirabegron group and 81.4% in the vibegron group.

Both mirabegron and vibegron were associated with statistically significant improvements in OABSS and QoL at 4 and 12 weeks compared with baseline, but there was no significant difference compared with each other. The secondary outcomes reported in the study, which are directly relevant to the decision problem, are reported in Table 12. When considering the relative efficacy of mirabegron and vibegron reported by Kinjo *et al.* (2023), it should be considered that vibegron was administered at a lower dose than will be used in the UK, whereas mirabegron was administered at the UK licensed dose.

Table 12. Head-to head efficacy comparison of mirabegron (50 mg) vs. vibegron (50 mg) from Kinjo *et al.* (2023).

Outcome	Mirabegron 50 mg		Vibegron 50 mg		Statistical significance*
	Baseline	12 weeks	Baseline	12 weeks	
Mean daily micturitions (SD)	9.39 (2.65)	8.34 (2.28)	9.30 (2.98)	7.87 (1.87)	p=0.929
Mean episodes of UUI (SD)	1.76 (1.68)	0.6 (1.053)	1.78 (1.60)	0.26 (0.57)	p=0.440

Episodes of urgency (SD)	2.29 (1.69)	0.92 (1.11)	2.66 (1.74)	0.92 (1.25)	p=0.641
Abbreviations: SD, standard deviation; UUI, urinary urge incontinence * Statistical significance between treatment arms (Student's t test). All values compared with baseline using repeated measures of variance were p<0.001.					

B.3.6.2.4 Sato et al. (2023)

In the trial reported by Sato *et al.* (2022), a total of 104 patients were randomised to the mirabegron 50 mg arm (n=52); and vibegron 50 mg arm (n=52). Nine of the 104 patients withdrew during the treatment period (6 in mirabegron rm, 3 in vibegron arm). Regarding the primary outcome, vibegron was associated with a decrease in total OABSS of -4.26 (95% -5.21 to -3.32) at 12 weeks compared with baseline, whereas mirabegron reduced OABSS by -4.50 (95% CI -5.42 to -3.58). This was a non-significant numerical difference of -0.31 (95% CI -1.66 to 1.04) in favour of vibegron (p=0.717). There were no significant differences between groups in any of the secondary efficacy outcomes.

B.3.6.2.4 Shin et al. (2023)

In the trial reported by Shin et al. (2023) (106), the baseline mean number of micturitions per day was 11.63±5.14 (SD) in the intervention group, compared with 10.96±2.47 in the placebo group. Following 12 weeks treatment, this had reduced to 9.04±3.32 in the vibegron group, and 9.57±2.41 in the placebo group. The LSM difference between groups was -1.17 (95% -1.91 to -0.43, p=0.0021) in favour of vibegron. In terms of UUIs, the LSM difference between the groups after 12 weeks was -2.25 (95% CI to -0.52) in favour of vibegron (p=0.0019). There were also significant differences reported in favour of mirabegron for total incontinence episodes (p=0.0031) and volume of urine voided per micturition, which was 25.89 mL (95% CI 12.79 to 39.00 mL) greater in the vibegron group (p=0.0001). There were numerically fewer episodes of nocturia associated with vibegron (-0.14, 95% CI -0.39 to 0.12), although this was not significant (p=0.2948).

There were immediate and significant improvements in total OABSS at 4 and 12 weeks.

In the PGI assessment, 88.24% of patients were satisfied (PGI ≤3) (P=0.0037) and 68.24% of patients were very satisfied (PGI ≤2) with the treatment (P<0.0001).

B.3.6.2.4 Wada et al. (2023)

Wada et al. (2023) (107) reported that both mirabegron and vibegron significantly improved OABSS (-4.3±3.4 vs -5.3±3.4, per day, respectively), daytime frequency (-1.0±2.0 vs -1.6±2.0 per day), nighttime frequency (-0.3±1.0 vs -0.4±0.9 per night), mean volume voided (35±47 vs 42±47 ml) and maximum voided volume (55±96 vs 57±109 mL). There were no statistically significant differences between mirabegron and vibegron in these parameters.

Following the completion of the trial, 15 and 33 of the 57 patients preferred mirabegron (26%) and vibegron (58%), respectively, with 9 patients (16%) stating no preference.

B.3.7 Subgroup analysis

B.3.7.1 Men and women

In the EMPOWUR trial, sex (female vs male) was a stratification factor for randomisation and was a prespecified subgroup analysis. The co-primary outcomes (number of micturitions and episodes of UUI) are reported in Table 13, and for daily micturitions, taken from the FAS, reported graphically inFigure 17. Whilst statistical significance over placebo was retained in the female population, results for males were non-significant. This may have been due to type II error relating to the relatively small sample size in this population (total male sample size 217, 14.8% of patients randomised).

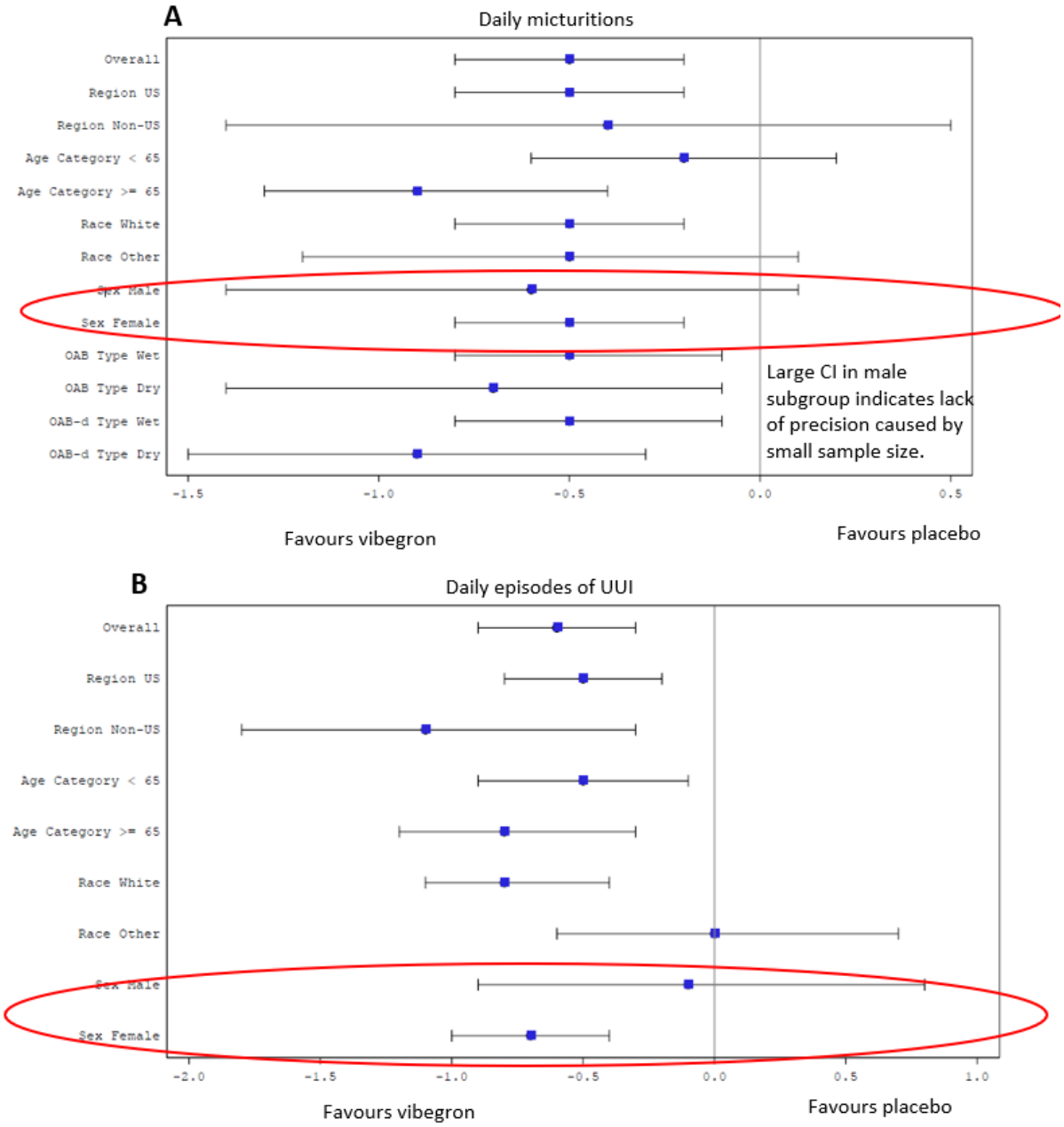
The other studies identified did not report subgroup analyses for differences in sex (102-104).

Table 13. Subgroup MMRM analysis of the co-primary outcomes at 12 weeks by sex (male or female) from EMPOWUR study.

Sex	Outcome	Placebo	Vibegron	Tolterodine
Change in daily micturitions				
Male	Mean change from baseline (95% CI)	-1.1 (-1.7 to -0.5) n=69	-1.7 (-3.3 to -1.2) n=75	-1.0 (-1.6 to -0.4) n=65
	Active difference*		-0.6 (-1.4 to 0.1)	0.1 (-0.7 to 0.9)
Female	Mean change from baseline (95% CI)	-1.4 (-1.7 to -1.1) n=406	-1.9 (-2.2 to -1.6) n=417	-1.7 (-2.0 to -1.5) n=318
	Active difference*		-0.5 (-0.8 to -0.2)	-0.3 (-0.7 to 0.0)
Change in daily episodes of UUI (FAS-I dataset)				
Male	Mean change from baseline (SD)	-1.57 (2.580) n=38	-1.35 (1.865) n=42	-2.08 (1.931) n=33
Female	Change from baseline (SD)	-1.44 (2.359) n=334	-2.1 (2.552) n=341	-1.71 (2.348) n=253

Abbreviations: CI, confidence intervals, FAS, full analysis set; FAS-I full analysis set in people with incontinence (wet OAB); MMRM, mixed model repeated measures.
* Difference between intervention and placebo.

Figure 17. Forest plot showing subgroup analysis of the effect of sex on the change in daily number of micturitions (A) and daily episodes of UUI (B).



B.3.7.2 Previous treatment

Subgroup analysis of previous treatment was performed *post hoc* in the EMPOWUR trial. Staskin *et al.* (2020) reported subgroup analyses that showed that the efficacy of vibegron was maintained among patients with prior exposure to OAB pharmacotherapy (8) (Table 14). Patients in the vibegron group with a history of prior anticholinergic use reported statistically significant improvements in the average daily number of micturitions of -2.1 (95% CI -2.6 to -1.6) and UUI episodes of -1.5 (95% CI -2.0 to 1.0) from baseline to week 12. These

outcomes were numerically greater than those observed for placebo in number of micturitions (-1.3, 95% CI -1.8 to -0.8) and UUI episodes (-0.8 , 95% CI -1.3 to -0.3).

No statistical testing was conducted for these subgroups in the EMPOWUR trial due to the limited sample size (116). However, *post hoc* statistical analyses using the unpaired t test with pooled variance showed these results approached statistical significance, with values of p-0.0674 and p=0.07 for micturitions and UUIs, respectively. It is important to consider that EMPOWUR was not powered for subgroup analyses and it is likely significance was not reached due to type 2 error (125). These data are represented graphically in Figure 18. In summary, these subgroup analyses reported vibegron was effective regardless of previous anti-muscarinic treatment, with no evidence of difference between these groups.

Patients in the vibegron group with a prior history of mirabegron use also had improvements in the average daily number of micturitions (-2.8 ± 3.8) and UUI episodes (-1.6 ± 2.6) from baseline to week 12. These reductions were numerically greater than those observed in the placebo group for both micturitions (0.0 ± 2.2]) and UUI episodes (-0.3 ± 1.6)

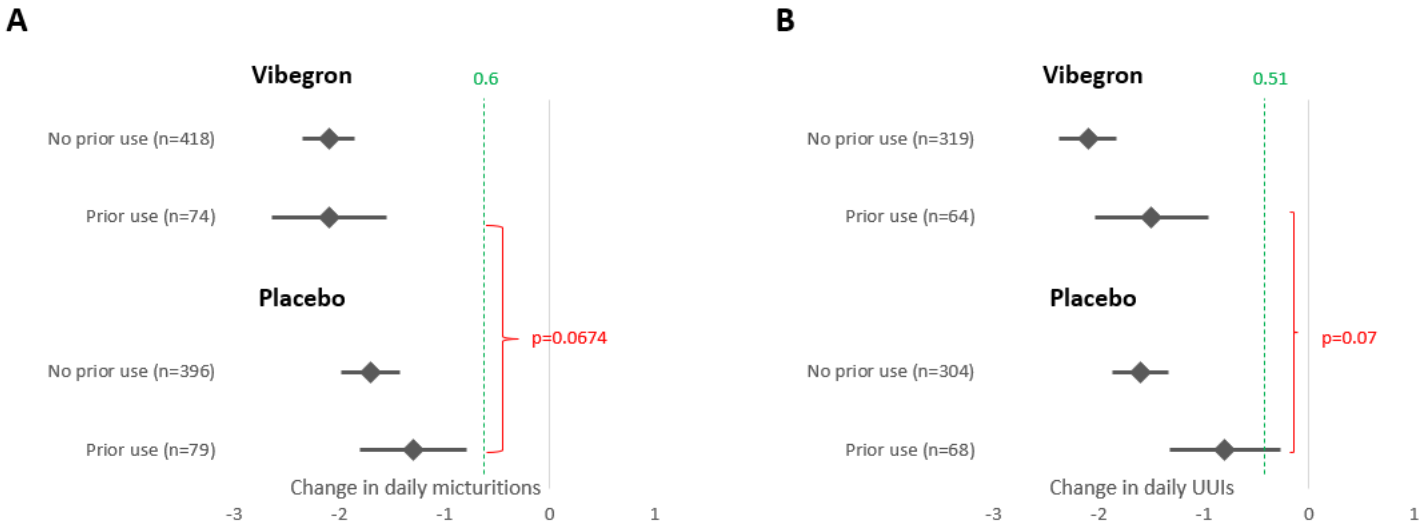
Table 14. Mean (SD) change from baseline to Week 12 in co-primary outcomes by type of prior OAB pharmacotherapy, EMPOWUR study (FAS and FAS-I).

Subgroup	Placebo	n	Vibegron	n	Tolterodine	n
Co-primary outcome: daily number of micturitions (FAS dataset)						
Prior anticholinergic use	-1.3 (2.3)	79	-2.0 (2.4)	74	-1.5 (1.9)	48
No prior anticholinergic use	-1.7 (2.8)	396	-2.1 (2.6)	418	-1.8 (2.7)	330
Prior mirabegron use	0.0 (2.2)	25	-2.8 (3.8)	18	-1.3 (2.0)	31
No prior mirabegron use	-1.7 (2.7)	450	-2.0 (2.5)	474	-1.8 (2.7)	347
Co-primary outcome: daily episodes of UUI (FAS-I dataset)						
Prior anticholinergic use	-0.8 (2.2)	68	-1.5 (2.2)	64	-1.0 (1.8)	39
No prior anticholinergic use	-1.6 (2.4)	304	-2.1 (2.5)	319	-1.9 (2.4)	247
Prior mirabegron use	-0.3 (1.6)	21	-1.6 (2.6)	14	-0.7 (1.4)	18
No prior mirabegron use	-1.5 (2.4)	351	-2.0 (2.5)	369	-1.8 (2.3)	268

Abbreviations: FAS, full analysis set; FAS-I, full analysis set for incontinence; OAB, Overactive Bladder; SD,standard deviation; UUI, urge urinary incontinence.

The other studies identified did not report subgroup analyses for differences in prior treatment (102-104).

Figure 18. Forest plot showing subgroup analyses of patients who were treatment naïve or who had previously received anti-muscarinic drugs for the outcomes of A) Daily micturitions B) Episodes of UUI.



Abbreviations: UUI, urgency urinary incontinence

The Forest plots report the change from baseline ion the respective subgroups. The p values (red) are the differences between treatment naïve vibegron and treatment naïve placebo groups. The green values report the between-group differences used for the power calculations in EMPOWUR (change from baseline). This is the implicit minimally important difference for these outcomes.

B.3.8 Meta-analysis

No meta-analyses were undertaken due to heterogeneity in the included studies, particularly concerning the dose of vibegron.

B.3.9 Indirect and mixed treatment comparisons

Summary

- As there was a lack of directly applicable head-to head studies available comparing vibegron (75 mg) with mirabegron, an ITC was performed. Studies informing the ITC were identified from the SLR (Section B.3.1).
- Ten studies were identified which were suitable for analyses. These included the EMPOWUR and EMPOWUR-EXT studies, and eight studies on mirabegron. These studies were used to inform multiple networks, with key outcomes relevant to the decision problem reported.
- In terms of the primary outcomes of interest, the daily number of micturitions and number of UUI episodes, there was no statistically significant difference between vibegron and mirabegron observed at 12 weeks or any other time point.
- Vibegron was associated with a statistically significant increase in the volume of urine voided compared with mirabegron at 12 weeks and a trend to significance at other time points, suggesting possible improved efficacy in this objective outcome.
- There was no evidence of a difference between vibegron and mirabegron in terms of serious adverse events (SAEs), discontinuation due to AEs, headache, hypertension, UTI, dry mouth, or constipation. Whilst the analyses reported vibegron may be associated with a greater number of overall AEs, it is likely this was due to study heterogeneity

B.3.9.1 Methods

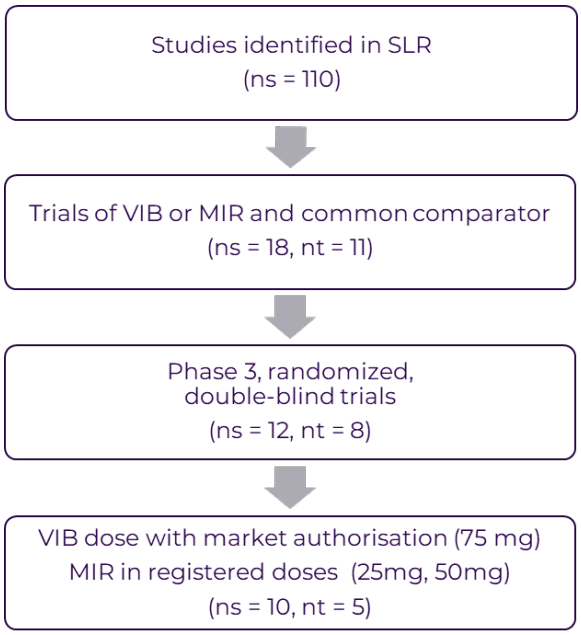
The objective of this ITC was to compare the efficacy and safety of vibegron, used at a dose of 75 mg in line with anticipated UK market authorisation, with mirabegron in registered European Medicines Agency (EMA) dosages (25 mg or 50 mg) in patients with OAB. This was necessary as the main body of evidence for both drugs did not include head-to-head

studies. There are no head-to-head trials of vibegron and mirabegron using the anticipated licensed 75mg dose of vibegron.

B.3.9.1.1 Study selection

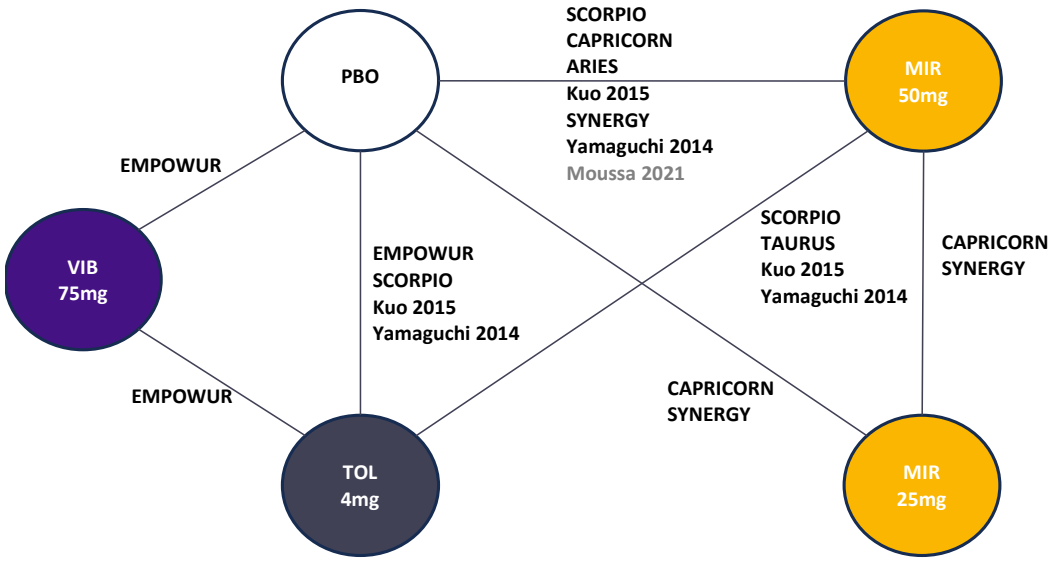
The initial identification of studies suitable for the ITC was based on the SLR (97), described in Section B.3.1 and Appendix D.1.1. The application of the additional inclusion/exclusion criteria for the ITC reduced the one 118 studies included in SLR (original and updated searches) to 10. As a result, eight studies were excluded from the networks due to being the incorrect study phase, having inadequate methodology (e.g. not masked), inappropriate population, or not having suitable comparators. The obtained networks link vibegron 75mg and mirabegron 25mg or 50mg through placebo and tolterodine ER 4 mg, consist of five treatments and are spanned by ten studies (Figure 19). Most of the outcomes studied were derived from the network illustrated in with placebo being the common anchor. For outcomes at 4,8, and 12 weeks, full networks were usually available (Figure 20Figure 20). There was some variation in the specific studies informing the network, and notably, outcomes reported at 52 weeks more restricted (Figure 21).

Figure 19. Selection of studies for ITC.



Abbreviations: MIR, mirabegron; ns, number of studies; nt, number of treatments; SLR, systematic literature review; VIB, vibegron.

Figure 20. Typical network used in the ITC 12 (weeks).



Abbreviations: ITC, indirect treatment comparison; MIR, mirabegron; PBO, placebo TOL, tolterodine; VIB, Vibegron.

This specific network is the comparison of daily micturitions at 12 weeks.

Figure 21.Typical network used in the ITC (52 weeks).

Abbreviations: ITC, indirect treatment comparison; MIR, mirabegron; TOL, tolterodine; VIB, Vibegron.

B.3.9.1.2 Description of included studies

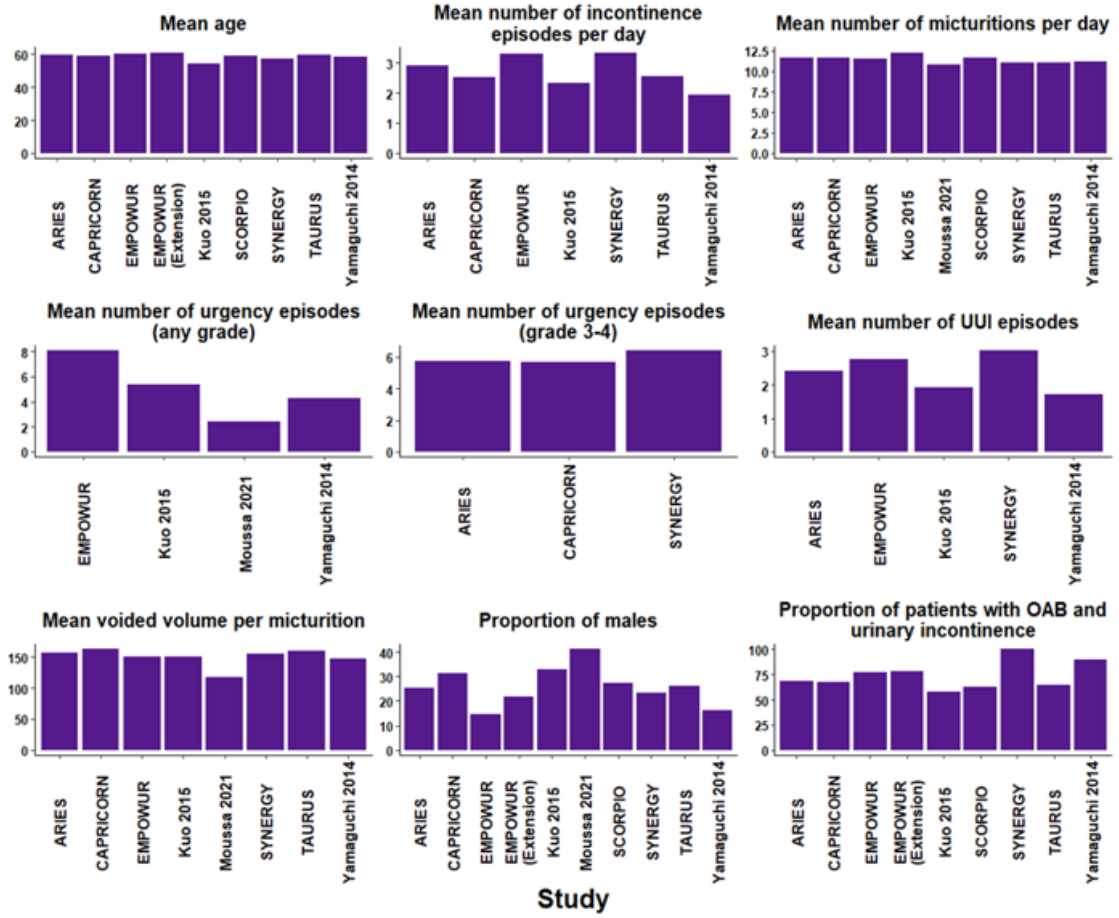
The studies included in the ITC are listed in Table 15. The baseline characteristics of the study participants are reported in Figure 22.

Table 15. Description of studies selected in ITC.

Study	Author and Year	Number of patients*	Study duration	Number of arms*	Treatment
ARIES	Nitti 2014 (126)	1328- (895)	12 weeks	3 (2)	•Mirabegron 50mg •Placebo
CAPRICORN	Herschorn 2013 (77)	1305	12 weeks	3	•Mirabegron 25mg •Mirabegron 50mg •Placebo
EMPOWUR	Staskin 2020 (8)	1463	12 weeks	3	•Vibegron 75mg •Tolterodine ER 4mg •Placebo
EMPOWUR (Extension)	Staskin 2021 (108)	505	40 weeks (52 in total)	2	•Vibegron 75mg •Tolterodine ER 4mg
Kuo 2015	Kuo 2015 (127)	994	12 weeks	3	•Mirabegron 50mg •Tolterodine ER 4mg •Placebo
Moussa 2021	Moussa 2021 (128)	95	12 weeks	2	•Mirabegron 50mg •Placebo
SCORPIO	Khullar 2013 (129)	1978 (1482)	12 weeks	4 (3)	•Mirabegron 50mg •Tolterodine ER 4mg •Placebo
SYNERGY	Herschorn 2017 (130)	3398 (1274)	12 weeks	6 (3)	•Mirabegron 25mg •Mirabegron 50mg •Placebo
TAURUS	Chapple 2013 (93)	2444 (1624)	12 months	3 (2)	•Mirabegron 50mg •Tolterodine ER 4mg
Yamaguchi 2014	Yamaguchi 2014 (131)	1105	12 weeks	3	•Mirabegron 50mg •Tolterodine 4mg •Placebo

Abbreviations: ER, extended release
*Value in parenthesis regards to data relevant for ITC

Figure 22. Baseline characteristics of the included studies.



B.3.9.1.3 Comparisons of interest

The ITC analysis was planned to compare vibegron 75mg with mirabegron 25mg or 50mg regarding efficacy and safety outcomes. Although several outcomes and time periods of treatment were analysed, for the purposes of this submission, the focus is placed on the efficacy outcomes used in the cost-effectiveness analysis of the TA290 company submission (90), described in Section B.2, and the overall safety and tolerability profiles of mirabegron and vibegron, namely:

- Change from baseline in mean number of micturitions per day at 12 weeks. This outcome was a co-primary endpoint of the EMPOWUR trial (FAS) (8) for vibegron and a coprimary endpoint of the MTC used to inform TA290 (90). Timepoints at 4, 8 and 52 weeks were also reported.
- Change from baseline in mean number of UUI episodes per day at 12 weeks. This outcome was a co-primary endpoint of the EMPOWUR trial (FAS-I) (8). Total incontinence was used in the cost-effectiveness model used in TA290 (90), as it was the co-primary outcome used in the SCORPIO trial (75). However, clinical experts indicated that UUI was now considered the more appropriate outcome, as it better reflected the mechanism of action of the drugs (10, 11). Although both endpoints are closely related, the effect observed in total incontinence may be attenuated through the occurrence of stress incontinence (10). Timepoints at 4, 8 and 52 weeks were also reported, with a full comparison of total incontinence provided in Appendix D.2.3.2 (Figure 18).
- Adverse events. Total AEs, SAEs, and AEs causing discontinuation were analysed. As AEs may not become apparent immediately, time periods at 12 weeks and 52 weeks were considered.
- Comparing AEs between studies is known to be problematic due to differences in the methodology of data collection, definitions, and classification (e.g. descriptions of severity) (132). Because of this, a granular approach was undertaken to compare AEs with an incidence of 2% or greater in the EMPOWUR trial, with the following safety outcomes included at 12 and 52 weeks:
    - Dry mouth
    - Hypertension
    - Urinary tract infection
    - Constipation
    - Headache

B.3.9.1.4 Statistical analyses

The ITC analysis was conducted in a Bayesian framework, using a Markov chain Monte Carlo (MCMC) method as implemented with the JAGS software packages(133). Further details of the methodology of the ITC are reported in Appendix D.2.2. Further results of the ITC (additional outcomes and time frames) are reported in Appendix D.2.3. The full ITC technical report is available on request (134).

B.3.9.2 Efficacy results

B.3.9.2.1 Number of micturitions per day

The number of micturitions per day were reported at four different timepoints: 4 weeks, 8 weeks, 12 weeks, and 52 weeks. In total, nine studies (including the EMPOWUR-EXT study) reported the effect of four active treatment arms (vibegron 75 mg, mirabegron 25 mg, mirabegron 50 mg, tolterodine 4 mg) and placebo at one or more of these timepoints (Appendix D.2.3.1.1).

For the primary end point of 12 weeks, eight studies reported mean CFB or difference in mean CFB in number of micturitions per day after 12 weeks. Data for the network analysis was provided for four active treatment arms (vibegron 75 mg, mirabegron 25 mg, mirabegron 50 mg, tolterodine 4 mg) as well as placebo. For these analyses, a random effects model was selected as the one associated with the lower deviance information criteria (DIC), with the exception being the outcome at 52 weeks, where only two studies informed the analysis meaning a fixed effects model was required. The random effects of the network meta-analysis (NMA) did not show any statistically significant differences in number of micturitions per day between vibegron 75mg and all comparators at 12 weeks. At this time point, there was almost no difference reported between mirabegron 50 mg and vibegron 75 mg, with a median difference of 0.1 additional micturitions associated with vibegron (credibility interval [CrI] -0.53 to 0.58). The point estimates for daily micturitions were either very similar or favoured vibegron for all comparator and time points (see Section B.3.9.5 Uncertainties in the indirect and mixed treatment comparisons.

There was no signal of difference between vibegron and the other interventions at the timepoints analysed (Figure 23). Comparative results of the NMA for all the treatments in the network are reported in Table 16. At 12 weeks, the network heterogeneity was assessed as being moderate, with a global I^2 of 51.4%. In addition, statistically significant inconsistency was identified between direct and indirect evidence, with Q_B = 13.09 and p value = 0.01. Further information on study heterogeneity, including at other time points, are presented in Appendix D.2.3.1.1.

Table 16. NMA results: Median difference in change from baseline in number of micturitions per day – 12 weeks

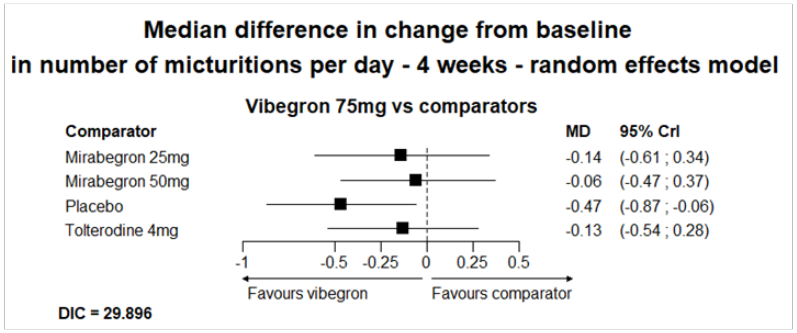
Mirabegron 25mg	Mirabegron 50mg	Placebo	Tolterodine 4mg	Vibegron 75mg
Mirabegron 25mg	-0.04 (-0.41, 0.32)	0.46 (0.10, 0.83)	0.17 (-0.23, 0.6)	**-0.03** **(-0.65, 0.61)**
0.04 (-0.32, 0.41)	Mirabegron 50mg	0.51 (0.29, 0.73)	0.21 (-0.02, 0.49)	**0.01** **(-0.53, 0.58)**
-0.46 (-0.83, -0.10)	-0.51 (-0.73, -0.29)	Placebo	-0.29 (-0.54, -0.02)	**-0.49** **(-1.02, 0.04)**
-0.17 (-0.6, 0.23)	-0.21 (-0.49, 0.02)	0.29 (0.02, 0.54)	Tolterodine 4mg	**-0.20** **(-0.74, 0.32)**
0.03 (-0.61, 0.65)	-0.01 (-0.58, 0.53)	0.49 (-0.04, 1.02)	0.20 (-0.32, 0.74)	**Vibegron 75mg**

Abbreviations: CrI, Credibility Interval; MD, Median Difference;

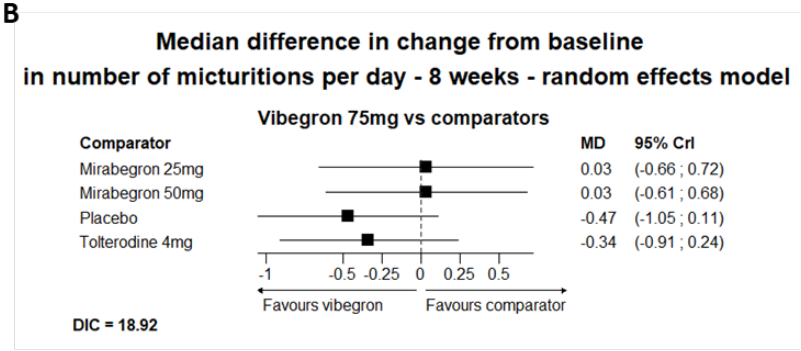
Legend: Results as MD (95% CrI). Cells of column X and row Y represent the comparison X vs Y, e.g. MD Mirabegron 25mg vs Mirabegron 50mg is 0.04 (-0.32, 0.41). The MDs < 0 are beneficial for the first drug in a comparison.

Figure 23. Forest plots comparing efficacy of treatments in reducing number of micturitions.

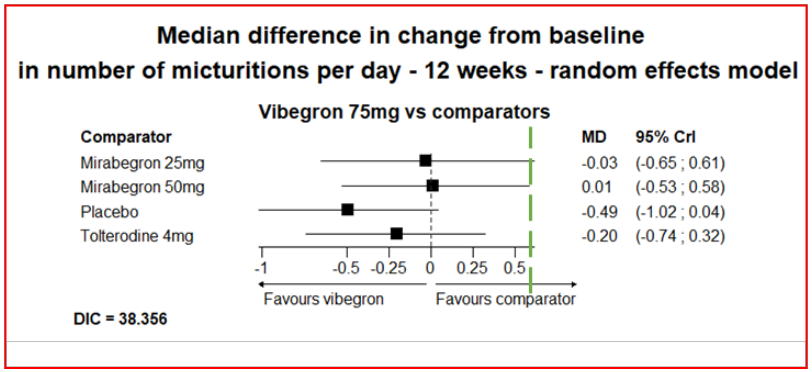
A



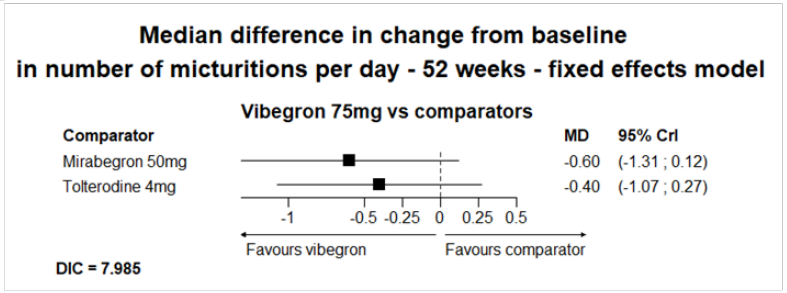
B



C



D



Abbreviations: CrI, credibility interval; DIC, deviance information criteria; MD, median difference.
Key: A, MD in number of micturitions from baseline at 4 weeks; B, MD in number of micturitions from baseline at 8 weeks; C, MD in number of micturitions from baseline at 12 weeks. This was the primary endpoint of the included studies, with the green broken line represents the between-group difference used to calculate the study sample size (0.6); D, MD in number of micturitions from baseline at 52 weeks (analysis comprised of 2 studies with tolterodine as the common comparator.

B.3.9.2.2 Number of UUI episodes

Seven studies reported mean CFB or difference in mean CFB in the number of UUI episodes after 12 weeks. The network links vibegron 75 mg, mirabegron 25 mg, mirabegron 50 mg, tolterodine 4mg and placebo. As with the number of micturitions, random-effects models were selected as being associated with the better fit for 4, 8 and 12 weeks and a fixed effects model used for 52 weeks. No statistically significant inconsistency was identified between direct and indirect evidence (Q_B = 0.56, p value = 0.97). No network heterogeneity was found as the global I^2 was equal to 0%

At 12 weeks, the NMA showed a statistically significant reduction in number of UUI episodes associated with vibegron 75 mg compared with placebo, with a median difference of -0.58 (95% CrI -0.93 to -0.22). There was a non-significant trend in favour of vibegron 75 mg compared with mirabegron 50 mg, with a median difference of -0.22 (95% CrI -0.59 to 0.15). It is notable that the point estimates for UUI favoured vibegron when compared with all comparators and at all time points.

There were no statistically significant differences at 12 weeks for comparisons of vibegron 75 mg compared with mirabegron 25 mg and compared with tolterodine 4 mg (Table 17). However, for these comparisons, the point estimates were numerically in favour of vibegron 75 mg. Similar results were observed for 4 and 8 weeks, and 52 weeks. When the NMA compared the EMPOWUR-EXT (108) and TAURUS trials (mirabegron 50 mg) (93), vibegron was found to be superior to tolterodine and mirabegron, with a median difference over the latter of -0.62 (95 CrI -1.13 to -0.10). These results are presented graphically in Figure 24.

Table 17. NMA results: Median difference in change from baseline in number of UUI episodes – 12 weeks

Mirabegron 25mg	**Mirabegron 50mg**	**Placebo**	**Tolterodine 4mg**	**Vibegron 75mg**
Mirabegron 25mg	-0.04 (-0.25, 0.16)	0.31 (0.10, 0.52)	-0.03 (-0.28, 0.22)	**-0.26** **(-0.67, 0.15)**
0.04 (-0.16, 0.25)	Mirabegron 50mg	0.36 (0.21, 0.50)	0.01 (-0.16, 0.18)	**-0.22** **(-0.59, 0.15)**
-0.31 (-0.52, -0.10)	-0.36 (-0.50, -0.21)	Placebo	-0.35 (-0.53, -0.17)	**-0.58** **(-0.93, -0.22)**
0.03 (-0.22, 0.28)	-0.01 (-0.18, 0.16)	0.35 (0.17, 0.53)	Tolterodine 4mg	**-0.23** **(-0.59, 0.13)**
0.26 (-0.15, 0.67)	0.22 (-0.15, 0.59)	0.58 (0.22, 0.93)	0.23 (-0.13, 0.59)	**Vibegron 75mg**
Abbreviations: CrI, Credibility Interval; MD, Median Difference;				

Legend: Results as MD (95% CrI). Cells of column X and row Y represent the comparison X vs Y, e.g. MD Mirabegron 25mg vs Mirabegron 50mg is 0.04 (-0.16, 0.25). The MDs < 0 are beneficial for the first drug in a comparison.

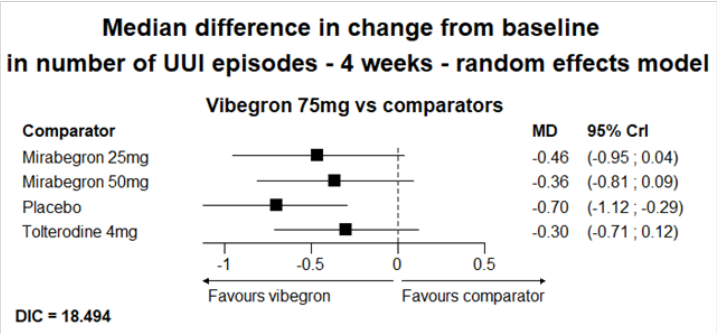
B.3.9.2.3 Other efficacy outcomes

Two other efficacy outcomes were assessed in the ITC, namely the total incidence of incontinence episodes and the volume of urine per micturition. Results for these outcomes at 12 weeks are illustrated graphically inFigure 25. Vibegron was associated with a significantly fewer episode of incontinence compared with placebo (MD -0.63, 95% CrI -1.03 to -0.24) and was close to significance compared with tolterodine (MD -0.37, 95% CrI -0.78 to 0.02). Vibegron was statistically superior compared with mirabegron (50 mg) at 52 weeks, with a median of -0.82 (95% CrI -1.38 to -0.26) (see Appendix D.3.2, Figure 18D). These results were closely related to those reported for UUIs, and give confidence to the equivalence of vibegron and mirabegron, as the incidence of incontinence was a parameter used to inform the CEM used in TA290 (Section B.2.1.2.1 Key efficacy inputs

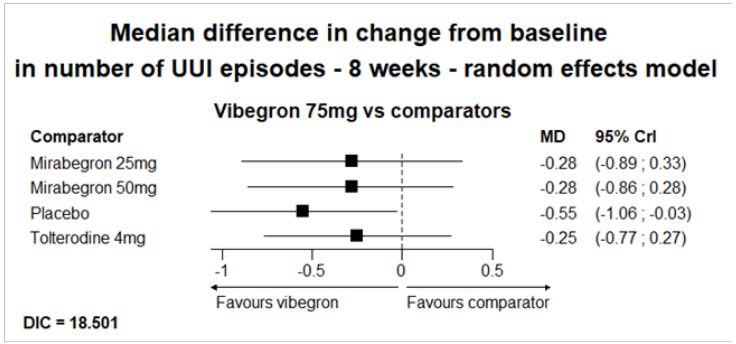
Vibegron significantly increased the volume of voided urine compared with mirabegron 25 mg (MD 17.41 mL, 95% CrI 7.75 to 27.47 mL), mirabegron 50 mg (MD 9.47 mL, 95% CrI 0.57 to 18.23 mL), and placebo (MD 21.87 mL, 95% CrI 13.22 to 30.44 mL). Full details on these analyses, including a description of heterogeneity and consistency, and results at 4, 8, and 52 weeks, are reported in Appendix D.2.3.2).

Figure 24. Forest plots comparing efficacy of treatments in reducing number of UUIs.

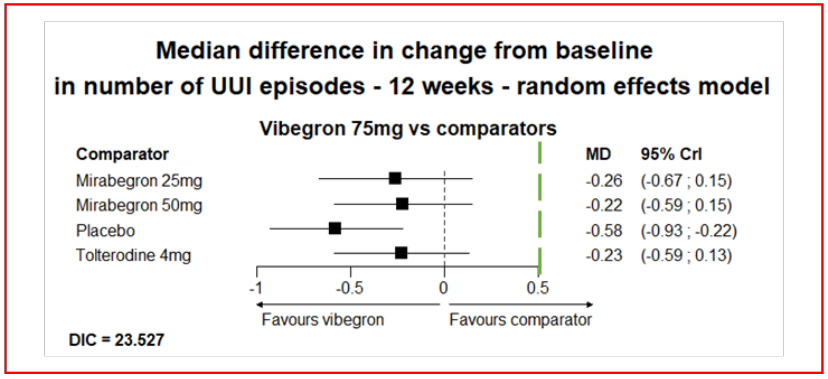
A



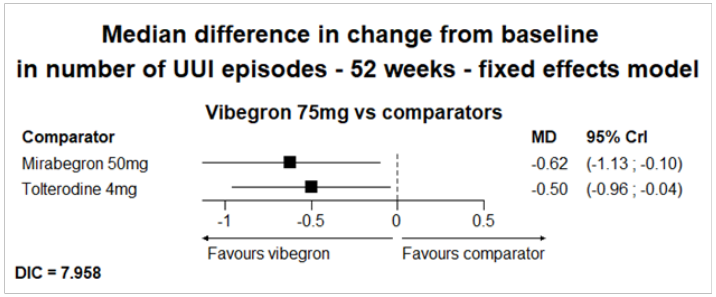
B



C

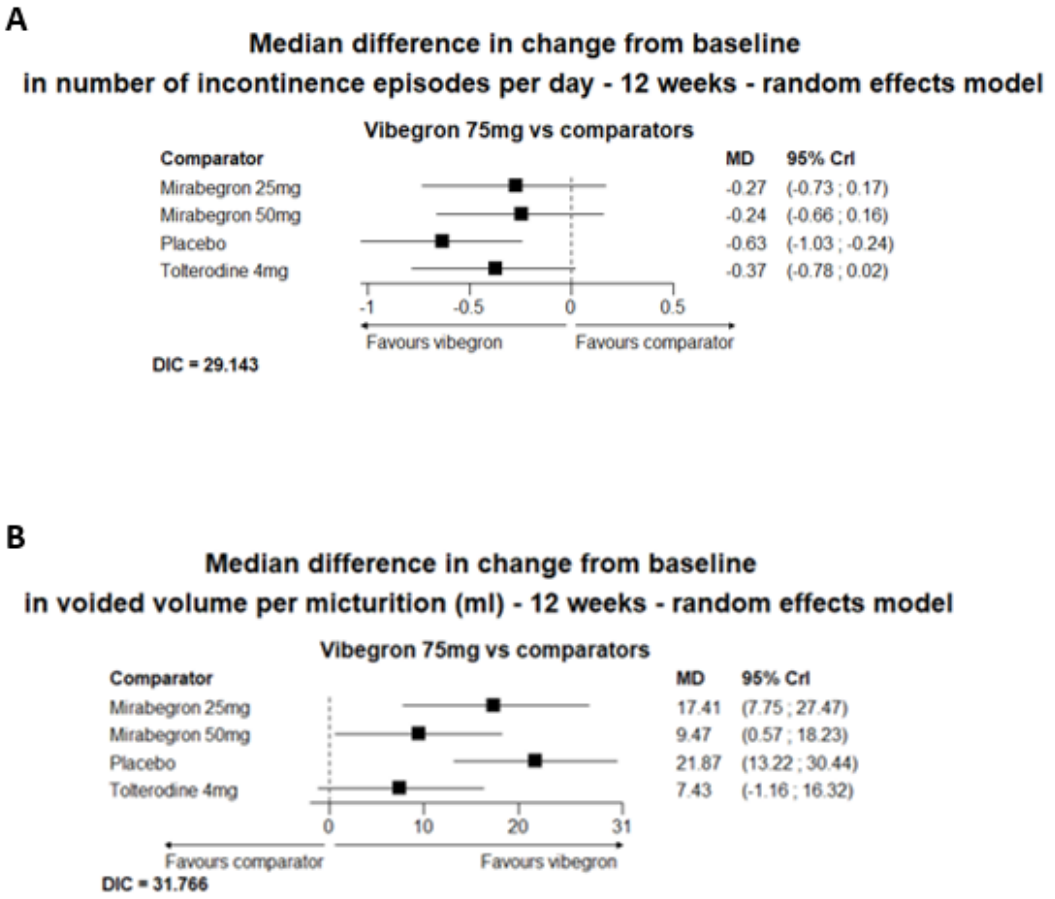


D



Abbreviations: CrI, credibility interval; DIC, deviance information criteria; MD, median difference; UUI, urinary urge incontinence.
Key: A, MD in number of UUI episodes from baseline at 4 weeks; B, MD in number of UUI episodes from baseline at 8 weeks; C, MD in number of UUI episodes from baseline at 12 weeks. This was the primary endpoint of the included studies, with the green broken line represents the between-group difference used to calculate the study sample size (0.51); D, MD in number of UUI episodes from baseline at 52 weeks (analysis comprised of 2 studies with tolterodine as the common comparator

Figure 25. Forest plot comparing efficacy of interventions in terms of total incontinence episodes and volume voided at 12 weeks.



Abbreviations: CrI, credibility interval; DIC, deviance information criteria; MD, mean difference;
Key: A, MD in number of incontinence episodes from baseline at 12 weeks; B, MD in volume of urine voided, change from baseline at 12 weeks (mL).

B.3.9.3 Global adverse events results

For outcomes on the global AEs (that is, aggregated data) associated with mirabegron and vibegron, data were available at 12 and 52 weeks (see Figure 20 and Figure 21Figure 21. for example networks). For data reporting at 12 weeks the random effects model proved to be the best fit. For data reporting at 52 weeks, a fixed effect model was used (this outcome point was always informed by the EMPOWUR-EXT (108) and TAURUS studies (93); therefore no heterogeneity data were reported. Results were reported as ORs, with results <1 indicative that intervention was associated with fewer AEs than the comparator. The key results for the analyses are reported graphically in Figure 26. For further details, see Appendix D.2.3.2.

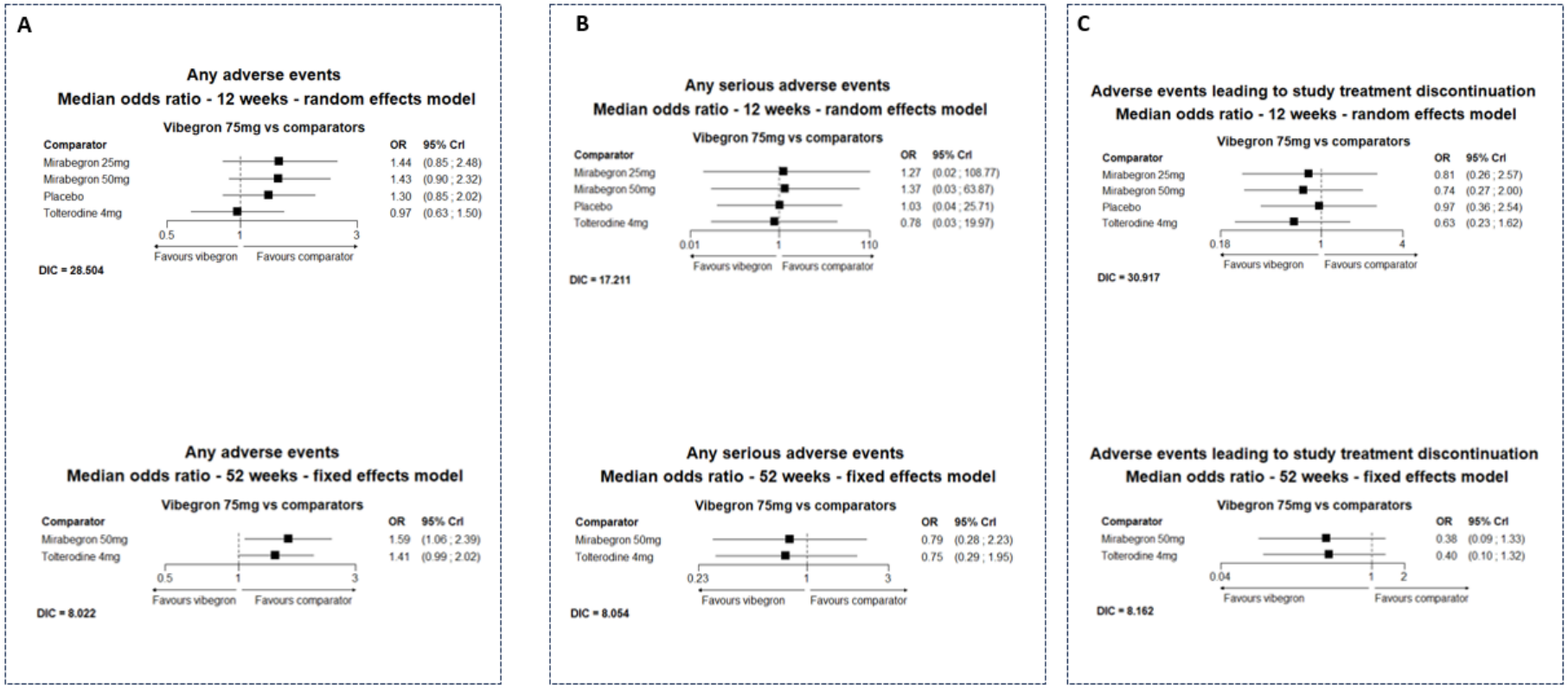
B.3.9.3.1 Adverse events due to any cause

Eight studies (EMPOWUR Extension and Moussa 2021 included) reported the number of patients with AEs due to any cause after 12 or 52 weeks. Depending on the timepoint the evidence was available for vibegron 75mg, mirabegron 25mg, mirabegron 50mg, tolterodine 4mg and placebo.

In total, six studies (including Moussa 2021) reported number of patients with AEs due to any cause after 12 weeks of treatment. All studies, with the exception of Moussa *et al.* (2021) (128) reported the data after additional follow-up period of 2 or 4 weeks. The network heterogeneity was assessed as being low, with a global I_2 of 44.7%. No statistically significant inconsistency was identified between direct and indirect evidence (Q_B= 0.55, p=0.76).

There was no significant difference between vibegron and mirabegron or tolterodine at 12 weeks. However, at 52 weeks, there were significantly more AEs due to any cause observed with vibegron compared with mirabegron 50 mg, with an OR of 1.59 (95% CrI 1.06 to 2.39). Results are presented in Figure 26A.

Figure 26. Forest plot showing global (aggregated) AEs at 12 and 52 weeks.



Abbreviations: AE, adverse event; CrI, credibility interval; DIC, deviance information criteria; OR, odds ratio.
Key: A, any AE; B, any serious AE; C, any AE adjudicated to have led to study discontinuation.

B.3.9.3.2 Serious adverse events

In total, four studies reported the number of patients with SAEs due to any cause after 12 weeks of treatment. All studies reported the data after additional follow-up period of 2 or 4 weeks. All studies, except for Moussa *et al.* (2021) (128), reported the data after additional follow-up period of 2 or 4 weeks. The results were available for all considered treatments, i.e., vibegron 75mg, mirabegron 25mg, mirabegron 50mg, tolterodine 4mg and placebo. Data for mirabegron 50 mg, tolterodine 4mg and vibegron (75 mg) were available at 12 weeks. The network heterogeneity was assessed as being low, with a global I^2 of 44.7%. More details are presented in Figure 26B. No statistically significant inconsistency was identified between direct and indirect evidence (Q_B = 0.55, p=0.76).

The were no statistically significant differences reported in the odds of having a SAE between vibegron and any of the comparators at 12 or 52 weeks (Figure 26. B). However, it should be noted that the case counts were relatively low for this outcome.

B.3.9.3.3 Adverse events leading to study treatment discontinuation

At 12 weeks, a total of seven studies reported number of patients with AEs leading to study treatment discontinuation. All studies reported the data after additional follow-up period of 2 or 4 weeks. The results were available for all considered treatments, i.e., vibegron 75mg, mirabegron 25mg, mirabegron 50mg, tolterodine 4mg and placebo. The network heterogeneity was assessed as being low, with a global I^2 of 0%. More details are presented in Appendix Figure 18. No statistically significant inconsistency was identified between direct and indirect evidence (Q_B = 4.73, p=0.19).

There were no statistically significant differences between vibegron and any of the comparators at 12 or 52 weeks. However, in all cases the point estimates were numerically in favour of vibegron (Figure 26C).

B.3.9.4 Specific adverse events results

The specific AEs were all reported at an incidence of ≥2% in the EMPOWUR (8) and EMPOWUR-EXT (108) studies. Results for 12 weeks are reported in Figure 27 and for 52 weeks in Figure 28. Note that because individual AEs were relatively uncommon, the case counts were low and credible intervals wide, denoting considerable uncertainty in the results.

B.3.9.4.1 Headache

In total, five studies reported number of patients with headache after 12 weeks of treatment. All studies, except for Moussa *et al.* (2021) (128), reported the data after additional follow-up

period of 2 or 4 weeks. The network heterogeneity was assessed as being low, with a global I^2 of 0%. No statistically significant inconsistency was identified between direct and indirect evidence (Q_B=3.44, p=0.33).

There was no significant difference observed between vibegron and the comparator interventions at 12 weeks (Figure 27A) or 52 weeks (Figure 28A).

B.3.9.4.2 Hypertension

In total, six studies reported number of patients with hypertension after 12 weeks of treatment. All studies reported the data after additional follow-up period of 2 or 4 weeks. No statistically significant inconsistency was identified between direct and indirect evidence (Q_B=2.31, p=0.51).

There was no significant difference observed between vibegron and the comparator interventions at 12 weeks (Figure 27B) or 52 weeks (Figure 28B).

B.3.9.4.3 Urinary tract infection

In total, five studies reported number of patients with UTI after 12 weeks of treatment. All studies reported the data after additional follow-up period of 2 or 4 weeks. The network heterogeneity was assessed as being low, with a global I^2 of 8.7%. No statistically significant inconsistency was identified between direct and indirect evidence (Q_B=1.42, p=0.70).

There was no significant difference observed between vibegron and the comparator interventions at 12 weeks (Figure 27C) or 52 weeks (Figure 28C), although it is noted that all the analyses numerically favoured vibegron.

B.3.9.4.4 Dry mouth

Eight studies reported number of patients with dry mouth after 12 weeks of treatment. All studies reported the data after additional follow-up period of 2 or 4 weeks. The results were available for all considered treatments, i.e., vibegron 75mg, mirabegron 25mg, mirabegron 50mg, tolterodine 4mg and placebo. The network heterogeneity was assessed as being moderate, with a global I^2 of 50.6%. No statistically significant inconsistency was identified between direct and indirect evidence (Q_B = 5.16, p=0.16).

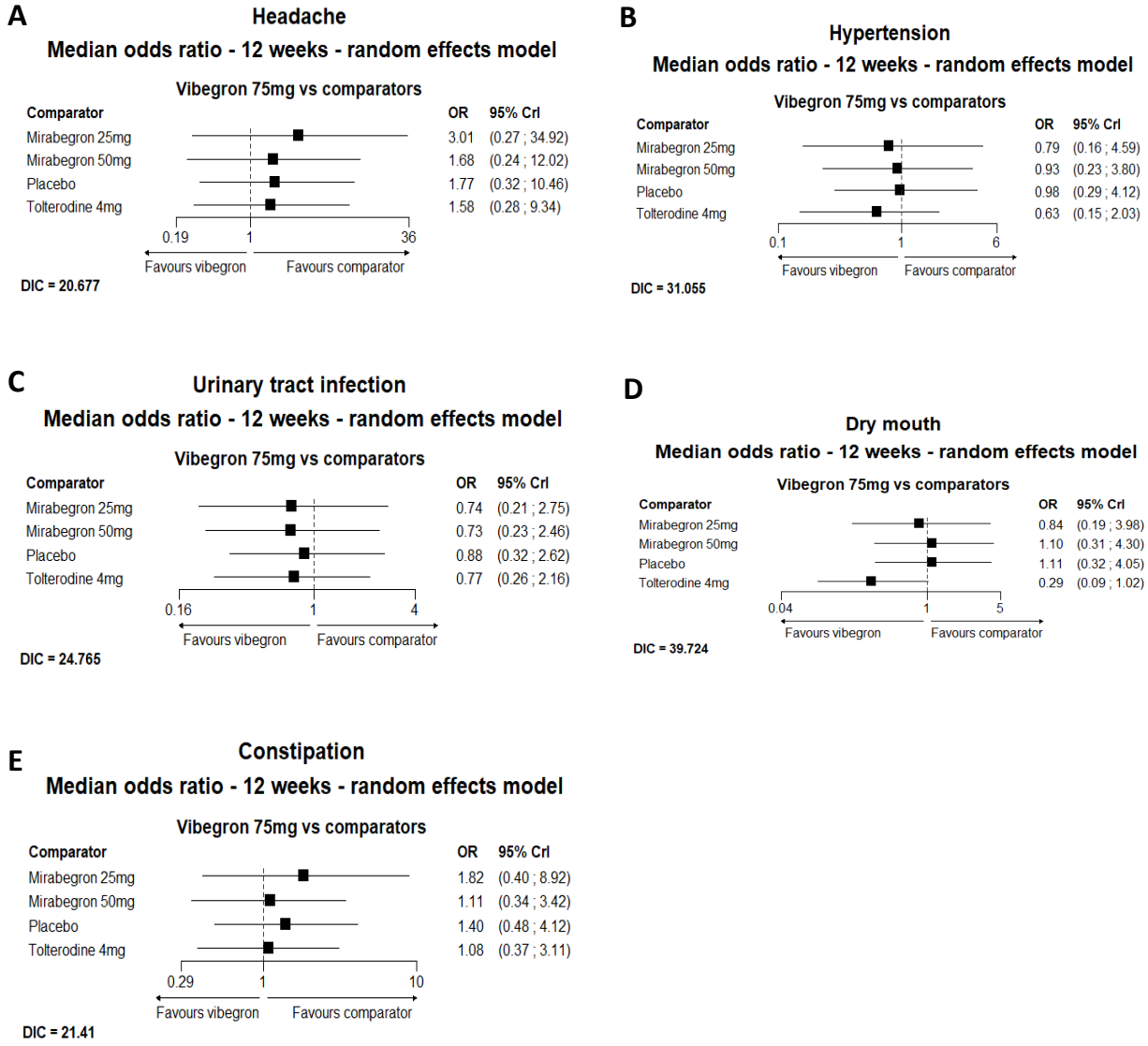
There were no statistically significant differences observed between vibegron and mirabegron at 12 or 52 weeks. However, vibegron was statistically superior to tolterodine at 52 weeks (Figure 28D) with an OR of 0.33 (95% CrI 0.1 to 0.91) and approached significance at 12 weeks with an OR of 0.29 (95% CrI 0.09 to 1.02) (Figure 27D).

B.3.9.4.5 Constipation

In total, six studies reported number of patients with constipation after 12 weeks of treatment. All studies, except for Moussa *et al.* (2021) (128), reported the data after additional follow-up period of 2 or 4 weeks. No network heterogeneity was found as the global I^2 was equal to 0%. No statistically significant inconsistency was identified between direct and indirect evidence (Q_B = 0.83, p-value = 0.66).

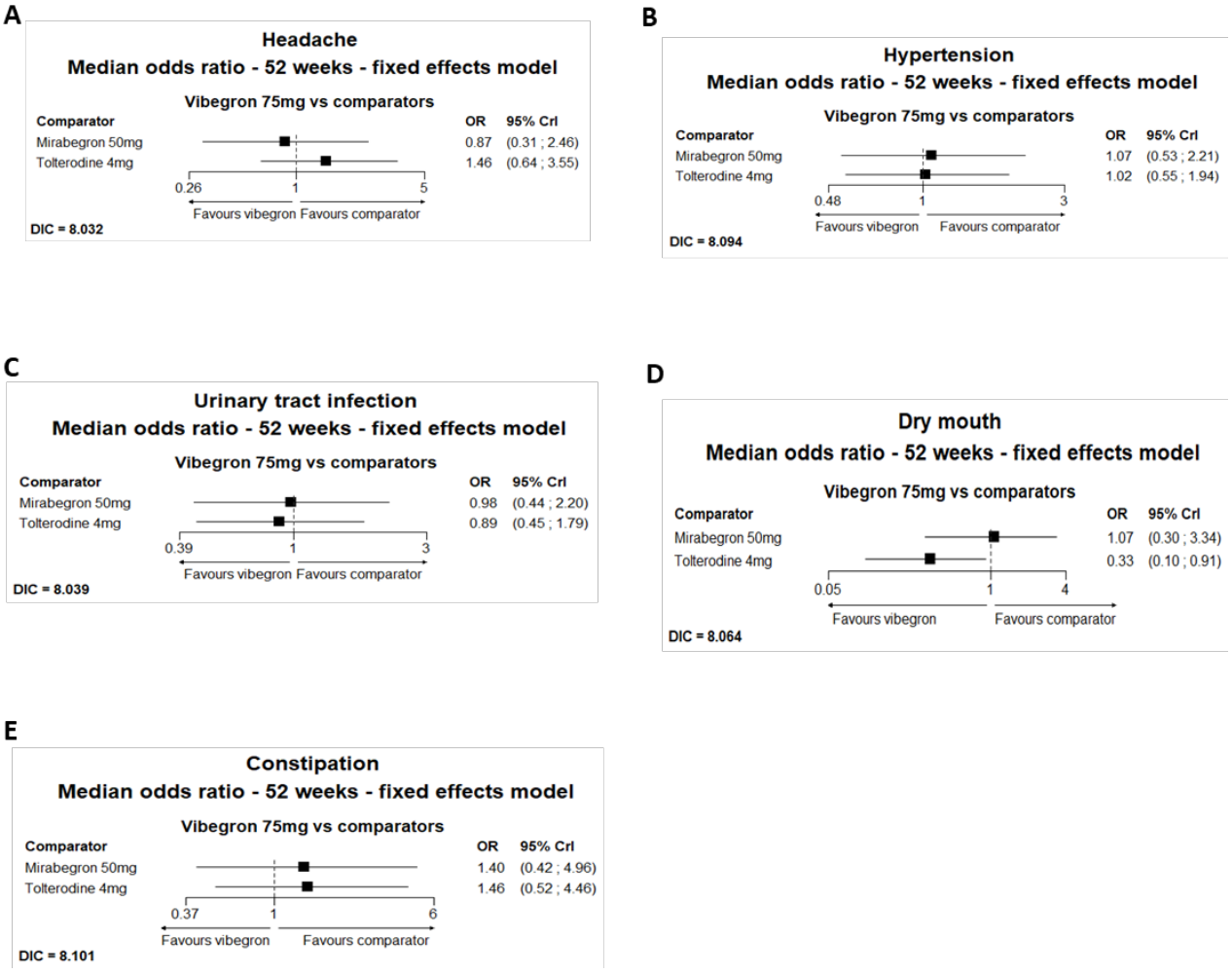
There was no significant difference observed between vibegron and the comparator interventions at 12 weeks (Figure 28E) or 52 weeks (Figure 28Figure 28E).

Figure 27. Forest plot showing individual AEs (≥2% incidence) at 12 weeks.



Abbreviations: AE, adverse event; CrI, credibility interval; DIC, deviance information criteria; OR, odds ratio.
Key: A, headache; B, hypertension; C, urinary tract infection; D dry mouth; E, constipation.

Figure 28. Forest plot showing individual AEs (≥2% incidence) at 52 weeks.



Abbreviations: AE, adverse event; CrI, credibility interval; DIC, deviance information criteria; OR, odds ratio.
Key: A, headache; B, hypertension; C, urinary tract infection; D dry mouth; E, constipation.

B.3.9.5 Uncertainties in the indirect and mixed treatment comparisons

Two head-to-head parallel open-label RCTs were identified that directly compared the safety and efficacy of mirabegron and vibegron (102, 105). However, these trials were relatively small, open-label, lacked a placebo control arm, and were assessed as being at high risk of bias (Section B.3.5). Additionally, these studies had limited generalisability because vibegron was prescribed at a dose of 50 mg (rather than the anticipated UK dose of 75 mg). Therefore, to understand the comparative safety and efficacy of these drugs more fully, an ITC was undertaken, with particular focus on the outcomes that informed the cost-effectiveness model used in TA290 (90, 91), as discussed in Section B.2.

Briefly, the ITC reported there was no evidence of difference between mirabegron and vibegron in the primary outcomes of number of micturitions and episodes of UUI at 12 weeks (Figure 23C and Figure 24C, respectively). The point estimate for the change in number of daily micturitions associated with vibegron was almost the same to that of mirabegron 50 mg, with a median of 0.1 additional micturitions associated with vibegron, with the CRIs crossing zero (CrI -0.53 to 0.58). However, although NMAs are not designed to formally test for non-inferiority, this can be inferred using the fixed-margin method, as recommended by the NICE Decision Support Unit (DSU) (135), by establishing a non-inferiority margin. Typically, this is based on the minimal clinically important difference (MCID) (136), which can be derived using historical data, preferably from placebo controlled RCTs (137). For the current analysis, the non-inferiority margin was inferred from the between-group difference used in the power calculation from the EMPOWUR trial (116) (Section B.3.4.1 EMPOWUR trial. This value of 0.6 was within the upper CrI of the NMA, indicating non-inferiority, giving reassurance that there were no important differences between the drugs in terms of reduction in daily micturitions. For the other key estimate, the number of episodes of UUI at 12 weeks, the point estimate of -0.22 (CrI -0.59 to 0.15) was clearly in favour of vibegron, indicating possible superiority. The upper CrI for this outcome was well below the between-group difference of 0.51 used in the power calculation of the EMPOWUR trial (116).

Thus, by using the *a priori* between-group differences taken from the EMPOWUR trial as proxies for the MCID, in line with NICE guidance (135), it can be implied that vibegron is non-inferior to mirabegron for the outcomes of daily micturitions and episodes of UUI, the former of which was a key efficacy outcome used in TA290 (7), and the latter of which was closely related to the second key outcome (i.e. total number of incontinence episodes) used in this health technology appraisal (HTA) (Section B.2.1.2.1 Key efficacy inputs).

There was also evidence that vibegron trended towards superiority to mirabegron in terms of reducing total incontinence episodes (Figure 25A). This is important, as this outcome was used to inform the cost-effectiveness model of TA290 (7). Additionally, there was statistical evidence that vibegron increased the void volume of micturitions (Figure 25B). The latter data may be particularly significant because it is a more objective ("hard") outcome than the other primary outcomes (as it is a physical measurement rather than a diary outcome) and implies possible superiority of vibegron. These results were broadly consistent with a previously published ITC (4).

In terms of safety, AEs were compared at both 12 and 52 weeks, so longer lasting or chronic AEs, or those slower to materialise, could be captured. When the total number of AEs were compared, there were significantly more events reported in the vibegron group at 52 weeks compared with mirabegron (Figure 26A). However, this trend was not observed with serious AEs (Figure 26B), and AEs resulting in discontinuation were numerically in favour of Vibegron (Figure 26C). The observation that vibegron may result in less discontinuations compared with mirabegron is important as discontinuation was a mechanism that was included in the cost-effectiveness model of TA290 (7). Furthermore, there was no evidence that mirabegron or tolterodine were different when relatively common, specific AEs were compared, including dry mouth (Figure 27D) and constipation (Figure 27E) at 12 weeks, which were both used to inform the cost-effectiveness model of TA290 (Section B.2).

Moderate-to-high statistical heterogeneity between trials reporting on the same direct comparisons was also identified for daily micturitions at 12 weeks. Statistically significant inconsistency was found between direct and indirect evidence for daily micturitions at 12 weeks and voided urine volume at 4 weeks. This limits the inferences that can be made regarding these comparisons.

The observation of increased AEs at 52 weeks associated with vibegron was probably artefactual, illustrating some of the uncertainty and limitations of the ITC. This comparison was restricted to two studies, the EMPOWUR-EXT (108) and TAURUS trials (93), limiting the sample size and case count for this comparison. This may have been insufficient to test the null hypothesis between vibegron and mirabegron for the efficacy and safety outcomes, and made the results subject to type 1 error (138). However, it is also possible there were methodological differences between the trials, as the reported incidence of AEs associated the common comparator, tolterodine, was different, being 59.7% (n=485/812) in TAURUS (93) compared with 62.6% (n=171/273) in EMPOWUR-EXT (108). These disparate estimates indicate the presence of differences in the two studies, which was confirmed by a statistical test (z-test) that showed significant differences (p=0.028) in these proportions. Additionally, when raw data from the EMPOWUR trial is considered, the total number of AEs

at 12 weeks in the vibegron arm (38.7%) were not statistically different to placebo (33.3%), and were fewer than observed with tolterodine (38.6%) (8).

Consistent reporting of AEs in trials is a known challenge (139), and includes differences in terminology, measurement, data collection and reporting. For instance in this case, it was noted that whilst EMPOWUR-EXT (108) employed the Medical Dictionary for Regulatory Activities (v20.1) (140) for categorisation of AEs, the method of categorisation was not described in TAURUS (93).These factors were confirmed as potential issues by experts during the clinical engagement (10, 11), with the additional consideration that global measurement of total AEs are not a useful indicator of how dangerous or bothersome they are (10). However, the incidence of serious AEs were too few to make meaningful comparisons. For this reason, the experts agreed that a more useful, objective measurement was the incidence of AEs that led to study discontinuation. For this outcome, the point estimates were in favour of vibegron for all comparisons made, including against placebo (Figure 26C). At 52 weeks, the OR of study discontinuation due to occurrence of AEs in the vibegron group was 0.38 compared with mirabegron (95% CrI 0.09 to 1.33).

Thus, despite the application of the most robust methods available, this NMA had some limitations causing uncertainty. As with all ITCs, the analysis is limited by the assumptions of similarity and consistency among trials, as well as the quality of published methods and results. Whilst we tested for statistical heterogeneity and inconsistency, this does not necessarily consider nuances in the informing data. For instance, patient baseline characteristics differed between trials, mainly with the respect to mean number of urgency episodes, mean number of UUI episodes and proportion of males, as illustrated in Figure 22. Furthermore, in addition to the reporting of AEs, the included studies used various definitions for the outcomes assessed (e.g. using 3 day or 7 day diaries) and, different classification measures of urgency and UUI episodes. However, all the outcomes were assessed as absolute change from baseline, and, additionally, it has been demonstrated that minor differences in methods of patient self-reporting of symptoms, for instance the duration of the diary, do not significantly impact results (141). Finally, whilst we considered the EMPOWUR trial was at low risk of bias, we did not formally appraise the trials informing mirabegron safety and efficacy. These factors may have impacted on the overall generalisability and representativeness of the results reported in these studies.

Nevertheless, despite these limitations, the results as a whole indicate that vibegron is at least as effective (non-inferior) as mirabegron, with the data on volume of urine voided pointing to possible superiority. Further data is required to further clarify this. Vibegron also appeared to be as well-tolerated in terms of the key safety outcomes as mirabegron. Whilst no significant differences were observed in incident hypertension, this may have been

related to the low case count, especially regarding the vibegron arm, with only 9 case (out of 545) identified (8), making the comparison subject to type 2 error (138).

B.3.10 Adverse reactions

Summary

- In the EMPOWUR trial, no meaningful differences were reported in TEAEs between treatment groups (vibegron, placebo and tolterodine). Serious AEs were rare with no difference between groups. AEs leading to drug discontinuation occurred in 1.5%, 1.1% and 2.3% in the vibegron, placebo, and tolterodine groups respectively.
- The EMPOWUR-EXT study reported there were no clinically meaningful differences were observed between the treatment groups in the overall incidence or severity of AEs or SAEs.
- In the placebo-controlled studies of Yoshida *et al.* (2018), Mitcheson *et al.* (2019), and Shin *et al.* (2023) treatments were well tolerated with no discernible differences between treatment arms for most AEs.
- The head-to head trial of vibegron vs. mirabegron by Kinjo *et al.* (2023) reported no differences in TEAEs between study arms. The study by Sato *et al.* (2023) reported more AEs overall in the vibegron arm compared with the mirabegron arm, but was based on a very small number of patients.

B.3.10.1 EMPOWUR studies

In the EMPOWUR study, the incidence of any TEAE was 33.3% in the placebo group, 38.7% in the vibegron group, and 38.6% in the tolterodine group (8). Any AE of clinical interest occurred in 7.4% of patients in the placebo group, 6.6% in the vibegron group, and 8.8% in the tolterodine group. Serious AEs (SAEs) were uncommon in all groups, occurring in 1.1% in the placebo group, 1.5% in the vibegron group, and 2.3% in the tolterodine group. AEs leading to discontinuation occurred in 1.1% in the placebo arm, 1.7% in the vibegron arm, and 3.3% in the tolterodine arm.

One patient in the tolterodine died of stroke, UTI, and sepsis; the death was adjudicated as being unrelated to study treatment. The most commonly reported AEs (occurring in ≥2% of patients in the vibegron, tolterodine, or placebo groups) are presented in Table 18. Notably, hypertension, an AE of special interest due to vibegron's adrenergic mechanism of action,

was uncommon, and occurred at the same rate among patients who received vibegron or placebo (both 1.7%).

Post hoc subgroup analysis of EMPOWUR found that older patients had a greater frequency of TEAEs in all treatment arms (110). However, there was no evidence of an increased risk of hypertension of other cardiovascular (CV) outcomes associated with vibegron.

Table 18. AEs reported by ≥2% of patients in the vibegron, tolterodine, or placebo groups over 12 weeks, EMPOWUR study (safety analysis set).

Endpoint	Placebo (n = 540)	Vibegron (n = 545)	Tolterodine (n = 430)
Hypertension *	1.7%	1.7%	2.6%
Urinary tract infection	6.1%	5.0%	5.8%
Headache *	2.4%	4.0%	2.6%
Nasopharyngitis	1.7%	2.8%	2.6%
Diarrhoea	1.1%	2.2%	2.1%
Nausea	1.1%	2.2%	1.2%
Upper respiratory infection	0.7%	2.0%	0.5%
Dry mouth †	0.9%	1.7%	6.5%
Constipation †	1.3%	1.7%	1.4%

* *A priori* safety end point of interest according to trial protocol.
† Included as safety endpoint of interest in TA290. Constipation occurred <2% of patients in all groups.

B.3.10.1.1 EMPOWUR-EXT extension study

The EMPOWUR-EXT study showed a favourable safety and tolerability profile for vibegron even after a prolonged treatment period over approximately one year (108). This timeframe was more reflective of real-world settings. No clinically meaningful differences were observed between groups in the overall incidence or severity of AEs or SAEs (Table 19). Although similar incidences of the most commonly reported AEs were observed across groups, dry mouth was reported more frequently with tolterodine (5.2%) compared with vibegron (1.8%). The incidence of hypertension remained relatively low (8.8%) and similar to tolterodine (8.6%).

Treatment-related SAEs included moderate collagenous colitis among vibegron treated patients, and moderate syncope and severe cardiac failure among tolterodine-treated patients. One death was reported in the vibegron group, but the study investigator adjudicated it was not related to the study drug. Only four (1.5%) patients in the vibegron group discontinued treatment due to an AE over the extension study treatment period. No treatment discontinuations in the vibegron group were attributable to incident hypertension.

Table 19. Safety and tolerability, EMPOWUR-EXT (safety analysis set extension).

N (%)	Vibegron n = 273	Tolterodine n = 232
Patients with ≥1 treatment-emergent AE	171 (62.6)	126 (54.3)
Patients discontinuing study medication owing to an AE	4 (1.5)	8 (3.4)
Patients with ≥1 treatment-emergent SAE	9 (3.3)	10 (4.3)
SAEs considered treatment related by the investigator	1 (0.4)	2 (0.9)
AEs (>2% for vibegron)		
Hypertension	24 (8.8)	20 (8.6)
UTI	18 (6.6)	17 (7.3)
Headache	15 (5.5)	9 (3.9)
Diarrhoea	13 (4.8)	4 (1.7)
Nasopharyngitis	13 (4.8)	12 (5.2)
Constipation	10 (3.7)	6 (2.6)
Nausea	10 (3.7)	7 (3.0)
Upper respiratory tract infection	10 (3.7)	1 (0.4)
Bronchitis	8 (2.9)	3 (1.3)
Anemia	7 (2.6)	2 (0.9)
Hyperglycemia	7 (2.6)	2 (0.9)
Residual urine volume increased	7 (2.6)	3 (1.3)
Back pain	6 (2.2)	3 (1.3)
Musculoskeletal pain	6 (2.2)	1 (0.4)
Abbreviations: AE = adverse event; SAE = serious adverse event; UTI = urinary tract infection.		

B.3.10.2 Other studies

The EMPOWUR Phase 3 trial (8) was the only study that investigated vibegron at the UK licensed dose of 75 mg. Other studies mainly administered vibegron at a dose of 50 mg or 100 mg. Higher doses of drugs would be expected to increase the incidence and severity of type A drug AEs (142), although many TEAEs will be incidental (as evidenced by similar rates in placebo groups).

Yoshida *et al.* (2018) reported the incidence of any TEAE was similar across treatment groups, ranging from 27.4% in the placebo group to 33.3% in the imidafenacin group (104). For vibegron 50 mg, 28.1% of patients experienced TEAEs, compared with 30.4% who received the drug at 100 mg. Rates of drug-related TEAEs were relatively uncommon, ranging from 5.1% in the placebo group, 5.4% in vibegron 50 mg group, 7.6% in vibegron 100 mg group, to 10.3% in the imidafenacin group. There was no evidence of a safety related dose response for vibegron.

In the study by Mitcheson *et al.* (2018) (103), of the 1,393 patients treated, 43.6%, 15.9%, and 0.6% experienced one or more AEs, drug-related AEs, and SAEs, respectively (103). Treatment discontinuations were uncommon, with 2.1%, 1.1%, and 0.1% of patients

discontinuing treatment because of an AE, a drug-related AE, or an SAE, respectively. Across all treatment groups, the most frequently reported AEs were dry mouth (5.3%), headache (4.2%), UTI (4.1%), and nasopharyngitis (3.7%), with dry mouth occurring more frequently with tolterodine compared with any dose of vibegron monotherapy (1.5% to 4.7%). Of the AEs deemed to be related to the study treatment, the most frequently reported events were dry mouth (4.7%), constipation (2.2%), headache (1.8%), and fatigue (1.1%). The proportions of patients with an SAE or who discontinued therapy due to a drug-related AE ranged from 0.0% to 3.0%, across all treatment groups. In general, it was concluded vibegron was well tolerated at all tested doses.

The study by Kinjo *et al.* (2023) reported head-to-head safety data on mirabegron and vibegron. In this study, vibegron was administered as a 50 mg dose, less than the licensed UK dose (75 mg). The incidence of TEAEs reported in the trial is presented in Table 20. The overall incidence of TEAEs was similar, with 17.5% reporting TEAEs receiving mirabegron, and the corresponding value of 15.7% for vibegron (p=0.650). The most frequent TEAE was constipation, which was similar in both groups (10.3% and 11.8% for mirabegron and vibegron respectively, p=0.821). The rate of discontinuation due to TEAEs was also similar in both groups (6.2% and 6.8% for mirabegron and vibegron respectively, p=0.861). The reasons for these discontinuations were constipation in 1 and 5 patients in the mirabegron and vibegron group, respectively; exanthem in 2 and 1 patients in the mirabegron and vibegron group, respectively; difficulty of urination in 1 patient in each group; and elevated BP and headache in 1 patient in the mirabegron group.

Table 20. TEAEs reported in the study by Kinjo *et al.* (2023).

	Mirabegron group (n=97) n (%)	Vibegron group (n=102) n (%)	p value*
Total TEAEs	17 (17.5)	16 (15.7)	0.650
Constipation	10 (10.3)	12 (11.8)	0.821
Dry mouth	1 (1.0)	1 (1.0)	0.967
Exanthem	2 (2.1)	1 (1.0)	0.159
Elevated PVR	1 (1.0)	2 (2.0)	0.321
Palpitations	1 (1.0)	0	0.320
Elevated BP	1 (1.0)	0	0.320
Headache	1 (1.)	0	0.320
Abbreviations: BP, blood pressure; PVR, post-void residual urine; TEAE, treatment emergent adverse event. * Fisher's exact test			

The TEAEs reported by Sato *et al.* (2023) (105) are reported in Table 21. The authors reported a higher overall rate of TEAEs in the vibegron arm, but the numbers were low (with most TEAEs occurring in a single person), and causality was not established. There were no significant changes in BP or heart rate in either group.

Table 21. TEAEs reported in the study by Sato *et al.* (2023) (SAF)

	Mirabegron (n=47) n (%)	Vibegron (n=52) n (%)	p value
Dry mouth	6 (12.8)	8 (15.4)	0.78
Constipation	1 (2.1)	6 (11.5)	0.12
Arthralgia	0	1 (1.9)	1.0
Urinary retention	0	1 (1.9)	1.0
Gastritis	2 (4.3)	0	0.22
Cramp	0	1 (1.9)	1.0
Dyspnoea	0	1 (1.9)	1.0
Dizziness	0	1 (1.9)	1.0
Palpitations	0	1 (1.9)	1.0
Total (patients)	9 (19.1)	20 (38.5)	0.047
Abbreviations: SAF, safety analysis set; TEAE, treatment emergent adverse event.			

The AEs reported in the study by Shin *et al*. (2023) (106) are reported in Table 22. The overall incidence of any AEs was similar between groups, occurring in 23.81% in the vibegron group and 22.12% in the placebo group. All AEs in both groups were graded as mild or moderate in intensity and no deaths or serious AEs were reported. Hypertension was only observed in 2 people, both in the placebo group (1.92%) of placebo group.

Table 22. AEs reported in the study by Shin *et al*. (2023)

		Vibegron 50 mg (n=105)	Placebo (n=104)
		Number (%)	Number (%)
All		25 (23.81)	23 (22.12)
Most common AEs*			
	Pyuria	4 (3.81)	1 (0.96)
	UTI	1 (0.95)	4 (3.85)
	Dry mouth	1 (0.95)	3 (2.88)
	Dysuria	3 (2.86)	0 (0.0)
	Drug-related AEs	6 (5.71)	3 (2.88)
Most common drug-related AEs †			
	Dry mouth	1 (0.95)	3 (2.88)
	Dysuria	2 (1.9)	0 (0.0)
	Serious AEs	0 (0.0)	2 (1.92)
	Drug-related serious AEs	0 (0.0)	0 (0.0)
AEs leading to permanent discontinuation of study drug		5 (4.76)	0 (0.0)

Abbreviations: AE, adverse event; UTI, urinary tract infection

* Incidence ≥2% in any group

† Incidence ≥2% in any group

The conference abstract reporting on the study by Wada et al. (2023) (107) that 3 patients withdrew from treatment due to AEs, including dizziness in one person receiving mirabegron, and constipation and elevated postvoid residual urine (PVR) in patients receiving vibegron.

B.3.11 Conclusions about comparable health benefits and safety

Summary

- A SLR was undertaken to identify all published RCTs on vibegron and mirabegron. Suitable studies were used to inform an ITC which showed that vibegron is at least non-inferior to mirabegron in terms of efficacy, safety, and tolerability profile, and therefore should be considered equivalent with respect to these.
- In common with mirabegron, vibegron is proven to be more effective than placebo and is likely to have improved efficacy compared with antimuscarinic drugs. Vibegron does not cause anticholinergic effects like dry mouth, which is a significant reason for discontinuation of first-line pharmacotherapy.
- Vibegron 75 mg has been shown to be at least as effective and well-tolerated as mirabegron 50 mg in a bespoke ITC. Head-to-head studies of vibegron versus mirabegron, using the unlicensed dose of 50 mg vibegron, are supportive of this assertion.
- Subgroup analyses indicate that, like mirabegron, vibegron is effective in both treatment naïve individuals and in people who have previously used anti-muscarinic drugs.
- As well as reducing the symptoms of OAB, vibegron has been shown to directly improve HRQoL.
- Vibegron also has specific advantages over mirabegron which cannot be practicably captured in an economic model. Namely, vibegron is administered in a simple crushable one-tablet regimen, it has fewer contraindications (including in people with pre-existing severe hypertension), does not require dose adjustments in people with hepatic and renal impairment, and has few drug-drug interactions.

Despite the widespread prevalence of OAB and the burden it poses, there is still a significant unmet need for those affected in terms of improving efficacy and continued adherence to treatment (Section B.1.3.6). Conventional pharmacological management of OAB is predicated on the use of antimuscarinic drugs which have been proven to be of benefit for symptomatic relief (143). However, their effective use is hindered by their AE and tolerability profile, leading to poor adherence and early discontinuation (Section B.1.3.5.2). Mirabegron, a β_3 agonist, was recommended for second-line pharmacological use by NICE in 2013

(TA290) (7) (Section B.1.3.5.3). Vibegron is a new generation of β_3 agonist which has fewer contraindications and a simpler dosing regimen (in some populations) compared with mirabegron (Section B.1.2). It has improved selectivity and affinity to the β_3-AR, which confers some theoretical advantages compared with mirabegron (81). The evidence from this submission shows that in practice, vibegron has a similar but differentiated AE and tolerability profile compared with mirabegron and is at least as effective (non-inferior) in terms of clinical efficacy.

The SLR identified six parallel RCTs with unique patients (Phase 2 or 3) (8, 102-106), an extension trial (108), and a cross-over trial (107) that provided evidence on the effectiveness and safety of vibegron. In total, there is experimental evidence to support the use of vibegron from over 4000 trial participants. Of the included studies, the most relevant to inform the decision problem was the EMPOWUR trial (8) and its extension study EMPOWUR-EXT (108). This was because this study was assessed as being at low risk of bias and was the only study that administered vibegron at 75 mg per day, the sole dose anticipated for licensed use in the UK (1), meaning data from this study was directly generalisable.

As with most trials in people with OAB, EMPOWUR reported significant improvements from baseline associated with placebo (144), relating to factors such as regression to mean and the Hawthorne effect (10, 11). The EMPOWUR study reported statistical superiority compared with a matching placebo in its co-primary outcomes at 12 weeks, with micturitions decreasing by an adjusted mean of 1.8 episodes per day for vibegron compared with 1.3 for placebo ($p<0.001$) and 1.6 for tolterodine. In the FAS-I group, UUI decreased by an adjusted mean 2.0 episodes per day for vibegron compared with 1.4 for placebo ($p<0.0001$) and 1.8 for tolterodine (8). These improvements were apparent 2 weeks after starting treatment. Moreover, vibegron was also superior to placebo in all the key secondary outcomes measured (Table 8), and these improvement persisted for at least 52 weeks (108). The use of vibegron was not associated with any safety issues, including *a priori* AEs of special clinical interest, such as hypertension (Table 18).

The findings of EMPOWUR were fully reflected in the other studies identified (102-107). This included evidence that vibegron improves disease-specific HRQoL (8, 104, 106) and nocturia (104, 106). Together with the EMPOWUR study, the collective evidence base provided positive evidence of benefit for all the outcomes identified in the scope (Table 1). These are summarised in Table 23.

Table 23. Summary of results aligned with outcomes specified in the scope.

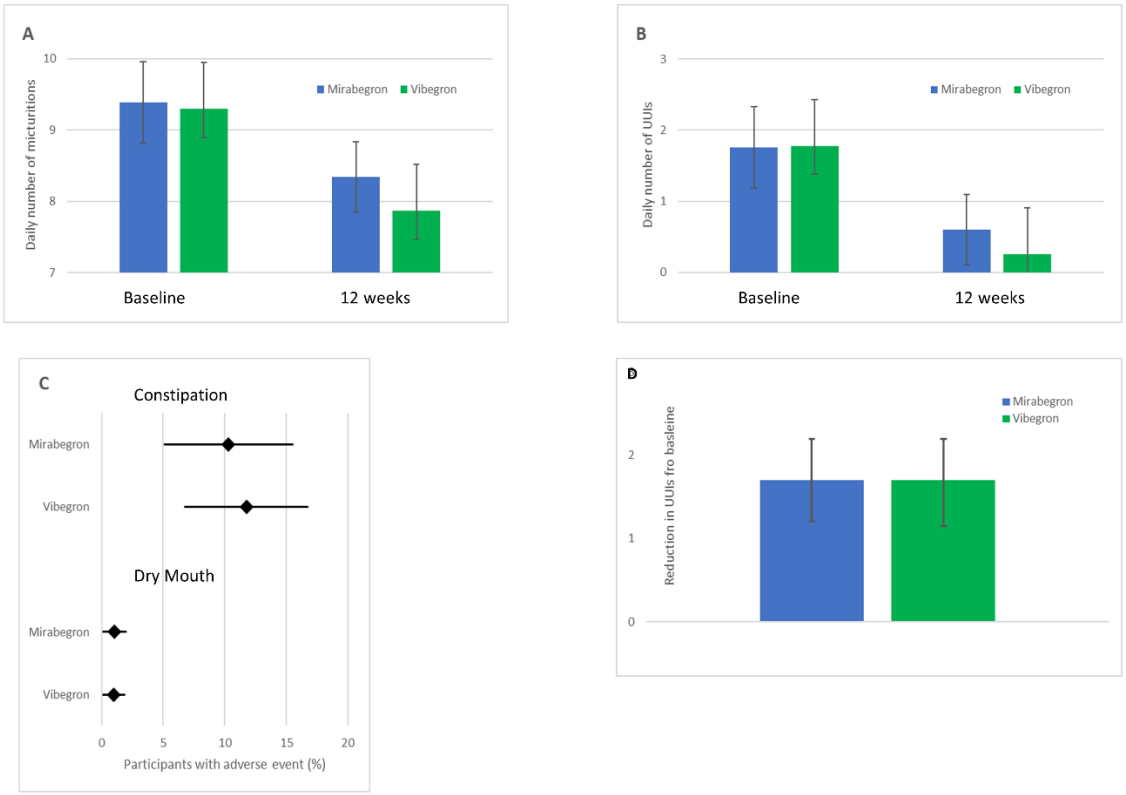
Outcome specified in scope	Key source of evidence*	Summary of results	Comment
Symptoms of urgency	EMPOWUR study (8) Section B.3.6.1.2 Section B.3.9 (ITC)	Statistical superiority over placebo. Numerical superiority over tolterodine	Statistical superiority over placebo confirmed in other studies (103, 104, 108) Vibegron (50 mg) not different to mirabegron (50 mg) in head to head trials (102, 105).
Urinary frequency	EMPOWUR study (8) Section B.3.6.1.2 Section B.3.9 (ITC)	Statistical superiority over placebo. Numerical superiority over tolterodine Non-inferiority* to mirabegron.	Key outcome used CEM of in TA290. Statistical superiority over placebo confirmed in other studies (103, 104, 108) Vibegron (50 mg) not different to mirabegron (50 mg) in head to head trials (102, 105) or ITC (75 mg).
Frequency of urge urinary incontinence	EMPOWUR study (8) Section B.3.6.1.3	Statistical superiority over placebo. Numerical superiority over tolterodine Non-inferiority* to mirabegron.	Key outcome used CEM of in TA290. Statistical superiority over placebo confirmed in other studies (103, 104, 108) Vibegron (50 mg) not different to mirabegron (50 mg) in head to head trials (102, 105) or ITC (75 mg).
Nocturia	Yoshida *et al.* (2018) (104) Shin et al. (2023) (106) Section B.3.6.2.2	Statistical superiority over placebo.	Nocturia was not included as an outcome in the CEM of TA290.
Adverse effects of treatment	EMPOWUR study (8) Section B.3.10.1 Section B.3.9 (ITC)	Similar AE profile to placebo. No safety signal observed in AEs of special interest.	Similar AE profile to placebo confirmed in other studies (103, 104, 108) Similar AE profile to mirabegron (102)
Health-related quality of life.	EMPOWUR study (8) Yoshida *et al.* (2018) (104) Shin et al. (2023) (106) Section B.3.6.1.3 Section B.3.6.2.1	Significant improvements in OAB-q and PGI compared with placebo.	No significant improvement in EQ-5D was observed. OAB is considered to be relatively insensitive to changes in generic HRQoL.

Abbreviations: AE, adverse events; CEM, cost-effectiveness model; ITC, indirect treatment comparison; OAB-q, overactive bladder questionnaire; PGI, patient global impression; TA, technology assessment.
* Non-inferiority margin derived from between group difference derived from the power calculation used in the EMPOWUR trial.

Vibegron belongs to the same class of drugs as mirabegron and thus it is biologically plausible for both drugs to have similar efficacy and AE profiles. This supposition was tested in two ways, firstly, through the data reported from two direct head-to-head trials of vibegron compared with mirabegron, and secondly, through an ITC which included data from the EMPOWUR trial and corresponding RCTs on mirabegron with common comparators.

Both the RCTs by Kinjo *et al.* and Sato *et al.* (2023) (102) directly compared mirabegron (50 mg) with vibegron (50 mg). Additionally, Wada *et al*. (2023) reported on a cross-over trial comparing the drugs (vibegron dose 75 mg) (107). These studies appear to have been exploratory analyses with no clear hypotheses set. The authors reported that there were no significant difference between the drugs in all the measured outcomes, including those used in the cost-effective model of TA290 (91). Additionally, the key efficacy outcomes from the parallel trials are reported graphically in Figure 29 and show that, for the purpose of economic evaluation, mirabegron and vibegron may be considered equivalent.

Figure 29. Outcomes relevant to the cost-effectiveness model of TA290, reported by Kinjo *et al.* (2023) and Sato (2023).



Legend. Panels A, B, and C are derived from data from Kinjo *et al.* (2023) (102). Panel A reports the outcome of daily micturitions at baseline and 12 weeks. Panel B reports the outcome of daily urgency urinary incontinence at baseline at 12 weeks. Panel C compares the proportion of participants who experienced dry mouth or constipation. Panel D reports on data from Sato *et al.* (2023) (105). It reports the change from baseline in the number of UUIs for both interventions. Error bars are 95% confidence intervals.

Whilst the data from the head-to-head studies (2023) provided good evidence of the equivalence of vibegron and mirabegron, there are caveats to this. Firstly, the populations were restricted to post-menopausal women with OAB, so was not fully representative of the population defined in the scope. Secondly, the sample sizes were relatively small compared with other studies in this field (n=213 for Kinjo and n=104 for Sato), and they were both set in single tertiary care centres. The studies therefore lacked generalisability and precision.

Thirdly, these studies were assessed to be at high risk of bias, as subjects and investigators were not blinded to treatment. And finally, most importantly, whilst the routine dose of mirabegron was used (50 mg) (18), vibegron was also administered at a dose of 50 mg, which is a lower dose than is anticipated to be licensed in the UK (1). It can be speculated that this may have reduced the efficacy of vibegron relative to mirabegron, whilst over-estimating its tolerability.

To counter the limitations of the head-to-head study, an ITC was carried out using the benchmark data from EMPOWUR (Section B.3.9). These analyses reported there were no statistically significant differences in the number of daily micturitions when vibegron 75 mg was compared with mirabegron (25 mg or 50 mg) or tolterodine 4 mg. There was also no difference in the number of UUIs or total episodes of incontinence reported. However, for both the comparisons made for these outcomes, the point estimates were numerically in favour of vibegron 75mg at all timepoints, and statistically superior at 52 weeks. Vibegron also reported statistically superior improvements in the volume of urine voided at 12 weeks compared with mirabegron.

Although vibegron was reported to be associated with significantly more total AEs than mirabegron, this may have been due to study heterogeneity concerning how these events were measured and reported, and these results were not supported by more granular analyses. There were no significant differences detected between vibegron and mirabegron regarding headache, incident hypertension, UTI, dry mouth or constipation, the latter two outcomes of which were used to inform discontinuation rates in TA290 (90). Thus, vibegron demonstrated non-inferiority in all the outcomes relevant to TA290 (see Figure 30). Additionally, vibegron was associated with numerically fewer patients discontinuing treatment compared with mirabegron (25 or 50 mg) or tolterodine (4 mg) at 12 weeks and mirabegron (50 mg) at 52 weeks (Figure 26Figure 26), Despite issues with heterogeneity and low sample sizes and case counts, overall, the results of the ITC clearly demonstrate equivalence or non-inferiority of the vibegron and mirabegron in all outcomes of interest to this submission.

Due to the adrenergic properties of vibegron, new onset or worsened hypertension was a predefined AE of clinical interest in the EMPOWUR trial (8). There were only minimal changes in BP observed, with protocol increases in BP observed in 5/540 (0.9%), 4/545 (0.7%) and 8/430 (1.9%) in vibegron, placebo and tolterodine groups respectively (116). The effect of vibegron on BP has been investigated in a placebo-controlled trial (19). In this study, in which 214 participants were randomised to receive vibegron (75 mg, n=96) or placebo (n=101), no significant differences between treatments were seen in CFB in mean 24 hour systolic BP (LSM, 0.6 mmHg), diastolic BP (–0.2 mmHg) or heart rate (1.0 beats per

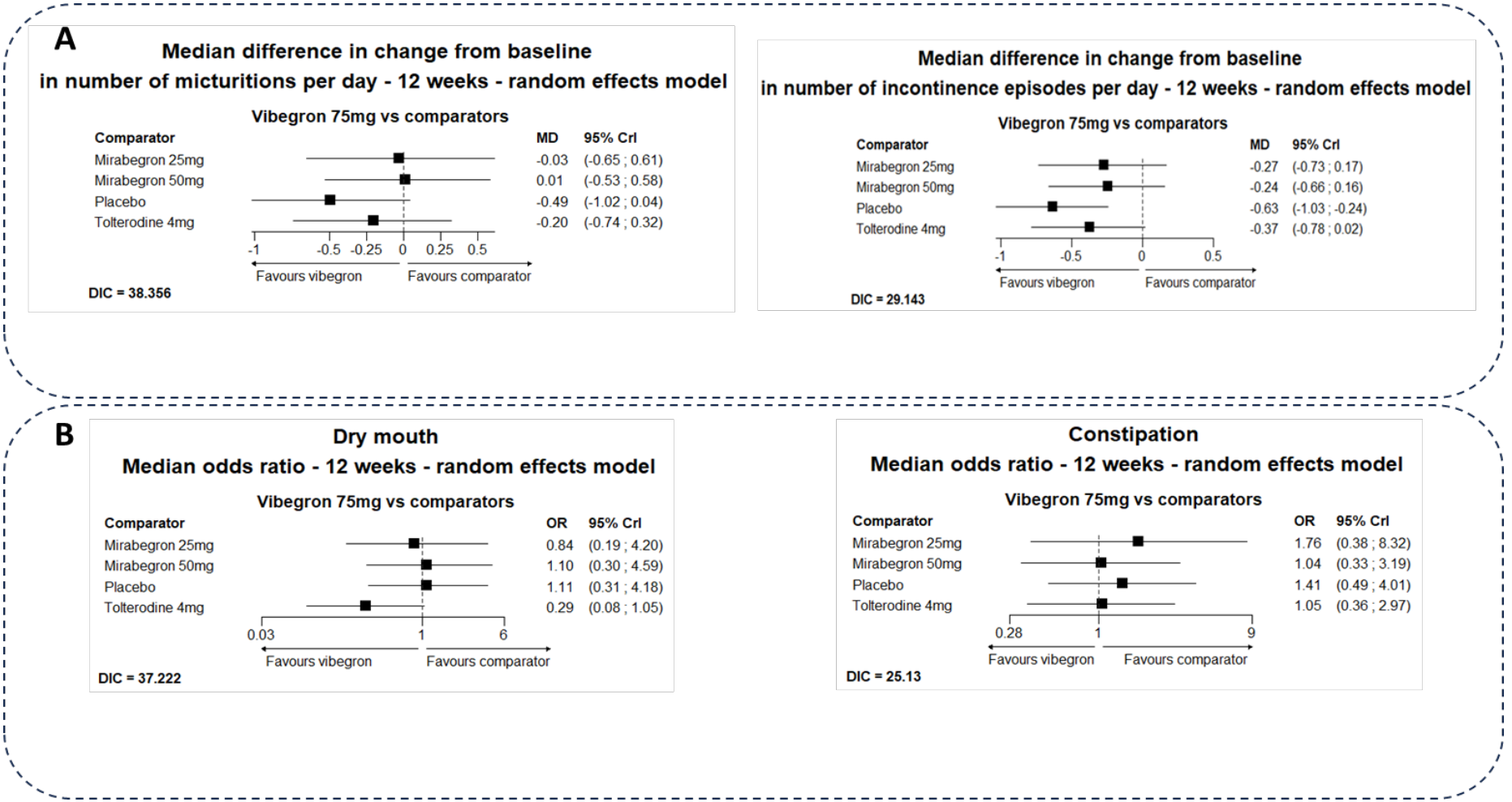
minute). Rates of incident hypertension were comparable, occurring in five patients in the vibegron group and four patients in the placebo group. Thus, vibegron does not appear to have a negative impact on BP, which is reflected in its marketing authorisation where it is not contraindicated in people with pre-existing hypertension.

A final consideration is that as vibegron is anticipated to be an alternative to mirabegron, it would be indicated in the population in whom anti-muscarinic drugs are contraindicated or clinically ineffective, or who have unacceptable side effects, in accordance with NICE TA290 (7). This indicates a group broadly synonymous with non-treatment naïve patients. Therefore, the efficacy of vibegron in people who had previously received anti-muscarinic drugs was investigated using subgroup analyses (Section B.3.7.2 Previous treatment These analyses clearly showed the benefit of vibegron with significant longitudinal improvements in daily micturitions and episodes of UUI at 12 weeks. However, whilst, these analyses (comprising approximately 15% of participants in EMPOWUR) were insufficiently powered to demonstrate statistical superiority of vibegron over placebo, there was no signal that vibegron was less effective in this subgroup.

It was not possible to use these subgroup data in the ITC to indirectly compare the use of vibegron and mirabegron in treatment naïve and non-naïve people with OAB, because there were no published primary data in this group receiving mirabegron. However, in the company submission for TA290 (90), the company performed subgroup analysis on this cohort using a pooled meta-analysis of patients from the ARIES (76), SCORPIO (75) and CAPRICORN (77) trials. The company reported a CFB in the treatment naïve group in the number of daily micturitions of -1.84 (95% CI -2.04 to -1.64) based on a sample size of 636 subjects. This was similar to the value reported for vibegron in the subgroup analysis from EMPOWUR of -2.1 (95% CI -2.6 to -1.6) based on a sample size of 74 subjects and gives confidence of the equivalence of these drugs in this population.

In summary, the evidence strongly supports that vibegron is at least as safe and effective in the treatment of OAB as mirabegron. Whilst OAB rarely has serious physical sequelae for the person affected, it is an illness which can greatly negatively affect quality of life (145). Vibegron has been directly observed to improve HRQoL using disease specific instruments (Section B.3.6.1.3). In addition to this, patient satisfaction with vibegron has been reported as being very high (104, 106). When trial participants who had experienced the use of both mirabegron and vibegron were asked about their experiences, most reported a preference for vibegron over mirabegron (107).

Figure 30. ITC results relevant to TA290 in terms of A) efficacy and B) adverse events.



Abbreviations: CEM, cost-effectiveness model; CrI, credibility interval; DIC, deviance information criteria; ITC, indirect treatment comparison; MD, mean difference; OR, odds ratio; TA, technology appraisal; UUI, urinary urge incontinence.
Key: Key primary efficacy outcomes from ITC used to inform CEM of TA290 (number of micturitions and number of episodes of UUI; B, key safety outcomes from ITC used to inform CEM of TA290 (dry mouth and constipation determined the rate of drug discontinuation)..

B.3.12 Ongoing studies

Three studies on vibegron have been identified which are anticipated for completion, or partial completion, within the next year.

The Composur study (NCT05067478) has the full title “Composur, A Patient-centric, Phase IV, Open-label, Prospective, Real World US Study to Evaluate Vibegron on Patient Treatment Satisfaction, Quality of Life, and Healthcare Resource Utilization in Overactive Bladder is anticipated” (146). The study completion date is anticipated in September 2024. Composur is a prospective cohort study with an enrolment of 400 individuals with OAB which will compare outcomes following vibegron administration in people who have previously received mirabegron or are mirabegron naïve.

The COURAGE study (NCT03902080) “Study to Evaluate the Efficacy, Safety and Tolerability of Vibegron in Men With Overactive Bladder (OAB) Symptoms on Pharmacological Therapy for Benign Prostatic Hyperplasia (BPH)” was completed in June 2023 and is awaiting publication (147). This is a Phase 3 double-blind, randomized, placebo-controlled, multi-centre study with an enrolment of 1105 men with OAB. The study aims to assess the efficacy of vibegron compared with placebo in men with OAB symptoms who are receiving pharmacological therapy for BPH, as defined by micturition and urgency episodes.

The Optum study is a retrospective study that used a pharmacy claims database in the US to assess vibegron adherence and persistence compared with mirabegron and anticholinergics in a real world population of patients with OAB (80). This study, available currently as an abstract, is due to publish in 2024.

B.4 Cost-comparison analysis

Summary

- A cost comparison analysis was justified on the basis that vibegron was shown to be at least as effective with a comparable tolerability/toxicity safety profile to mirabegron. This was evidenced through an ITC of the drugs (Section B.3.9) and three head-to-head trials (Sections B.3.3.3.3, B.3.3.3.4 and B.3.3.3.6). In particular, there were no differences between the drugs in the key parameters that informed the cost-effectiveness model of TA290 (Section B.2).
- A simple cost-calculator was developed. This showed that vibegron was associated with an annual cost of [redacted], compared with mirabegron which had an annual cost of [redacted], a per patient saving of [redacted] in favour of vibegron. There were no uncertainties identified in these analyses.
- Vibegron costs were therefore at least [redacted]% lower compared with mirabegron and considered likely to be associated with significant cost savings to the NHS.

B.4.1 Changes in service provision and management

Vibegron is to be used in the same line of treatment as mirabegron in people with symptoms of OAB in whom antimuscarinic drugs are contraindicated or clinically ineffective, or who have unacceptable side effects, in line with NICE guidance TA290 (148). There are no changes anticipated in terms of service provision and management with the inclusion of vibegron in the treatment pathway. There are no differences anticipated in terms of resource use between vibegron and mirabegron.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

The aim of the analysis is to evaluate the costs associated with vibegron, compared with those for mirabegron for the treatment of OAB from the perspective of the NHS in England. As reported in Section B.3.9, vibegron is at least as effective as mirabegron with a comparable tolerability/toxicity safety profile. Based on this, a simple cost calculator was developed. The calculator captures the annual drug acquisition costs associated with vibegron and mirabegron in the treatment of OAB patients, based on the assumption that the inclusion of vibegron in the treatment pathway will not result in any changes in healthcare resource use, including monitoring the condition and management of AEs.

A cost-comparison approach is supported by available published evidence which demonstrates that vibegron is associated with at least similar outcomes to mirabegron in OAB patients (4). The approach is further supported by the results of an updated ITC comparing vibegron to mirabegron (Section B.3.9), as well as two head-to-head trials comparing mirabegron and vibegron (both 50 mg dose), and a cross-over trial, discussed in Section B.3. The updated ITC study included ten Phase 3, double-blind, controlled trials of vibegron or mirabegron in patients with OAB, and the results suggested that vibegron is associated with significant improvement in volume of urine voided at 4 and 12 weeks, and in UUI episodes at 52 weeks, compared with mirabegron. It is notable that the point estimates for UUI favoured vibegron when compared to mirabegron at all time points (Section B.3.9.2, Figure 24). Improvement in daily micturitions were similar between vibegron and mirabegron. There were also no significant differences between the drugs observed in any specific AE, including dry mouth and constipation (Section B.3.9.4). Note that dry mouth and constipation were the only AEs included in TA290 for mirabegron, as these AEs are most bothersome to patients and likely to drive treatment discontinuation (7). In terms of AEs leading to discontinuation, although there were no statistically significant differences between vibegron and mirabegron at 12 or 52 weeks, the point estimates favoured vibegron numerically. The decision to use a cost-comparison approach has been validated by a health economic expert (149).

Based on the above information, a cost comparison approach whereby treatment efficacy, safety, and treatment discontinuation rates were all set to equal was deemed appropriate. Annual drug acquisition costs for the intervention and comparator, respectively, were calculated to demonstrate the difference in drug acquisition cost in a typical year. Discounting was not considered due to the short time horizon. Table 24 presents a summary of the cost-comparison analysis.

Table 24. Summary of the cost-comparison analysis

Feature	Chosen approach
Population	Adults with OAB symptoms for whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects (see Section B.4.5 Subgroup analysis)
Number of OAB patients eligible for non-antimuscarinic pharmacological treatments in England*	331,155

Intervention	Vibegron (75mg once daily)
Comparator	Mirabegron (50mg once daily)
Outcome	Annual drug acquisition cost
Perspective	NHS and personal social services in England and Wales
Time horizon	1 year
Discounting	Not discounted
Note: *This number was estimated based on the following assumption: prevalence of OAB in adult patients is 11.8%, mortality in general population is 1.03%, 27% people with OAB symptoms will seek pharmacological treatment, and 23.5% of those who seek treatment cannot tolerate or do not respond adequately to antimuscarinics.	

B.4.2.2 Intervention and comparators' acquisition costs

The acquisition costs of the intervention and comparator technologies are reported in Table 25. The acquisition cost for mirabegron was based on the list price in the British National Formulary (95). The listed price of vibegron was obtained from the company and is confidential. The doses and dosing frequency were obtained from the Summary of Product Characteristics (SmPC) for each drug (1, 18).

Table 25. Acquisition costs of the intervention and comparator technologies

	Vibegron	**Mirabegron**
Pharmaceutical formulation	Tablet	Tablet
(Anticipated) care setting	Primary (patients take at home)	Primary (patients take at home)
Acquisition cost (excluding VAT) *	[redacted]	£29.00 (list price)
Method of administration	Oral	Oral
Doses	75mg	50mg
Dosing frequency	Once daily	Once daily
Dose adjustments	NA	Manufacturer advises dose reduction to 25 mg once daily in moderate hepatic impairment or if eGFR 15–29 mL/minute/1.73 m^2. Avoid if eGFR less than 15 mL/minute/1.73 m^2
Average length of a course of treatment	Indefinite	Indefinite
Average cost of a course of treatment (acquisition costs only)	N/A	N/A
(Anticipated) average interval between courses of treatment	N/A	N/A
(Anticipated) number of repeat courses of treatment	N/A	N/A

* Indicates whether this acquisition cost is list price or includes an approved patient access scheme or other nationally available price reduction. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.

B.4.2.3 Intervention and comparators' healthcare resource use and associated costs

Based on the results from the ITC studies that vibegron is at least as efficacious as mirabegron with a differentiated but overall comparable tolerability and toxicity profile (4), no difference in healthcare resource use such as AE management, monitoring and incontinence pad usage is expected, and therefore no further healthcare resource use were included in the cost-comparison analysis. Administration costs were not included as both vibegron and mirabegron are treatments administered orally at home. Additionally, the analysis assumed there were similar costs for subsequent therapies following treatment discontinuation between vibegron and mirabegron. This assumption is a conservative approach, as the point estimate for adverse events leading to treatment discontinuation reported in the ITC was in favour of vibegron (OR=0.74 at 12 weeks, and OR=0.38 at 52 weeks), (see B.3.9.3.3 Adverse events leading to study treatment discontinuation). Considering subsequent therapies include surgery, botulinum toxin injections and nerve stimulation, all of which are associated with a high cost, a lower rate of discontinuation in the vibegron arm would likely incur lower subsequent therapy costs, compared to mirabegron.

B.4.2.3.1 Adverse reaction unit costs and resource use

Costs and resource use associated with AEs were not included in the cost-comparison analysis, based on the assumption that vibegron has a similar safety profile to mirabegron. This assumption is supported by results from two previously published ITC studies (4, 150). The omission of these costs is not expected to have a significant impact on the base-case results.

B.4.2.3.2 Miscellaneous unit costs and resource use

No further costs or resource use were included in the cost-comparison analysis.

B.4.2.4 Expert validation

The suitability of a cost comparison approach to the economic analysis, using a simple cost calculator, was confirmed during technical engagement with a health economist (149). Two clinical experts were also engaged during the development of this submission. Both the experts confirmed the approach taken to economic analysis was appropriate (10, 11).

B.4.2.5 Uncertainties in the inputs and assumptions

There were no uncertainties associated in the inputs as the analysis only considered annual drug acquisition cost. A summary of assumptions adopted in the cost-comparison analysis is presented in Table 26.

Table 26. Assumptions adopted in the cost-comparison analysis.

Assumption	Description
Equivalent efficacy	The analysis conservatively assumed that the treatment efficacy is the same between vibegron and mirabegron.
Comparable safety profile	The analysis assumed that the probability of adverse events was the same between vibegron and mirabegron, therefore, adverse events were not modelled.
Monitoring	The analysis assumed that both treatments required the same monitoring, therefore, the cost of monitoring was not modelled.
Discontinuation	The analysis assumed that the probability of discontinuing treatment was the same between vibegron and mirabegron, therefore, discontinuation was not modelled.
Next line of treatment	The analysis assumed the probability of moving to the next line of treatment was the same between vibegron and mirabegron. Therefore, costs of subsequent treatment were not modelled.

B.4.3 Base-case results

The total annual drug acquisition cost of vibegron was [redacted] lower than that of mirabegron, as presented in Table 27.

Table 27. Base-case results at list price

Technology	Total annual drug acquisition cost	Cost difference (vibegron minus mirabegron)
Vibegron	[redacted]	[redacted]
Mirabegron	£353.08	-

B.4.4 Sensitivity and scenario analyses

No sensitivity and scenario analyses were conducted, as there were no substantial uncertainties associated with the base-case inputs.

B.4.5 Subgroup analysis

No subgroup analysis was performed as no differences in efficacy and safety were expected across subgroups for vibegron versus mirabegron (Section B.4.2.1 Features of the cost-comparison analysis). The efficacy and safety data that informed the assumption of non-

inferiority between the drugs was derived from the aggregated data from the EMPOWUR trial and equivalent trial data for mirabegron, because:

- This population is consistent with NICE guidance TA290 for mirabegron (7). In TA290, whilst the final recommendation is that mirabegron is restricted to a population for whom antimuscarinic drugs are contraindicated or clinically ineffective, the decision to approve mirabegron was made based on the results of the CEM which was conducted in the general OAB population consisting of treatment naïve and treatment experienced patients.
- In the final appraisal determination of TA290, the committee considered that there was no statistically significant difference between the effects of mirabegron in treatment-naïve and pre-treated populations and that there was no plausible pharmacological reason why the clinical effectiveness of mirabegron would differ between these groups. Thus, the recommendations were not made on the basis of different drug efficacies between these groups.
- There is no subsequent evidence from the EMPOWUR trial that the efficacy of vibegron is different between treatment naïve and pretreated groups, or the enrolled population overall (Section B.3.7.2.).

Given that the efficacy and tolerability of vibegron is at least non-inferior to mirabegron and that this is independent of prior treatment status, there was no rationale or method to conduct subgroup analysis in the cost comparison analysis.

B.4.6 Interpretation and conclusions of economic evidence

This economic analysis compared the drug acquisition cost of vibegron with mirabegron for treating symptoms of OAB, from the perspective of the NHS of England. The analysis was consistent with the cost-comparison addendum to the *Guide to the methods of technology appraisal* (151), which states a cost-comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE TA guidance for the same indication. Results from key clinical placebo controlled RCTs of vibegron (8, 103, 104, 108), two head-to-head RCTs between vibegron and mirabegron (102, 105), a cross-over trial of vibegron and mirabegron (107), two published ITC studies (4, 152) and the bespoke ITC conducted as part of this submission (Section B.3.9) that compared vibegron and mirabegron, have provided evidence for the similarity between vibegron and mirabegron and supported a cost-comparison case.

Results from the cost-comparison analysis demonstrate that vibegron is associated with an annual cost saving of [redacted] per patient, compared to mirabegron. Considering the high prevalence of OAB symptoms (16.5% of adults in Europe (36)), switching to vibegron may be associated with a substantial cost saving for the NHS.

There are no important uncertainties associated with the cost-comparison analysis, however, the analysis is associated with a limitation in a small subgroup of patients. Mirabegron is not recommended in patients with severe renal or hepatic impairment, uncontrolled hypertension, or those receiving specific drugs which may interact with mirabegron (of which, the consequences of dabigatran, digoxin and eliglustat are predicted to be potentially severe) (153). Therefore, in this subgroup of patients, mirabegron is not a valid comparator to vibegron. In the absence of data to inform the proportion of OAB patients with these contraindications, it is not feasible to conduct an economic analysis in this patient subgroup. However, it is expected that the impact of this subgroup on the base-case results would be limited.

In conclusion, it has been unequivocally demonstrated that vibegron meets the cost-comparison criteria and should be recommended as an option for treating patients with OAB symptoms for whom antimuscarinic drugs are contraindicated, are not clinically effective, or have unacceptable drug-mediated adverse effects. Overall, the cost-comparison analysis demonstrates that the annual drug acquisition cost of vibegron is [redacted]% lower than that of mirabegron. The results indicate that, considering the relatively high prevalence and incidence of OAB symptoms in the general population, vibegron is likely to be associated with substantial cost savings to the NHS.

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Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It's a plain English summary of their submission written for patients participating in the evaluation. It's not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it's sent to you.

The Summary of Information for Patients template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

Notes for authors: Please complete the template using plain language, taking time to explain all scientific terminology. As you draft your response, please do not delete the intro text included in each section. It might be a useful reference for patient reviewers.

However, any text preceded by the words '**Notes for authors**' simply contains additional prompts for the company to advise them on the type of information that may be most relevant, and the level of detail they need to include. **You may delete this text where indicated.**

Section 1: submission summary

1a) Name of the medicine

Both generic and brand name.

Generic name: vibegron Brand name: Obgemsa™

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

Symptomatic treatment of adult patients with overactive bladder (OAB) syndrome

1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Anticipated August 2024

1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

No disclosures

Section 2: current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen. **You may delete this note text.**

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Overactive bladder (OAB) syndrome presents in patients as a sudden, increased desire to pass urine. These “urgency episodes” may also be accompanied by other lower urinary tract symptoms (LUTS) including an increased urinary frequency, a lack of voluntary control (termed “urge incontinence”), or the interruption of sleep due to the need to pass urine (termed “nocturia”)(1). In the human body the bladder is surrounded by a wall of muscle called the detrusor muscle. Under the control of the nervous system, the bladder stores urine when the detrusor muscle is relaxed, and releases urine when the detrusor muscle contracts. OAB is caused by excessive activity of the detrusor muscle. In OAB this overactivity can originate either from the detrusor muscle itself, or from abnormalities within the part of the nervous system that receives signals (from the brain) to instruct the muscle to relax or contract. Many conditions that affect the nervous system can also increase the risk of developing OAB symptoms such as spinal cord injury, multiple sclerosis and stroke (2, 3).

OAB is very common, estimated to affect 455 million people worldwide, and the number of people affected (prevalence) is expected to continue to increase (4). In the UK it is estimated that approximately 5.15 million people have OAB, which is 17% of the adult population (5). Research has shown that the risk of developing OAB symptoms and the severity of symptoms increases with age, particularly from the age of 60 years onwards (6). Nearly one-third of retired people in the UK are reported to experience OAB symptoms (5).

Current research shows that OAB symptoms can severely impact a person's overall health and quality of life. People with OAB experience a lack of voluntary bladder control and therefore may avoid visiting places with limited bathroom access. This may negatively interfere with activities of daily living, including work and leisure, and, as a result, the person's social and mental well-being may be negatively impacted (7). Studies have shown that people with OAB tend have higher levels of depression, anxiety, and embarrassment/shame when compared with those without the condition (8-10). Quality of life can also be negatively impacted in terms of lower levels of work productivity, sexual function and satisfaction, and overall health (11). Lastly, inadequate management of OAB may also result in or further worsen other bothersome and/or serious medical conditions, such as falls/fractures, and depression/anxiety (12).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Diagnosis of OAB by healthcare professionals is made by following several processes to identify signs and symptoms that characterise OAB and to exclude other disorders which can cause lower urinary tract symptoms (LUTS) (13). Other conditions that affect urination can include metabolic disorders or urinary tract infections, and OAB will be diagnosed in the absence of these (14).

On presentation of a person with LUTS, healthcare professionals will take a full medical history to identify relevant urinary symptoms and behaviours, as well as current medical prescriptions and conditions ("comorbidities") which may affect the bladder (13). During initial assessment it is important that the lack of urinary control ("urgency incontinence") is characterised as being different to the involuntary loss of urine on effort or physical exertion such as from sporting activities, or on sneezing or coughing, which is called "stress urinary incontinence". Some people may have both urge and stress incontinence symptoms and will then be diagnosed as having "mixed urinary incontinence" (14). In this case, the predominant cause of incontinence is treated first (15).

Healthcare professionals may perform a physical examination of the body around the abdomen to assess for abnormalities or indications for the retention of urine (13). In men, the possible presence of an enlarged prostate causing obstruction and outflow complications will be considered (16, 17). Optional blood tests may also be performed, for instance to assess the cause of an enlarged prostate (17). In women, a history of childbirth or prior surgery may be asked, and a physical examination may be performed to assess or rule out the possibility of pelvic floor disorders, as well as the occurrence of vaginal prolapse or atrophy in those women who are post-menopausal (13, 17).

Laboratory tests may be carried out on a sample of the patient's urine ("urinalysis") to look for and rule out the presence of blood, or possible urinary tract infection (UTI) which may affect urination (13, 17). Patients may be asked to complete a 3-day bladder diary to help the healthcare professional to understand the nature and frequency of micturition (urination), urgency and nocturia. Finally, in some cases, patients may be asked to have their urine collected and measured to determine flow rates and bladder capacity in order to help confirm diagnosis of OAB (17).

Vibegron is a new treatment for OAB that the National Institute for Health and Care Excellence (NICE) are currently assessing. Vibegron will only be prescribed after OAB is diagnosed and usually

after antimuscarinic drugs have been tried. There are no additional diagnostic tests needed in order to prescribe vibegron, although patients may be asked to monitor their symptoms going forward.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

- Please also consider:

  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.

  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

A number of different treatments ("interventions") are available for the management of OAB and whether they are recommended will depend on the patient's response to previous treatment(s) including how it makes them feel (side effects). In guidelines used by healthcare professionals, recommended interventions are used in a sequential manner sometimes referred to as "treatment pathways" involving "lines of treatment". The treatment pathways used to manage OAB syndrome in the UK is presented in Figure 1, with details outlined below.

Lifestyle changes and physical therapies

Before starting treatment for OAB, people will be assessed for any medical conditions or risk factors which could contribute to their OAB symptoms, such as advanced age, diabetes mellitus, obesity and urinary tract infections (18). It is important to adequately manage contributory health conditions (comorbidities). Both men and women are typically educated on healthy bladder habits and are given lifestyle advice that may help mitigate symptoms such as improving their diet, reducing fluid intake, managing their weight, and stopping smoking (19). Physical therapy can also be considered in the management of OAB which might include urgency control techniques to help ignore the sudden, increased desire to urinate, as well as bladder training to help progressively increase the intervals between urination (19). Additionally, the use of a bladder diary and pelvic floor muscle training (in women) may also be recommended (19).

Antimuscarinic drugs

If conservative lifestyle and physical techniques fail to adequately manage symptoms, medical drugs ("pharmacotherapy") may be recommended. Typically, the first line drug treatments consist of a group of drugs called "antimuscarinics". Antimuscarinic drugs are taken by mouth and work by relaxing the detrusor muscle of the bladder, helping it fill and store urine. Options available on the NHS include oxybutynin, tolterodine, fesoterodine, solifenacin, trospium, darifenacin, and propiverine (20). In England, the choice of antimuscarinic drug is largely guided by cost, or on "what works" best for the patient (individual patient trials) (21).

Antimuscarinic drugs have been shown to improve some OAB symptoms, however, improvements in some patients may be modest (22). Importantly, before antimuscarinic drugs are prescribed, a full history and assessment of other medications the person may be taking is needed, to reduce the chance of unwanted effects (15). Antimuscarinic drugs can cause a range of side effects such as a dry mouth, constipation, blurred vision, and heart complications (22). Research has shown there to be an increased risk of dementia and harm to a patient's cognition (23-25), especially in

older patients (26, 27). Using antimuscarinic drugs in combination drugs with anti-cholinergic effects at the same time may result in a cumulative anticholinergic burden (28). Therefore, antimuscarinic drugs for OAB should not be used in people at increased risk of dementia and caution should be used wen prescribing multiple drugs with potentially similar anticholinergic effects.

Mirabegron

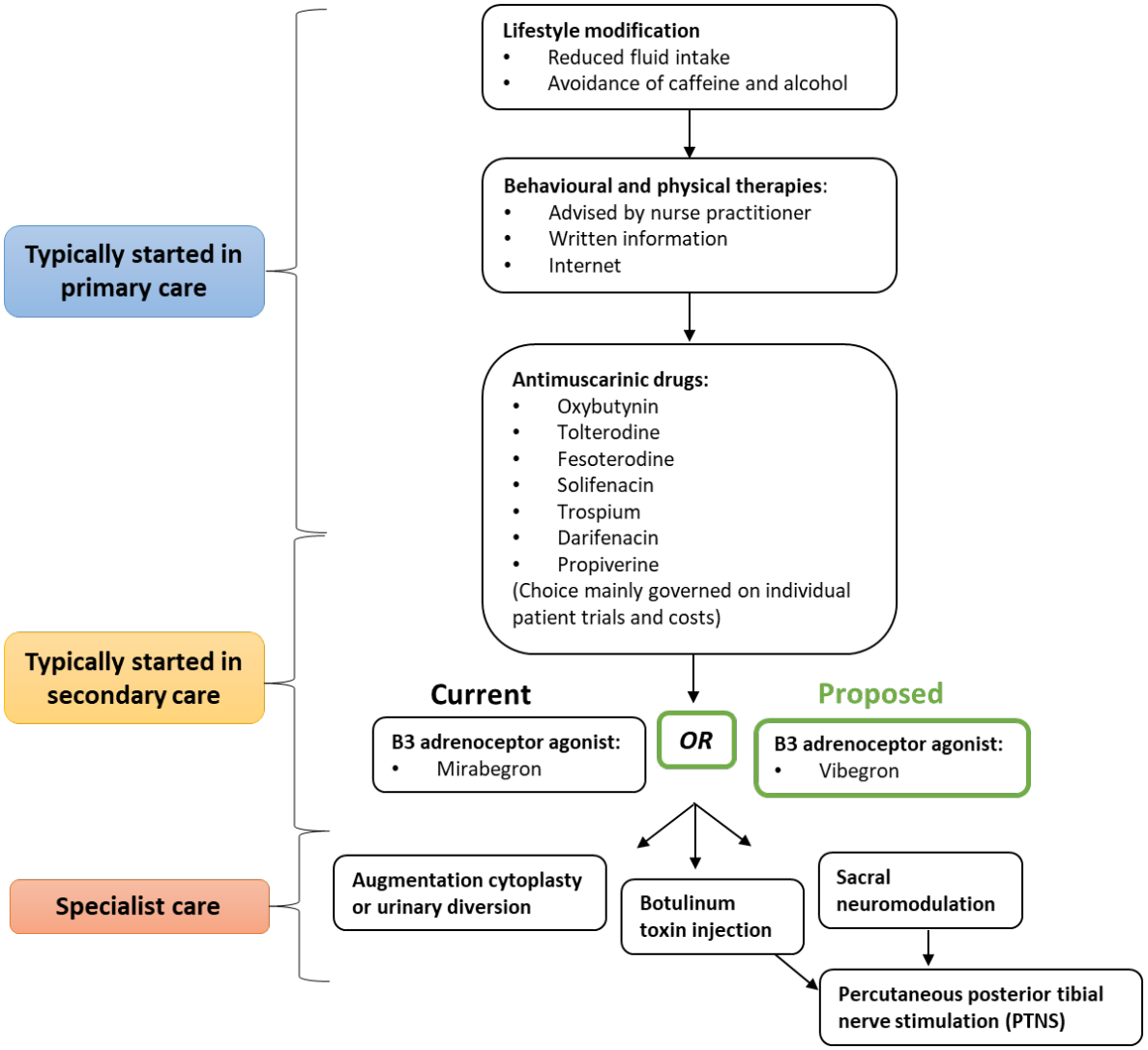
For patients with OAB who can't take or tolerate (because of side effects) antimuscarinics drugs, or in whom antimuscarinic drugs do not adequately control symptoms, there is currently only one second line drug treatment which may be offered (29). This drug is called mirabegron, which is a type of drug called a "beta-3-adrenoreceptor agonist" (β_3 adrenoceptor agonist). Like antimuscarinic drugs, this is taken by mouth (orally). Mirabegron also helps the detrusor muscle relax, but works in a different way to antimuscarinic drugs. Mirabegron is usually used instead of antimuscarinic treatment, not in addition to it (30). Although mirabegron is an option available in primary care (GPs), treatment with mirabegron is usually initiated in secondary care (clinics).

Evidence has shown that more patients persist taking mirabegron ("adhere") compared with antimuscarinic drugs (31), which helps make it an effective long-term treatment for OAB. However, mirabegron is not suitable for everyone, as the drug may affect how other medical drugs works ("drug interactions") (32, 33). Additionally there is an increased risk of causing harm from taking mirabegron in people with very high blood pressure, which means that mirabegron is not recommended for use in these people (34).

Surgery and procedures

In the large majority of cases, lifestyle advice and pharmacotherapy will sufficiently treat OAB, with surgical and procedural interventions normally only being considered in rare, severe, or non-responsive ("refractory") cases. Options available on the NHS include botulinum toxin A injections; sacral nerve stimulation, posterior tibial nerve stimulation (PTNS); augmentation cystoplasty; and, as a last resort, urinary diversion surgery (35). They are performed in specialist care.

Figure 1. Current patient pathway with proposed position of vibegron.



2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Evidence suggests that discontinuation rates of antimuscarinic drugs for treatment of OAB are actually significantly higher than that reported in clinical trials (22).

A patient survey in the USA, reported that out of 5392 patients asked on their use of antimuscarinic drugs for treating their OAB symptoms, 24.5% (1322 patients) said they had discontinued one or more muscarinic drugs prescribed for them. The top 4 reasons for stopping their OAB medication included the treatment not meeting their expectations, switching to new medications, treatment side effects, and learning to get by without medication (36).

Additionally, in a Swedish study, patients with OAB who were given an antimuscarinic drug (tolterodine) were asked about how much their OAB symptoms bothered them and how they thought their overall health-related quality of life (covering areas such as coping, social interaction, concern and sleep) was affected (37). All the patients had previously never taken antimuscarinic drugs and the tolterodine drug was given as an extended-release tablet allowing the drug to be released in the body slowly throughout the day (37). The study found that patients reported significant improvements in their OAB symptoms and health-related quality of life compared to before starting tolterodine treatment, however at a 6 month follow up 49% of patients had discontinued their treatment (37).

The CYCLAMEN study aimed to find out about the treatment patterns and use of antimuscarinic drugs in England over and 18-month period (38). The study reported from the 35,269 patients included that 10.2% (3,609 patients) had been given more than one type of antimuscarinic drug and, by the end of the 18 months, fewer than 20% patients were still taking antimuscarinic drugs (38). Overall, the results of the study strongly suggest that antimuscarinic drug therapy is suboptimal in primary care in England (38). In the CYCLAMEN study only 2.7% patients received mirabegron after starting an antimuscarinic drug.

A large European study assessed the quality of life, and treatment satisfaction, use and continuation in patients with OAB who were given mirabegron (39). This 12-month study surveyed 862 patients across 8 countries and showed improvements in their symptom bother and health-related quality of life. At the end of the study 53.8% patients had continued to take mirabegron and no unexpected side effects were reported (39).

Section 3: the treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly. **You may delete this note text.**

3a) How does the new treatment work? What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Vibegron belongs to a group of drugs known as β_3-adrenegic receptor agonists which target the detrusor muscle surrounding the bladder. Vibegron acts by stimulating β_3-adrenegic receptors in the bladder, which, through neurological pathways involving the brain, instruct the bladder muscle to relax which results in the bladder having increased capacity to store urine (40). This is the same as how mirabegron works. It is also similar to how anti-muscarinic drugs work, except these drugs block the action of muscarinic receptors in the bladder, which ultimately has a similar bladder relaxing effect (22).

β_3-adrenegic receptors are part of a larger family of receptors which interact with part of the nervous system known as the sympathetic nervous system. Other adrenergic receptors, called β_1- and β_2-adrenergic receptors, are found in the cardiovascular (heart and blood vessels) and respiratory (lungs) systems (41). Importantly, vibegron has very little effect on β1- and β2 receptors (which otherwise could result in serious side effects) and instead mostly acts selectively on the β_3 variant. This means vibegron can be used in patients with pre-existing high blood pressure ("hypertension"). This is not the case for mirabegron in people who have severe hypertension (34). A further advantage of vibegron compared with mirabegron is that it has a lower potential to interact with other medications a person is taking (42). This is important in the treatment of OAB as people with this condition are often older and taking multiple drugs for other conditions.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

☐Yes

☒No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Vibegron does not have to be taken with other medicines. Usually, vibegron is used instead of or after antimuscarinic treatment or as an alternative option to mirabegron.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Vibegron is formulated in a 75 mg tablet which can be taken orally (by mouth), with or without food. Vibegron tablets can be crushed, making them easier to swallow when added to water or juice. Vibegron is taken once daily.

Other pharmacological treatments for OAB are also taken orally. However, other drug treatments require more frequent dosing or dose adjustments may be necessary.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Vibegron has been used to treat patients with OAB in one large pivotal phase 3 trial, the EMPOWUR study, which also carried out an extension of the study (EMPOWUR-EXT) in the anticipated UK licence dose of 75mg. In addition, 6 other studies have been conducted in patients with OAB using varying (3 to 100mg) unlicensed doses of vibegron. A summary of these trials is reported in Table 1.

Table 1. A summary of completed or ongoing trials relating to vibegron.

Study Name and code	Phase	Location	Patient Characteristics	Number of Patients	Treatments Used	Timeframe
Trials using anticipated UK licence vibegron dose (75mg)						
EMPOWUR (NCT03492281) (43)	3	Multinational (6 countries)	People (aged ≥18 years) with OAB	1,518	75mg vibegron vs placebo vs 4mg ER tolterodine	26 Mar 2018 – 7 Jan 2019
EMPOWUR-EXT (NCT03583372) (44)	3	United States	People (aged ≥18 years) with OAB who completed the EMPOWUR trial	506	75mg vibegron vs 4mg ER tolterodine	Jun 2018 – Jul 2019
Trials using alternative vibegron doses						
Yoshida et al 2018 (45)	3	Japan	People aged ≥20 years with OAB	1224	50,100mg vibegron vs placebo vs 0.1mg midafenacin	June 2015 - June 2016

Mitcheson et al 2019 (46)	2	United States	People with OAB		3,15, 50,100mg vibegron vs placebo vs 4mg ER tolterodine	April 2011 - October 2013
Kinjo et al 2023 (47)	NR	Japan	Women with OAB	213	50mg vibegron Vs 50mg mirabegron	January 2019 - December 2021
Sato et al 2023 (48)	NR	Japan	Post-menopausal women with OAB who have not received treatment before	104	50mg vibegron Vs 50mg mirabegron	December 2019 - September 2022
Shin et al 2023 (49)	NR	South Korea	People with OAB	210	50 mg vibegron Vs placebo	September 2020 - August 2021
Wada et al 2023 (50)	NR	Japan	Women (aged ≥50 years) with OAB who have not received treatment before	80	50 mg vibegron Vs mirabegron	NR

Abbreviation: ER, extended release; NR, Not reported; OAB, Overactive bladder

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

- Are any of the outcomes more important to patients than others and why?
- Are there any limitations to the data which may affect how to interpret the results?

Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Vibegron is to be administered in the UK at a dose of 75 mg per day. Therefore, the most relevant evidence on how effective vibegron is in the treatment of OAB comes from the phase 3 pivotal trial EMPOWUR (51), which compared vibegron 75 mg with placebo and an active comparator, tolterodine (4 mg). The main (primary) outcomes reported after 12 weeks' treatment. Some patients recruited in this trial also participated in an extended trial (EMPOWUR-EXT), which compared vibegron with tolterodine and reported outcomes at 52 weeks (52). In both studies, the patients were blinded, so they did not know which treatment they were receiving.

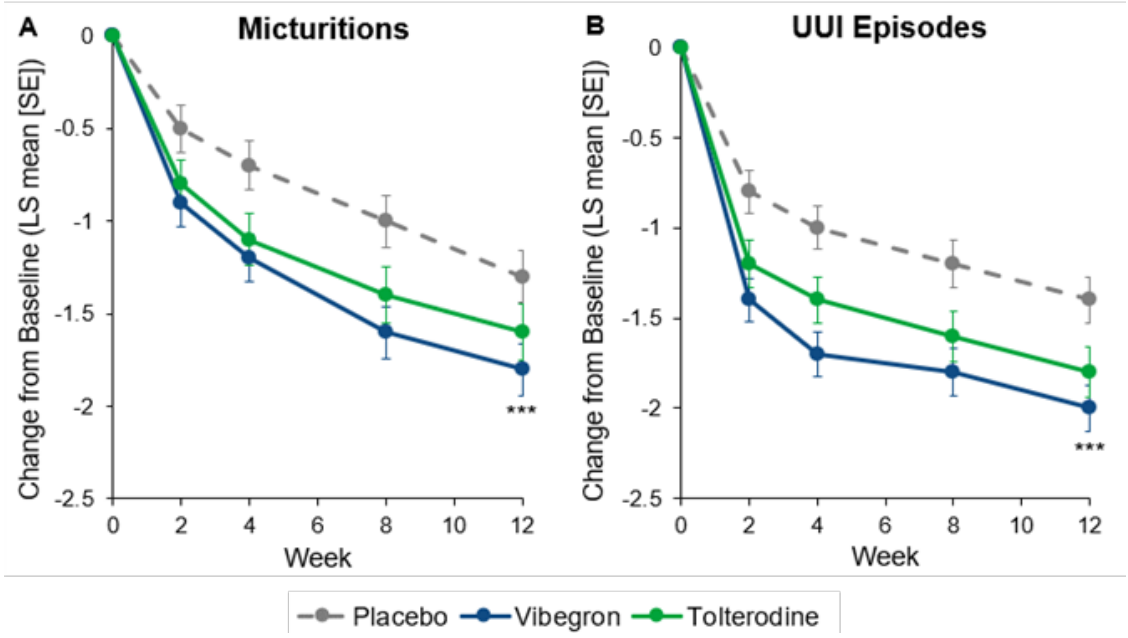
The primary outcomes of EMPOWUR (the outcomes selected in advance to show how effective the drug is) were the number of micturitions (defined as number of times a participant voided/urinated in the toilet) per day and the number of episodes of urgency urinary incontinence (UUIs) per day, (defined as when a person can't make the toilet in time). These were recorded by

the patients using a 7-day diary. At 12 weeks, EMPOWUR reported that vibegron was statistically superior to placebo in both these outcomes and numerically superior to tolterodine:

- Micturitions: difference from baseline of -1.8 for vibegron (n=492) compared with -1.3 for placebo (n=475), with a difference between interventions of -0.5 (95% confidence interval [CI] -0.8 to -0.2, p< 0.001).
- UUI episodes: difference from baseline of -2.0 for vibegron (n=383) compared with -1.8 for placebo (n=372) compared with 1.3 for placebo (n=475), with a difference between interventions of -0.6 (95% CI -0.9 to -0.3, p<0.0001).

These results are reported graphically in Figure 2. In terms of secondary outcomes (extra measurements giving information on the effectiveness of vibegron), vibegron was found to be statistically superior to placebo in terms of urgency episodes (times when there was a sudden desire to urinate, without incontinence), total episodes of incontinence (due to any cause), volume of urine voided (more is better), and OAB-q coping score (a measure of quality of life, see Section 3f).

Figure 2. Change from baseline in average daily number of (A) micturitions (FAS), (B) UUI episodes (FAS-I).

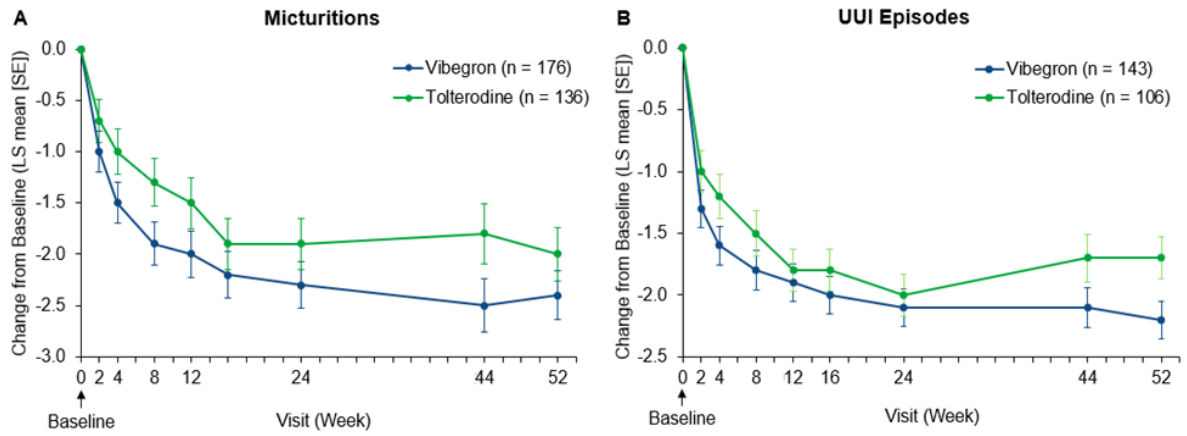


Abbreviations: FAS = full analysis set; FAS-I = full analysis set for incontinence; LS = least squares; SE = standard error; UUI = urge urinary incontinence.

Note: *** denotes p<0.001 for vibegron vs. placebo using a mixed model for repeated measures.

The EMPOWUR-EXT study showed the positive primary outcomes persisted for at least one year (52 weeks). Vibegron compared favourably with the active comparator, tolterodine, with numerically superior results (shown in Figure 3). Of note, 41% of patients treated with vibegron were effectively 'dry' at Week 52 (i.e. had zero incontinence episodes over 7 days), as evidenced by a 100% reduction in average daily number of UUI episodes.

Figure 3. LS mean change from baseline in average daily number of (A) micturitions (FAS-Ext) and (B) UUI episodes (FAS-I-Ext) over 52 weeks, EMPOWUR-EXT study.

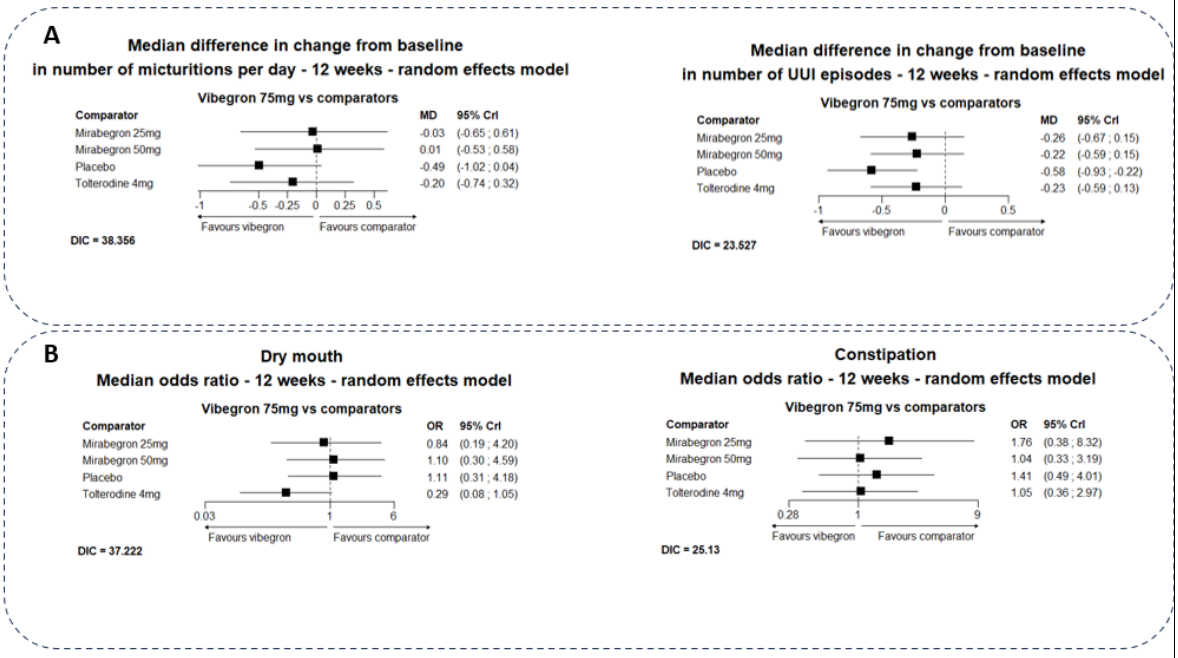


Abbreviations: FAS-Ext = full analysis set extension; FAS-I-Ext = full analysis set for incontinence extension; LS = least squares; SE = standard error; UUI = urge urinary incontinence.

As most drugs like vibegron behave in a "dose-response" manner (that is, they are possibly more effective at higher doses, but have possibly more side effects), the trials involving 50 mg vibegron (Table 1) are less informative than EMPOWUR and EMPOWUR-EXT. Nevertheless, these trials all demonstrated favourable results for vibegron.

Of particular interest are the head-to-head trials which compared vibegron directly with mirabegron (47, 48, 50). This is because, although these trials were small and assessed at being at high risk of bias (at risk of giving unreliable results), vibegron is intended to be an alternative to mirabegron in the patient pathway (Figure 1). These studies all reported that vibegron was at least as effective ("non-inferior") compared with mirabegron in the key efficacy outcomes (such as the number of daily micturitions and UUIs. Another way of comparing the effectiveness of vibegron with mirabegron, using the correct dose of vibegron, is to conduct an indirect treatment comparison (ITC). This is a statistical method where separate trials involving different interventions but having a common comparator (usually placebo) are combined using statistical techniques. Two published ITCs on vibegron compared with mirabegron concluded the drugs had similar efficacy, with vibegron being non-inferior to mirabegron (53, 54). In their submission to NICE, the company also performed a bespoke ITC, which showed vibegron was similar to or as effective as mirabegron (Figure 4). Because of these results, we can be confident that substituting mirabegron with vibegron 75 mg will not lead to worse outcomes for patients, in terms of drug effectiveness and key safety outcomes.

Figure 4. Results of bespoke ITC conducted by company (key parameters).



Abbreviations: CEM, cost-effectiveness model; CrI, credibility interval; DIC, deviance information criteria; ITC, indirect treatment comparison; MD, mean difference; OR, odds ratio; TA, technology appraisal; UUI, urinary urge incontinence.
Key: Key primary efficacy outcomes from ITC used to inform CEM of TA290 (number of micturitions and number of episodes of UUI; B, key safety outcomes from ITC used to inform CEM of TA290 (dry mouth and constipation determined the rate of drug discontinuation).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

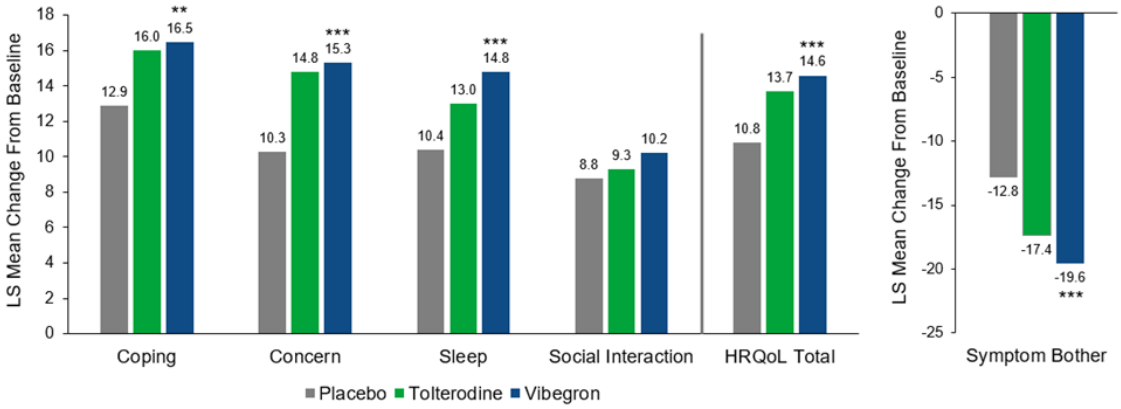
Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

OAB syndrome is a disorder that rarely has serious clinical effects but can have a very large impact on a person's quality of life. This is because OAB can negatively impact on a person's working and social life, for example, people may avoid activities where access to a toilet is limited (see Section 2a). For this reason, quality of life was an important outcome in the EMPOWUR trial (51).

There are two main methods of measuring quality of life. The first is by using disease specific quality of life tools, which are sensitive to the symptoms associated with that specific condition. EMPOWUR used the OAB-q tool, and reported that vibegron was numerically superior to tolterodine and statistically superior to placebo in the scores of coping, concern, sleep, health-related quality of life (HRQoL), and symptom bother (all $p<0.01$, illustrated graphically in Figure 5).

Figure 5. Mean change from baseline to Week 12 in OAB-q scores for coping, concern, sleep, social interaction, HRQoL total, and symptom bother, EMPOWUR study (FAS).



Abbreviations: FAS = full analysis set; HRQoL = health-related quality of life; LS = least squares; OAB = overactive bladder; OAB-q = overactive bladder questionnaire.

The second way of measuring the effect of a drug on quality of life is to use a generic measurement, such as the EQ-5D score favoured by NICE. The EMPOWUR trial (51) found no important differences between interventions (vibegron, placebo, or tolterodine) in terms of changes in EQ-5D. However, measures like EQ-5D tend to be less sensitive to detecting symptomatic changes in specific diseases like OAB. Also, the EMPOWUR trial was a short-term study, and may not have been long enough to detect a statistical difference. Generic measurements such as EQ-5D are often used because they allow for comparisons across different disease groupings, which helps health technology agencies such as NICE make decisions on how to fund drugs across disease groups.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The EMPOWUR trial (51) directly provided data on adverse events associated with vibegron, placebo and tolterodine. These are unwanted clinical occurrences which may (or may not) be related to the treatment the patient is receiving. (51). Any adverse event of clinical interest occurred in 7.4% of patients in the placebo group, 6.6% in the vibegron group, and 8.8% in the tolterodine group. Serious adverse events were uncommon in all groups, occurring in 1.1% in the placebo group, 1.5% in the vibegron group, and 2.3% in the tolterodine group. Adverse events leading to discontinuation (the patient stopping taking the drug) occurred in 1.1% in the placebo arm, 1.7% in the vibegron arm, and 3.3% in the tolterodine arm. Safety data from EMPOWUR, broken down to the level of individual adverse events, is reported in Table 2.

Table 2. Adverse events reported by ≥2% of patients in the vibegron, tolterodine, or placebo groups over 12 weeks, EMPOWUR study (safety analysis set).

Endpoint	Placebo (n = 540)	Vibegron (n = 545)	Tolterodine (n = 430)
Hypertension *	1.7%	1.7%	2.6%
Urinary tract infection	6.1%	5.0%	5.8%
Headache *	2.4%	4.0%	2.6%
Nasopharyngitis	1.7%	2.8%	2.6%
Diarrhoea	1.1%	2.2%	2.1%
Nausea	1.1%	2.2%	1.2%
Upper respiratory infection	0.7%	2.0%	0.5%
Dry mouth †	0.9%	1.7%	6.5%
Constipation †	1.3%	1.7%	1.4%

* A priori safety end point of interest according to trial protocol, relating to the mechanism of action of vibegron, which could theoretically increase blood pressure.

† Adverse events that informed the cost-effectiveness model of TA290.

No clinically meaningful differences were observed between vibegron and tolterodine groups in the overall incidence or severity of adverse events or serious adverse events in the EMPOWUR-EXT study (52), giving confidence in the longer-term safety and tolerability of the drug. Vibegron was associated with fewer episodes of dry mouth compared with tolterodine, which is a common side effect of antimuscarinic drugs. Overall, vibegron appears to be a well-tolerated drug with no important safety concerns identified.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Vibegron is of the same class of drug as mirabegron and shares the same mechanism of action as this drug. Both evidence from head-to-head trials (limited by the use of 50 mg dose of vibegron) and indirect statistical comparisons with the licensed 75mg dose indicate that vibegron is at least as effective in the treatment of OAB as mirabegron. In common with mirabegron, vibegron is proven to be more effective than placebo and is likely to have improved efficacy compared with antimuscarinic drugs. Vibegron does not cause anticholinergic effects like dry mouth, which is a significant reason for discontinuation of first line antimuscarinic drugs. However, vibegron has the following advantages over mirabegron:

- Vibegron is taken as a simple crushable one-tablet regimen. There is no need to adjust the dose for people with renal (kidney) or hepatic (liver) problems, and as it can be mixed with liquid it is suitable for people who have difficulty swallowing.
- There are fewer restrictions associated with vibegron use, for instance in people with pre-existing severe hypertension.
- Vibegron may be used in combination with other drugs used to treat other conditions, which is not always true for mirabegron. For instance, mirabegron should not be used with the blood thinning drug dabigatran (55). This is especially important in the older population, where many people are taking multiple drugs (“polypharmacy”).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Vibegron is intended as an alternative treatment option to mirabegron. There are no known disadvantages associated with the use of vibegron compared with mirabegron or antimuscarinic drugs.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

  If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?

Usually when a new drug treatment is assessed by NICE, it is not enough to show it is clinically effective, it must also be shown to be cost-effective. This means the drug provides value for money by providing additional benefits within a certain cost value. In 2013 NICE published guidance on Mirabegron for treating symptoms of overactive bladder (TA290) (60). NICE found that mirabegron was cost-effective compared with antimuscarinic drugs using a cost-effectiveness model (CEM) and was recommended for use in the NHS for people in whom antimuscarinic drugs are not effective, can't be used ('contraindicated'), or cause unacceptable side effects.

NICE have introduced a new process whereby a drug which is similar to a drug already used in the NHS can be recommended if it can be demonstrated it is at least equivalent ("non-inferior") in all important ways compared with the existing drug, on the basis of a "cost comparison". For this process, the new drug (the intervention) has to demonstrate it is at least as safe and effective as the current drug treatment (the comparator) and will not incur any additional costs. The company (Pierre Fabre) has submitted a cost-comparison to NICE based on this assumption.

Vibegron will be made available to the NHS at a lower NHS list price than mirabegron.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Vibegron is a new generation β_3-agonist intended for the treatment of OAB. Although it is not a first-in-class drug, vibegron has specific advantages compared with the sole other drug in this class (mirabegron), discussed in section 3h.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

There are no equality considerations anticipated with the introduction of vibegron into the NHS.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Bladder Health UK – Lifestyle changes in OAB. https://bladderhealthuk.org/overactive-bladder/oab-treatments/lifestyle-changes

British Association of Urological Surgeons (BAUS)- Information about bladder training. https://www.baus.org.uk/_userfiles/pages/files/Patients/Leaflets/Bladder%20training.pdfPatient

Patient Info UK – Patient information leaflet. What is overactive bladder syndrome? | Patient

Bladder Health UK – Support group. https://painuk.org/members/charities/cystitis-and-overactive-bladder-foundation-uk/

Further information on NICE and the role of patients:

- Public Involvement at NICE
- NICE's guides and templates for patient involvement in HTAs
- EFPIA – Working together with patient groups (PDF)
- National Health Council Value Initiative

4b) Glossary of terms

Cost-effectiveness is a method to examine both the costs and health outcomes of one or more interventions, that is, to establish value for money.

CEM: a cost-effectiveness model is an analytic framework used to synthesise information on a range of variables (natural history, clinical efficacy, health related quality of life, resource use and costs) in order to estimate the costs and benefits associated with two or more interventions.

ITC: an indirect treatment comparison a method of deriving a comparative estimate between two treatments (treatment A and treatment B) which are not directly compared in head to head trials (or other studies), but which have both been compared to another intervention (treatment C, often placebo).

LUTS: lower urinary tract symptoms is a collective term used to describe the problems related to the working of the bladder (which holds urine) and the urethra (the tube from the bladder to outside) through which urine passes when we urinate. OAB is a subtype of LUTS.

NICE: the National Institute for Health and Care Excellence is an executive non-departmental public body of the Department of Health and Social Care in England. Amongst other responsibilities, it evaluates the clinical and cost-effectiveness of new technologies seeking adoption into the NHS of England as part of the technology appraisal process.

Nocturia is the need for patients to get up at night on a regular basis to urinate. This not only disturbs sleep and quality of life, but also increases the risk of falls.

OAB: overactive bladder (syndrome) is where a person regularly gets a sudden and compelling need or desire to pass urine. This sensation is difficult to put off (defer) and this can happen at any time during the day or night, often without any warning. It differs from other types of bladder disorder, such as stress incontinence, where urine leaks under pressure due to weak muscle tone, or symptoms in men associated with blockage (e.g. enlarge prostate).

Quality of life is a concept that measures the wellbeing and happiness of a group or an individual. OAB is a condition which has a great impact on quality of life.

UUI: urgency urinary incontinence is the involuntary urine leakage associated with urgency and is amongst the most distressing symptoms of OAB.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison Appraisal

Vibegron for treating symptoms of overactive bladder ID 6300

Clarification questions

April 2024

File name	Version	Contains confidential information	Date
ID6300 Vibegron for treating symptoms of OAB clarification questions v0.3 CON _PF response_V1.0_08 MAY 24_CON redacted	1.0	Yes	08/05/2024

Notes for company

Highlighting in the template

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To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Missing references and files

A1. Priority question. If these have not been provided by the time the clarification questions have been received, please provide as soon as possible:

a) **The EMPOWUR study and EMPOWUR extension study CSR, SAP and Protocols.**
b) **CSRs, SAPs and Protocols for any other company sponsored study referenced in the CS.**
c) **The full ITC report.**
d) **The R code used to perform the NMAs, and the input data files read by the R script, such that the EAG can reproduce the NMAs.**
e) **Any other numbered references and data on file that has not yet been provided, including references cited as "available on request". This includes reference numbers 10, 11 and 149.**
f) **The full text corresponding to the Wada *et al.* 2023 abstract.**
g) **Full texts of each study included in the NMA that were not originally included in the supplied references, including Nitti 2014.**

All requested materials listed above have been provided and uploaded to NICE Docs.

A further note regarding use of the provided Rcodes and data files:

The data files are saved in Excel format with the analyses for safety and efficacy saved separately. Forest_plot.R and forest_plotOR.R are functions to plot the results and Summary_plots saves all the results to a Word file. In all files "path" should be changed to where the folder is saved at the beginning of each script. We have added comments where this should be done. Also of note, since we used Bayesian models and simulations results differ slightly (around 0.01 depending on scale) compared with the results from the report when we rerun analyses, but the differences should be minimal. This is usual with this type of analysis.

Also of note, the reference #126 "*Nitti 2014"* should be "*Nitti 2013"* This was due to a reporting error regarding the date of the articles. Additionally, an incorrect PDF reference was provided for #130 *Herschorn 2017* as part of the reference pack. The correct version will be resent alongside this response and will supersede the previously sent reference.

Indirect Treatment Comparisons

A2. Priority question. The EAG notes that the company has not included head-to-head studies of vibegron 50 mg and mirabegron 50 mg in the NMAs due to a lack of generalisability to the decision problem, as vibegron will only be available at 75 mg in the UK. Nevertheless, the EAG notes a meta-analysis of the evidence of vibegron 50 mg compared to mirabegron 50 mg from direct randomised trials may provide supporting evidence of the non-inferiority of vibegron 75 mg to mirabegron 50 mg. Please update the overall NMA to include the vibegron 50 mg as a node in the network, including all relevant RCTs of vibegron 50 mg.

Response

Respectfully, we have not undertaken this request because we do not agree that this approach is logical and do not believe analyses of this type will add insight into addressing the decision problem. The principal reason for this is because the

placebo-controlled RCTs reported by Yoshida et al. (2018) (1) and Mitcheson et al. (2019) (2) used vibegron at doses of 50 or 100 mg, whereas the RCT by Shin et al. (2023) used vibegron at a dose of 50 mg (3). However, vibegron will be available in the UK only at a dose of 75 mg without dose adjustment. Vibegron is a small molecule drug acting as an agonist on β_3 adrenoceptors. As such, the efficacy of vibegron and augmented adverse effects will be expected to be subject to a dose-response relationship (4). Therefore, the addition of network nodes and data reporting on vibegron at a dose of 50 or 100 mg into the NMA would merely add additional uncertainty. Please also note that in the NMA, the other active interventions included are mirabegron at 25 or 50 mg (disaggregated), and tolterodine at 4 mg extended release (ER). These drugs were selected for analysis at this level of granularity as they are available in the NHS at these doses.
We believe that the addition of the head-to-head parallel trials (5, 6) into the NMA will introduce a study selection bias, t. Furthermore, whilst results from the head-to-head trials (using doses not licensed in the UK) did indeed demonstrate non inferiority, we should note that these studies enrolled a restricted population of patients (post-menopausal women), had relatively small sample sizes, and were open label, so considered to be at high risk of bias. As these were not company studies, we do not have access to the individual patient data (IPD) for these studies. Finally, because of the methodological differences in the cross-over study reported by Wada et al. (2024) (7), it would not be possible to use this in the NMA.

A3. Priority question. The EAG notes that EQ-5D index score outcomes are available from EMPOWUR, and at least the following trials of mirabegron: SCORPIO, CAPRICORN and ARIES. To strengthen the case for clinical similarity between vibegron and mirabegron, please provide an NMA comparing the change from baseline in EQ-5D index score at Week 12, and Week 52 if data are available, between vibegron 75 mg, tolterodine 4 mg, placebo and mirabegron 50 mg.

Response

Respectfully, we have not undertaken this request for several reasons.

- Firstly, following our review of the reporting of health-related quality-of-life (HRQoL) reported in the mirabegron studies, we do not see any EQ-5D

values reported. Either HRQoL data were not reported (12-15), or it was reported using the treatment satisfaction visual analogue scale (TS-VAS) (9, 10, 16), which is not analogous to EQ-5D.

- Secondly, as you will be aware, mirabegron was evaluated by the single technology assessment (STA) route by NICE in 2013 (TA290) (8). The cost-effectiveness model (CEM) used in TA290 did not use raw utility data from the relevant trials of mirabegron, namely the ARIES (9), SCORPIO (10) and CAPRICORN (11) trials. Rather, the company used a linear regression model to estimate utility values for the 25 health states in the CEM, using reference data from SCORPIO (10). Thus, we cannot make a direct or indirect comparisons with the utility data used in the CEM, which ultimately guided NICE's recommendation decisions.
- Thirdly, even if EQ-5D were reported, we do not believe we can compare EQ-5D index and utility values derived in different trials without raising serious concerns about study heterogeneity and uncertainty. For example, EQ-5D values are conditional on the method used (EQ-5D-3L or EQ-5D-5L, visual analogue scale [VAS]) (17). Furthermore, EQ-5D are known to vary depending on the country and region (18).
- Finally, differences in EQ-5D values associated with treatment with mirabegron compared with vibegron are likely to be small and not amenable to further data synthesis. This is because generic HRQoL measures such as EQ-5D are known to be relatively insensitive to changes in OAB (19). This was observed in TA290, where it was noted that the value of the incremental quality adjusted life-years (QALYs) (derived from EQ-5D based utility scores) reported in the model were relatively small. For instance, the incremental gain in QALYs of mirabegron compared with tolterodine was 0.0005 (8).

We are also unaware of any published study that has compared EQ-5D values indirectly using an NMA. However, we have provided a naïve comparison of HRQoL results reported in the studies included in the NMA in Table 1. Of note, whilst EQ-5D were reported as exploratory analyses in both the EMPOWUR trial (20) and EMPOWUR-EXT (21), with neither study powered to detect statistical differences, in both studies vibegron was associated with numerical superiority compared with placebo or active comparator (tolterodine 4 mg ER).

Table 1 Adjusted mean change in EQ-5D by treatment arm at 12, 24, and 52 weeks in trials included in NMA

Study (Author, year)	Country	EQ-5D measurement	Instrument	Treatment arm	EQ-5D adjusted mean change from baseline ± SE (95% CI)		
					12 weeks	24 weeks	52 weeks
ARIES Nitti 2013 (9)	United States, Canada	TS-VAS	NR	Placebo (n=454)	+0.70 ± 0.16 (0.4-1.0)	NR	NR
				Mirabegron 50mg (n=442)	+1.55 ± 0.16 (1.2-1.9)	NR	NR
				Mirabegron 100mg (n=433)	+2.09 ± 0.16 (1.8-2.4)	NR	NR
CAPRICORN Herschorn 2013 (11)	United States, Canada, Czechia, Denmark, Finland, Germany, Hungary, Norway, Slovakia Spain, Sweden	TS-VAS	NR	Mirabegron 25 mg (n=410)	+1.54 ± 0.15	NR	NR
				Mirabegron 50 mg (n=426)	+1.88 ± 0.15	NR	NR
EMPOWUR Staskin 2020 (20)	United States, Canada, Hungary, Latvia, Lithuania, Poland	VAS	NR	Placebo (n=520)	+1.7 ± 14.20*	NR	NR
				Vibegron 75mg (n=526)	+3.4 ± 13.28*	NR	NR
				Tolterodine ER 4mg (n=417)	+2.4 ± 12.67*	NR	NR
		Index Score	NR	Placebo (n=520)	+0.0162 ± 0.12756*	NR	NR
				Vibegron 75mg (n=526)	+0.0300 ± 0.199590*	NR	NR
				Tolterodine ER 4mg (n=417)	+0.0312 ± 0.11379*	NR	NR
EMPOWUR (Extension)	United States	VAS	NR	40-weeks Vibegron 75mg (n=90)	NA	+5.0 ± 13.60* (n=86)	+4.3 ± 14.63* (n=83)

Staskin 2021 (22)				52-weeks Vibegron 75mg (n=176)	+4.5 ± 11.75* (n=175)	+4.3 ± 11.61* (n=168)	+5.3 ± 13.82* (n=166)
				40-weeks Tolterodine ER 4mg (n=83)	NA	+1.6 ± 10.77* (n=81)	+1.8 ± 13.28* (n=74)
				52-weeks Tolterodine ER 4mg (n=136)	+3.8 ± 12.89* (n=136)	+3.2 ± 13.00* (n=131)	+3.6 ± 13.03* (n=134)
		Index Score	NR	40-weeks Vibegron 75mg (n=90)	NA	0.0340 ± 0.14280* (n=86)	0.0361 ± 0.15787* (n=83)
				52-weeks Vibegron 75mg (n=176)	0.8625 ± 0.13426* (n=175)	0.0552 ± 0.13700* (n=168)	0.0774 ± 0.18459* (n=166)
				40-weeks Tolterodine ER 4mg (n=83)	NA	0.0226 ± 0.15060* (n=81)	0.0348 ± 0.17330* (n=74)
				52-weeks Tolterodine ER 4mg (n=136)	0.8831 ± 0.12447* (n=136)	0.0548 ± 0.14250* (n=131)	0.0553 ± 0.14324* (n=134)
Kuo 2015 Kuo 2015 (23)	Taiwan, Korea, China, India	NR	NR	NR	NR	NR	NR
Moussa 2021 Moussa 2021 (24)	Lebanon	NR	NR	NR	NR	NR	NR
SCORPIO Khullar 2013 (10)	Australia, Austria, Belarus, Belgium, Bulgaria, Czechia, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, Slovakia,	TS-VAS		Placebo (n=428)	+1.89 ± 0.146	NR	NR
				Mirabegron 50mg (n=414)	+2.55 ± 0.149	NR	NR
				Mirabegron 100mg (n=427)	+2.66 ± 0.146	NR	NR
				Tolterodine ER 4 mg (n=425)	+2.44 ± 0.147	NR	NR

	South Africa, Spain, Sweden, Switzerland, Ukraine, United Kingdom						
SYNERGY Herschorn 2017 (12)	Canada, Denmark, Germany, Italy, Netherlands, Norway, Poland, Spain, Sweden, Turkey, United Kingdom	NR	NR	NR	NR	NR	NR
TAURUS Chapple 2013 (16)	United States, Australia, Austria, Belarus, Belgium, Canada, Czechia, Denmark, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Switzerland, Ukraine, United Kingdom	TS-VAS	NR	Mirabegron 50 mg (n=812)	NR	NR	2.08 ± 0.17
				Mirabegron 100 mg (n=820)	NR	NR	+2.11 ± 0.16
				Tolterodine ER 4 mg (n=812)	NR	NR	+2.27 ± 0.16
Yamaguchi 2014 Yamaguchi 2014 (15)	Japan	NR	NR	NR	NR	NR	NR
Abbreviations: CI, confidence interval; EQ-5D, EuroQol-5D; NR, not reported; SE, standard error; TS, treatment satisfaction; VAS, visual analogue score *This information was taken from clinicaltrial.gov record for the trial as the information was not reported in the published article							

A4. Priority question. The company's evidence for a similar or non-inferior rate of treatment discontinuation comes from the NMAs of adverse events leading to study treatment discontinuation at Week 12 and Week 52. However, this does not cover all reasons for treatment discontinuation.

a) **Using the participant dispositions/flows from each trial (i.e., those reported in Appendix D1.2 for EMPOWUR, and equivalent data for TAURUS), please provide a comparison of the rate of treatment discontinuation up to 52 weeks for vibegron 75 mg, tolterodine 4 mg and mirabegron 50 mg from EMPOWUR, EMPOWUR-EXT and TAURUS.**
b) **Please provide a scenario around this analysis where participants who were eligible for EMPOWUR-EXT following the first EMPOWUR phase but did not enter the study are included as discontinuations in this comparison.**

Response a

We have provided the requested data for all trial included in the NMA in Table 2 (stratified by drug).

Response b

The extension study was planned to provide longer-term data on the safety and tolerability of vibegron. Approximately five hundred (500) subjects were considered sufficient to characterise the long-term safety profile of vibegron 75 mg once daily and to satisfy ICH guidance for 1-year exposure, and the extension study was designed with this in mind. Patients were recruited if they met the inclusion criteria. In total, [redacted] were entered into the extension with [redacted] not entering. It is important this was **not** because they discontinued treatment, but because the EMPOWER-EXT sample size was reached at which point enrolment ceased. The patients who left EMPOWUR and were not included in EMPOWUR-EXT were not followed up further. Given this, we are unable to provide a meaningful NMA scenario of discontinuation of vibegron using this dataset, as it is not a reflection of discontinuation.

A comparison of patients from the seminal and extension studies are provided in Table 3 taken from the published data. A further comparison of the patient

characteristics in those that entered the extension study compared with those that did not (data taken from the CSR) is provided in answer to question A19.

Table 2. Information on the reasons for patients discontinuing participation in the studies included in the NMA.

Study	Author and Year	Country	Treatment arm	Discontinuation, n (%)			Reason for Discontinuation Stratified by Occurrence Frequency, n (%)
				12 weeks	40 weeks	52 weeks	
ARIES	Nitti 2013 (9)	United States, Canada	Mirabegron 50mg (n=442)	59 (13.3%)	NA	NA	• Withdrew consent: 22 (5.0%) • Lost to follow-up: 9 (2.0%) • AE: 18 (4.1%) • Other: 5 (1.1%) • Protocol violation: 4 (0.9%) • Efficacy: 1 (0.2%)
			Mirabegron 100mg (n=433)	53 (12.2%)	NA	NA	• AE: 19 (4.4%) • Withdrew consent: 16 (3.7%) • Efficacy: 5 (1.2%) • Protocol violation: 5 (1.2%) • Other: 4 (0.9%) • Lost to follow-up: 3 (0.7%) • Eligibility criterion not met: 1 (0.2%)
CAPRICORN	Herschorn 2013 (11)	United States, Canada, Czechia, Denmark, Finland, Germany, Hungary, Norway, Slovakia Spain, Sweden	Mirabegron 25mg (n=433)	46 (10.6%)	NA	NA	• Withdrew consent: 12 (2.8%) • AE: 17 (3.9%) • Other: 5 (1.2%) • Efficacy: 4 (0.9%) • Protocol violation: 3 (0.7%) • Lost to follow-up: 3 (0.7%) • Did not take study drug: 1 (0.2%) • Eligibility criterion not met: 1 (0.2%)
			Mirabegron 50mg (n=440)	54 (12.3%)	NA	NA	• Withdrew consent: 18 (4.1%) • AE: 12 (2.7%) • Other: 10 (2.3%) • Protocol violation: 8 (1.8%) • Efficacy: 3 (0.7%) • Lost to follow-up: 3 (0.7%)
Kuo 2015	Kuo 2015 (23)	Taiwan, Korea, China, India	Mirabegron 50mg (n=372)	61 (16.4%)	NA	NA	• Withdrew consent: 21 • Eligibility criterion not met: 18 • AE: 9 • Efficacy: 4

							• Protocol violation: 4 • Lost to follow-up: 3 • Other: 2
Moussa 2021	Moussa 2021 (24)	Lebanon	Mirabegron 50mg (n=63)	10 (15.9%)	NA	NA	• Lost to follow-up: 4 • Withdrew consent: 3 • Protocol violation: 3
SCORPIO	Khullar 2013 (10)	Australia, Austria, Belarus, Belgium, Bulgaria, Czechia, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Switzerland, Ukraine, United Kingdom	Mirabegron 50mg (n=497)	57 (11.5%)	NA	NA	• AE: 25 • Withdrew consent: 9 • Eligibility criterion not met: 8 • Efficacy: 6 • Lost to follow-up: 3 • Protocol violation: 3 • Other: 2 • Did not take study drug: 1
			Mirabegron 100mg (n=498)	45 (9.0%)	NA	NA	• Withdrew consent: 17 • AE:16 • Protocol violation: 5 • Efficacy: 2 • Other: 2 • Lost to follow-up: 2 • Did not take study drug: 1
TAURUS	Chapple 2013 (16)	United States, Australia, Austria, Belarus, Belgium, Canada, Czechia, Denmark, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Switzerland,	Mirabegron 50mg (n=815)	NA	NA	186 (22.8%)	• Withdrew consent: 65 (8.0%) • AE: 52 (6.4%) • Efficacy: 34 (4.2%) • Lost to follow-up: 14 (1.7%) • Eligibility criterion not met: 7 (0.9%) • Other: 7 (0.9%) • Protocol violation: 6 (0.7%) • Did not take study drug: 1 (0.1%)
			Mirabegron 100mg (n=824)	NA	NA	179 (21.7%)	• Withdrew consent: 75 (9.1%) • AE: 49 (5.9%) • Efficacy: 25 (3.0%) • Protocol violation: 9 (1.1%) • Lost to follow-up: 7 (0.8%) • Other: 7 (0.8%) • Eligibility criterion not met: 7 (0.8%)

		Ukraine, United Kingdom					
Yamaguchi 2014	Yamaguchi 2014 (15)	Japan	Mirabegron 50mg (n = 380)	31 (8.2%)	NA	NA	• Adverse events: 15 • Withdrew consent: 8 • Inadequate efficacy: 4 • Protocol deviations: 3 • Other: 1
EMPOWUR	Staskin 2020 (20)	United States, Canada, Hungary, Latvia, Lithuania, Poland	Vibegron 75mg (n=547)	45 (8.2%)	NA	NA	• Lost to follow-up: 15 • Withdrew consent: 14 • AE: 8 • Other: 6 • Protocol violation: 2
EMPOWUR (Extension)	Staskin 2021 (22)	United States	Vibegron 75mg (n=92)	NA	13 (14.1%)	NA	• Withdrew consent: 6 (6.5%) • Lost to follow-up: 4 (4.3%) • AE: 1 (1.1%) • Death: 1 (1.1%) • Other: 1 (1.1%)
			Vibegron 75mg (n=181)	NA	NA	26 (14.3%)	• Withdrew consent: 11 (6.0%) • Lost to follow-up: 6 (3.3%) • AE: 3 (1.6%) • Withdrawn by investigator: 1 (0.5%) • Efficacy: 1 (0.5%) • Protocol violation: 1 (0.5%) • Other: 3 (1.6%)
EMPOWUR	Staskin 2020 (20)	United States, Canada, Hungary, Latvia, Lithuania, Poland	Tolterodine ER 4mg (n=431)	46 (10.7%)	NA	NA	• Withdrew consent: 13 • AE: 13 • Lost to follow-up: 10 • Withdrawn by investigator: 3 • Other: 3 • Efficacy: 1 • Protocol violation: 1 • Withdrawn by Sponsor: 1 • Death: 1
EMPOWUR (Extension)	Staskin 2021 (22)	United States	Tolterodine ER 4mg (n=91)	NA	19 (20.9%)	NA	• Withdrew consent: 7 (7.7%) • AE: 4 (4.4%) • Lost to follow-up: 3 (3.3%)

							• Withdrawn by investigator: 1 (1.1%) • Other: 4 (4.4%)
			Tolterodine ER 4mg (n=141)	NA	NA	18 (12.8%)	• Withdrew consent: 8 (5.7%) • AE: 4 (2.8%) • Lost to follow-up: 2 (1.4%) • Withdrawn by investigator: 1 (0.7%) • Withdrawn by Sponsor: 1 (0.7%) • Efficacy: 1 (0.7%) • Other: 1 (0.7%)
Kuo 2015	Kuo 2015 (23)	Taiwan, Korea, China, India	Tolterodine ER 4mg (n=377)	67 (17.8%)	NA	NA	• Withdrew consent: 24 • Eligibility criterion not met: 17 • AE: 15 • Lost to follow-up: 7 • Efficacy: 2 • Other: 2 • Protocol violation: 0
SCORPIO	Khullar 2013 (10)	Australia, Austria, Belarus, Belgium, Bulgaria, Czechia, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Switzerland, Ukraine, United Kingdom	Tolterodine ER 4mg (n=495)	50 (10.1%)	NA	NA	• AE: 24 • Withdrew consent: 9 • Lost to follow-up: 5 • Eligibility criterion not met: 4 • Efficacy: 3 • Protocol violation: 3 • Other: 2
SYNERGY	Herschorn 2017 (12)	Canada, Denmark, Germany, Italy, Netherlands, Norway, Poland, Spain,	Tolterodine ER 4mg (n=410)	36 (8.8%)	NA	NA	• AE: 12 • Protocol violation: 10 • Lost to follow-up: 6 • Efficacy: 3 • Withdrew consent: 3

		Sweden, Turkey, United Kingdom					• Other: 2
TAURUS	Chapple 2013 (16)	United States, Australia, Austria, Belarus, Belgium, Canada, Czechia, Denmark, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Switzerland, Ukraine, United Kingdom	Tolterodine ER 4mg (n=813)	NA	NA	192 (23.6%)	• Withdrew consent: 64 (7.9%) • AE: 49 (6.0%) • Lack of efficacy: 45 (5.5%) • Protocol violation: 11 (1.4%) • Eligibility criterion not met: 10 (1.2%) • Lost to follow-up: 7 (0.9%) • Other: 6 (0.7%)
Yamaguchi 2014	Yamaguchi 2014 (15)	Japan	Tolterodine 4mg (n = 378)	23 (%)	NA	NA	• Adverse events: 13 • Other: 5 • Inadequate efficacy: 2 • Protocol deviations: 2 • Withdrew consent: 1
Abbreviations: AE, Adverse Events; ER, extended release; NA, not applicable **Key:** Blue: Mirabegron; Orange: Vibegron; Grey: Tolterodine							

Table 3. Baseline characteristics of EMPOWUR and EMPOWUR-EXT 40 week cohort (randomised from placebo) and 52 week cohort (continuing active treatment).

Study	Author and Year	Treatment arm	Sex, n (%)	Mean Age, Years ± SD	OAB Type, n (%)	Mean baseline micturitions/day ± SD	Mean baseline UUI episodes/day ± SD
EMPOWUR	Staskin 2020 (8)	Placebo (n=520)	Female: 445 (85.6) Male: 75 (14.4)	61.0* ± 16.0**	Wet: 405 (77.9) Dry: 115 (22.1)	10.43* ± 3.99**	2.00* ± 2.57**
		Vibegron (n=526)	Female: 449 (85.4) Male: 77 (14.6)	63.0* ± 18.0**	Wet: 403 (76.6) Dry: 123 (23.4)	10.43* ± 3.57**	2.00* ± 2.85**
		Tolterodine (n=417)	Female: 352 (84.4) Male: 65 (15.6)	61.0* ± 17.0**	Wet: 319 (76.5) Dry: 98 (23.5)	10.67* ± 3.73**	2.00* ± 2.57**
EMPOWUR (Extension) 40-week cohort	Staskin 2021 (108)	Vibegron (n=92)	Female: 73 (79.3) Male: 19 (20.7)	58.8 ± 13.69	Wet: 71 (77.2) Dry: 21 (22.8)	12.14 ± 3.788	2.79 ± 2.883
		Tolterodine (n=91)	Female: 70 (76.9) Male: 21 (23.1)	62.1 ± 12.14	Wet: 70 (76.9) Dry: 21 (23.1)	11.28 ± 3.056	2.35 ± 2.485
EMPOWUR (Extension) 52-week cohort	Staskin 2021 (108)	Vibegron (n=181)	Female: 140 (77.3) Male: 41 (22.7)	62.1 ± 12.39	Wet: 146 (80.7) Dry: 35 (19.3)	11.39 ± 3.459	2.57 ± 2.788
		Tolterodine (n=141)	Female: 112 (79.4) Male: 29 (20.6)	60.6 ± 12.98	Wet: 108 (76.6) Dry: 33 (23.4)	11.30 ± 3.209	2.34 ± 2.127

*Median; **IQR

Abbreviations: IQR, Interquartile range; OAB, overactive bladder; SD, standard deviation; UUI, urge urinary incontinence

A5. Priority question. For each trial included in the NMAs for micturitions, UUI episodes and total incontinence episodes per day, please provide:

a) **The definition and measurement of each outcome used in each trial;**
b) **The definition of the analysis sets used for each outcome in each trial;**
c) **The statistical method used to model the outcome, e.g. MMRM between time X and time Y; and**
d) **If applicable, the method used to impute missing outcome data, and an assessment of the likely risk and direction of bias for each method.**

Response

We have provided the requested information in Table 4 below.

Table 4 Measurement, analysis and statistical definitions used for micturition, UUI episodes, and total incontinence episode outcomes in trials included in NMA

Study (Author, year)	Outcome definitions	Outcome measurement	Analysis set	Statistical methodology	Method to impute missing data
ARIES Nitti 2013 (9) NCT00662909	Micturitions were defined as urinations excluding incontinence only episodes.* Incontinence episodes were defined as any involuntary leakage of urine.* Study did not measure UUI episodes.	Number of micturitions and number of incontinence episodes were recorded by the patient in a diary for 3 days before each study visit. For each micturition and incontinence episodes, patients rated the degree of associated urgency according to the Patient Perception of Intensity of Urgency Scale.	Micturition, total incontinence episodes, and UUI episodes were performed using the FAS which included all randomized patients who took 1 dose or more of the double-blind study drug and had baseline and 1 or more post-baseline micturition measurements.	Micturition end points were analysed using an ANCOVA model including treatment, gender and geographic region as fixed factors, and baseline as a covariate. Mean changes from baseline, standard error, 95% CI and p values were calculated from these ANCOVA models. For incontinence episode end points, inferential analyses were performed using a stratified rank ANCOVA.	NR
CAPRICORN Herschorn 2013 (11) NCT00912964	Micturitions were defined as urinations excluding incontinence only episodes* Incontinence episodes were defined as any involuntary leakage of urine* UUI episodes were defined as involuntary leakage of urine accompanied by or immediately proceeded by urgency*	Incontinence episodes and micturitions were recorded in patient diaries for 3 days preceding each visit. For each micturition and incontinence episode, patients rated the degree of associated urgency according to the Patient Perception of Intensity of Urgency Scale.	Micturition outcomes were assess using the FAS which included safety analysis set patients (randomized patients who took ≥1 dose of study drug) with a micturition measurement in the baseline diary and ≥1 micturition measurement after baseline. Total incontinence and UUI episode endpoints were assessed using the FAS-I set which included FAS patients with ≥1 incontinence episode at baseline.	Inferential analyses for change from baseline in incontinence episodes were performed using a separate stratified rank analysis of covariance for each pairwise treatment group difference (mirabegron 25 and 50 mg vs placebo). Changes from baseline for micturition endpoints were analysed using an analysis of covariance model, including treatment, sex, and geographic region as fixed factors and baseline as a covariate.	NR

EMPOWUR Staskin 2020 (20) NCT03492281	Micturition is defined as "Urinated in Toilet" as indicated on the Patient Voiding Diary (PVD). The number of micturitions is defined as the number of times a participant voided in the toilet as indicated on the PVD* The number of UUI episodes is defined as the number of times a participant had checked "urge" as the main reason for the leakage in the PVD, regardless of whether more than one reason for leakage in addition to "urge" was checked* Total number of incontinence episodes were not assessed.	Patients were trained to use paper diaries and recorded micturitions, urgency, incontinence and reason for incontinence (urge, stress or other) in a 7-day voiding diary prior to study visits.	Number of micturitions was assessed using the FAS, which included all unique randomized patients ≤1 measured CFB in average daily number of micturitions. The FAS for incontinence included all unique randomized wet OAB cases with ≤1 measured CFB in average daily number of UUI episodes.	CFB were assessed for statistically significant differences between active treatment and placebo by a mixed model for repeated measure, with restricted maximum likelihood estimation. The model included terms for treatment, visit, sex, region (U.S. vs non U.S.), baseline score, interaction between visit and treatment, and (for FAS analyses) OAB category.	Multiple imputation was used for missing data.
EMPOWUR (Extension) Staskin 2021 (22) NCT03583372	Micturition is defined as "Urinated in Toilet" as indicated on the Patient Voiding Diary (PVD). The number of micturitions is defined as the number of times a participant voided in the toilet as indicated on the PVD*	Patients were trained to use paper diaries and recorded micturitions, urgency, incontinence and reason for incontinence (urge, stress or other) in a 7-day voiding diary prior to study visits.	The FAS extension included all randomized patients who received ≥1 dose of treatment and had ≥1 evaluable change from baseline micturition measurement during the extension study.	CFB were analysed using a mixed model for repeated measures with restricted maximum likelihood estimation. For patients who received 52 weeks of active treatment, the model included terms for treatment, visit, baseline stratification factors found to be significant in EMPOWUR (OAB [FASExt only], gender),	Multiple imputation methods were used to estimate missing values.

	The number of UUI episodes is defined as the number of times a participant had checked "urge" as the main reason for the leakage in the PVD, regardless of whether more than one reason for leakage in addition to "urge" was checked* Total number of incontinence episodes were not assessed.			baseline value and interaction of visit by treatment. The model included study visits on weeks 2, 4, 8, 12, 16, 24, 44 and 52. For patients who received 40 weeks of active treatment, the post hoc analysis model included terms for study visit, treatment, treatment by study visit interaction, baseline, OAB type (FAS-Ext only) and gender. A post hoc analysis of the difference in week 52 change from baseline in average daily number of UUI and total incontinence episodes between the vibegron and tolterodine groups was carried out using a mixed model for repeated measures on the observed values.	
Kuo 2015 Kuo 2015 (23)	Definitions of micturition, total incontinence and UUI not reported.	Micturitions, UUI episodes, and total incontinence episodes were recorded by the participants on a 3-day bladder diary before each visit during baseline and the follow-up period.	Micturition, total incontinence and UUI episode were assessed using the FAS. The FAS included SAF patients (all randomized patients who took at least one dose of study drug) who had completed a 3-day micturition diary at baseline and at least once post-baseline.	Changes in the mean number of micturitions/24 hr from baseline to final visit were analysed using analysis of covariance (ANCOVA), including treatment and region as fixed factors and baseline value as covariate. Comparison of the changes in the mean number of incontinence episodes and urgency incontinence episodes were performed by a stratified rank ANCOVA with baseline-standardized ranks as	NR

				covariates and region as a stratum.	
Moussa 2021 Moussa 2021 (24)	Definitions of micturition and UUI not reported. Total number of incontinence episodes were not assessed.	Micturitions and UUI episodes were recorded by the participants on a 3-day bladder diary before each visit during baseline and the follow-up period.	NR	Changes micturitions and UUI outcomes were compared between treatment and placebo groups using analysis of covariance (ANCOVA), adjusting for the baseline value. In each treatment and placebo group, changes in micturitions and UUI outcomes from baseline or week 1 to week 12 were assessed using the Wilcoxon signed-rank test (continuous outcomes) for paired data.	NR
SCORPIO Khullar 2013 (10) NCT00689104	Micturitions were defined as urinations excluding incontinence only episodes.* Incontinence episodes were defined as any involuntary leakage of urine.* UUI episodes were defined as the involuntary leakage of urine accompanied by or immediately proceeded by urgency.*	Micturitions, UUI episodes, and incontinence episodes were recorded by the participants on a 3-day bladder diary before each visit during baseline and the follow-up period.	Micturitions were assessed using the FAS which included all randomised patients who took at least one dose of the study drug and had at least a baseline and one postbaseline micturition measurement. UUI and incontinence episodes were assessed using the FAS-I, which consisted of all FAS patients who had at least one incontinence episode at baseline	Inferential analyses for change from baseline in incontinence episodes were performed using a separate stratified rank analysis of covariance (ANCOVA) for each pairwise treatment group difference (mirabegron 50 and 100 mg vs placebo). Change from baseline for micturitions were analysed using an ANCOVA model, including treatment, sex, and geographic region as fixed factors and baseline as a covariate.	Efficacy analyses at the final visit were performed using the last observation carried forward method.
SYNERGY Herschorn 2017 (12)	Definitions of micturition and UUI not reported. Total number of	Participants used 3-day bladder diaries to record micturitions and UUI episodes.	NR	Both numeric (LSM) and relative (median percentage) changes from baseline in bladder diary outcomes	NR

	incontinence episodes were not assessed.			(micturitions and UUI episodes) were evaluated. Numeric changes were analysed via analysis of covariance with baseline value, treatment, and region included in the model. Relative changes in bladder diary variables were analysed via nonparametric Wilcoxon test stratified by region.	
TAURUS Chapple 2013 (16) NCT00688688	Micturitions were defined as urinations excluding incontinence only episodes* Incontinence episodes were defined as any involuntary leakage of urine* UUI episodes were defined as the involuntary leakage of urine accompanied by or immediately proceeded by urgency*	Participants completed a 3-day micturition diary before study visits to record micturitions, incontinence, and UUI episodes.	Micturitions were assessed using the FAS which included all patients receiving one or more dose of the double- blind study drug with baseline and one or more postbaseline visit. UUI and incontinence episodes were assessed using the FAS-I set which includes all FAS patients who had one or more incontinence episode at baseline.	Two models were used to analyse micturitions, total incontinence and UUI outcomes. A repeated-measures model analysed change from baseline to study visits (time) to obtain adjusted means by treatment group and time. Factors in the repeated-measures model included previous study history, sex, geographic region, treatment group, time, treatment by time interaction, and sex by time interaction with baseline and baseline by time interaction as covariates. Change from baseline to final visit was analysed using an analysis of covariance (ANCOVA) model to obtain adjusted means for each treatment group. Factors in the ANCOVA model included previous study history, sex, geographic region, and treatment group with baseline as a covariate.	The final visit analysis used a last observation carried forward approach.

Yamaguchi 2014 Yamaguchi 2014 (15)	Definitions of micturition, total incontinence, and UUI not reported.	Participants completed a 3-day micturition diary prior to study visits to record micturitions, incontinence, and UUI episodes.	Micturitions, total incontinence episodes, and UUI episodes were assessed using the FAS which included patients who took study medication at least once and provided data for at least one variable before and after initiation of the treatment period.	For the micturitions, a two-sample t-test was used to compare mirabegron with placebo for change from baseline in mean number of micturitions/24 h at final assessment. The Wilcoxon rank-sum test was used for total incontinence and UUI episodes. A two-sided significance level of 5% was used all outcomes. For micturition, total incontinence episodes and UUI episodes, the differences in the change from baseline to final assessment between the placebo and the respective treatment groups and the two-sided 95% CI of the difference were calculated using ANOVA, with treatment group as a factor and baseline as a covariate.	NR
Abbreviations: ANCOVA, analysis of covariance; CFB, Change from baseline; CI, Confidence interval; FAS, full analysis set; FAS-I, full analysis set – incontinence; LSM, least squares mean; NR, not reported; OAB, overactive bladder; PVD, patient voiding diary; SAF, safety analysis set; U.S., United States; UUI, urinary urge incontinence *This information was taken from clinicaltrial.gov record for the trial as the information was not reported in the published article					

A6. Please provide a comparison of OAB-related inclusion and exclusion criteria for each trial included in the network meta-analyses (NMAs), including inclusion criteria relating to the severity of OAB symptoms (including but not limited to the proportion of dry vs wet OAB, frequency of micturitions, frequency of UUI episodes) and exclusion criteria relating to other lower urinary tract pathology.

Response

A summary of the OAB-related inclusion and exclusion criteria for each trial included in the network meta-analyses (NMAs) has been provided in Table 5 below as requested.

Table 5 OAB-related inclusion and exclusion criteria for trials included in the NMA

Study (Author and Year)	Inclusion criteria	Exclusion criteria
ARIES Nitti 2013 (9)	• OAB symptoms for ≥ 3 months: ▪ Average frequency of micturition of ≥ 8 / 24-hour during the 3-day micturition diary period. ▪ At least 3 episodes of urgency (grade 3 or 4) with or without incontinence during the 3-day micturition diary period.	• Patient is breastfeeding, pregnant, intends to become pregnant during the study, or of childbearing potential, sexually active and not practicing a highly reliable method of birth control. • Patient has significant stress incontinence or mixed stress/urge incontinence where stress is the predominant factor. • Patient has an indwelling catheter or practices intermittent self-catheterization. • Patient has evidence of a symptomatic urinary tract infection, chronic inflammation such as interstitial cystitis, bladder stones, previous pelvic radiation therapy or previous or current malignant disease of the pelvic organs. • Patient had an average total daily urine volume >3000 mL as recorded in the 3-day micturition diary period.
CAPRICORN Herschorn 2013 (11)	• OAB symptoms for ≥ 3 months: ▪ Average frequency of micturition of ≥ 8 / 24-hour during the 3-day micturition diary period. ▪ At least 3 episodes of urgency (grade 3 or 4) with or without incontinence during the 3-day micturition diary period.	• Patient is breastfeeding, pregnant, intends to become pregnant during the study, or of childbearing potential, sexually active and not practicing a highly reliable method of birth control. • Patient has significant stress incontinence or mixed stress/urge incontinence where stress is the predominant factor. • Patient has an indwelling catheter or practices intermittent self-catheterization. • Patient has evidence of a symptomatic urinary tract infection, chronic inflammation such as interstitial cystitis, bladder stones, previous pelvic radiation therapy or previous or current malignant disease of the pelvic organs. • Patient had an average total daily urine volume >3000 mL as recorded in the 3-day micturition diary period.
EMPOWUR Staskin 2020 (20)	• OAB symptoms for ≥ 3 months • Meets either the OAB Wet or OAB Dry criteria.	• Patient had an average total daily urine volume >3000 mL in the past 6 months or during the 14-day Run-in Period. • Has lower urinary tract pathology that could, in the opinion of the Investigator, be responsible for urgency, frequency, or incontinence. • Has a history of surgery to correct stress urinary incontinence, pelvic organ prolapse, or procedural treatments for BPH within 6 months of Screening.

		• Has current history or evidence of Stage 2 or greater pelvic organ prolapse (prolapse extends beyond the hymenal ring). • Patient is currently using a pessary for the treatment of pelvic organ prolapse. • Has a known history of elevated post-void residual volume defined as greater than 150 mL. • Has undergone bladder training or electrostimulation within 28 days prior to Screening or plans to initiate either during the study. • Has an active or recurrent (> 3 episodes per year) urinary tract infection by clinical symptoms or pre-defined laboratory criteria. • Has a requirement for an indwelling catheter or intermittent catheterization.
EMPOWUR (Extension) Staskin 2021 (22)	• Has completed participation in study RVT-901-3003 (Staskin 2020): ▪ OAB symptoms for ≥ 3 months ▪ Meets either the OAB Wet or OAB Dry criteria. • Has demonstrated ≥ 80% compliance with self-administration of Study Treatment in study RVT-901-3003.	• Patient had an average total daily urine volume > 3000 mL in the past 6 months or during the 14-day Run-in Period. • Has lower urinary tract pathology that could, in the opinion of the Investigator, be responsible for urgency, frequency, or incontinence. • Has a history of surgery to correct stress urinary incontinence, pelvic organ prolapse, or procedural treatments for BPH within 6 months of Screening. • Has current history or evidence of Stage 2 or greater pelvic organ prolapse (prolapse extends beyond the hymenal ring). • Patient is currently using a pessary for the treatment of pelvic organ prolapse. • Has a known history of elevated post-void residual volume defined as greater than 150 mL. • Has undergone bladder training or electrostimulation within 28 days prior to Screening or plans to initiate either during the study. • Has an active or recurrent (> 3 episodes per year) urinary tract infection by clinical symptoms or pre-defined laboratory criteria. • Has a requirement for an indwelling catheter or intermittent catheterization.
Kuo 2015 Kuo 2015 (23)	• OAB symptoms for ≥ 12 weeks: ▪ Average frequency of micturition of ≥ 8 / 24-hour period. ▪ An average episode of urgency or urge incontinence of one or more times per 24-hours period. • Subjects capable of walking to the lavatory without assistance and measuring the urine volume by him/herself.	• Subject having stress urinary incontinence as a predominant symptom. • Subject with transient symptoms suspected for overactive bladder. • Subject complicated with urinary tract infection, urinary stones, and/or interstitial cystitis or with a historical condition of recurrent urinary tract infection. • Subject complicated with bladder tumour/prostatic tumour or with the historical condition. • Subject confirmed to have a post-void residual volume of ≥100ml or with a clinically significant lower urinary tract obstructive disease.

		• Subject with indwelling catheter or practicing intermittent self-catheterization. • Subject giving radiotherapy influencing urinary tract functions, or thermotherapy for benign prostatic hyperplasia. • Subject giving surgical therapy which may influence urinary tract functions within 24 weeks before the study.
Moussa 2021 Moussa 2021 (24)	• An urgency score of ≥ 2 • A total score of ≥ 3 on the OAB symptom score (OABSS) • If patients were taking previously anticholinergic drugs for OAB, they were allowed to enter the study after a washout period of 4 weeks.	• Patients with polyuria with a daily urine volume > 3,000 mL. • Patients taking anticholinergic medications for OAB symptoms. • Patients with a history of benign prostatic hypertrophy. • Patients with stress urinary incontinence.
SCORPIO Khullar 2013 (10)	• OAB symptoms for ≥ 3 months: ▪ Average frequency of micturition of ≥ 8 / 24-hour during the 3-day micturition diary period. ▪ At least 3 episodes of urgency (grade 3 or 4) with or without incontinence during the 3-day micturition diary period.	• Subject is breastfeeding, pregnant, intends to become pregnant during the study, or of childbearing potential, sexually active and not practicing a highly reliable method of birth control. • Subject has significant stress incontinence or mixed stress/urge incontinence where stress is the predominant factor. • Subject has an indwelling catheter or practices intermittent self-catheterization. • Subject has evidence of a symptomatic urinary tract infection, chronic inflammation such as interstitial cystitis, bladder stones, previous pelvic radiation therapy or previous or current malignant disease of the pelvic organs. • Subject had an average total daily urine volume > 3000 mL as recorded in the 3-day micturition diary period.
SYNERGY Herschorn 2017 (12)	• OAB symptoms confirmed by a micturition bladder diary: ▪ Average frequency of micturition of ≥ 8 / 24-hour period. ▪ Urinary urgency and at least 3 urge urinary incontinence episodes within 3 days.	• Other than urge incontinence. • History of prostate/uterine or other female organ cancer. • Patients who received any drug used to treat UUI or OAB within 14 days before the study treatment period.
TAURUS	• OAB symptoms for ≥ 3 months: ▪ Average frequency of micturition of ≥ 8 / 24-hour during the 3-day micturition diary period.	• Patient is breastfeeding, pregnant, intends to become pregnant during the study, or of childbearing potential, sexually active and not practicing a highly reliable method of birth control. • Clinically significant bladder outflow obstruction at risk of urinary retention.

Chapple 2013 (16)	▪ At least 3 episodes of urgency (grade 3 or 4) with or without incontinence during the 3-day micturition diary period.	• Significant stress incontinence or mixed stress/urge incontinence where stress was the predominant factor. • An indwelling catheter or practiced intermittent self-catheterization. • 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. • Current nondrug treatment including electrostimulation therapy. • Use of medications intended to treat OAB. • Average total daily urine volume >3000 mL as recorded in the 3-d micturition diary.
Yamaguchi 2014 Yamaguchi 2014 (15)	• OAB symptoms for at least 24 weeks before initiation of the pre-investigational period: ▪ Average frequency of micturition of ≥ 8 / 24-hour period. ▪ Average of ≥ 1 episode of urgency or urge incontinence times per 24-hours period. ▪ At least 1 urge urinary incontinence episode per 24 hours. • Patient capable of walking to the lavatory without assistance and measuring the urine volume by him/herself.	• Patients without experience of urge incontinence before informed consent. • Patients given a clear diagnosis of stress incontinence. • Patients with transient symptoms suspected of overactive bladder (drug induced, psychogenic, etc) • Patients complicated with urinary tract infection, urinary stones, and/or interstitial cystitis. • Patients with a previous history of recurrent urinary tract infection. • Patients complicated with or with a history of bladder tumour or prostatic tumour. • Patients confirmed to have a post-void residual volume of ≥ 100 mL or with a clinically significant lower urinary tract obstructive disease. • Patients given medication for the treatment of lower urinary tract obstructive disease within 4 weeks before the pre-investigational period. • Patients with an indwelling catheter or practicing intermittent self-catheterization. • Patients given radiotherapy influencing urethral functions, or thermotherapy for benign prostatic hyperplasia. • Patients given surgical therapy which may influence urethral functions within 24 weeks before the pre-investigational period. • Patients with polyuria exceeding 3000 mL in mean daily urine volume.
Abbreviation: BPH, benign prostatic hyperplasia; OAB, overactive bladder; UTI, urinary track infection; UUI, urinary urge incontinence		

A7. In Table 10 of Appendix D there are no UUI episode data reported for SCORPIO. Please clarify if outcome data from SCORPIO were included in the UUI NMA or if SCORPIO did not report UUI episodes as an outcome.

Response

The SCORPIO trial, authored by Khullar et al. (2013) (10), reported episodes of incontinence and episodes of urgency as outcomes, but did not report episode of urgency urinary incontinence (UUIs) as an outcome.

A8. For comparator trials included in the NMA, data have been extracted from both primary publications and clinicaltrials.gov. Please:

a) Provide details of and a justification of the extraction hierarchy used if one was used.
b) Update the extraction tables and NMA inputs to use data reported in the primary publications, and only include data from other sources if these were not reported in the primary publication.

Response

Data used to inform the NMA were obtained as part of a clinical SLR described in Section B.3 of Document B and Appendix D. Data for the clinical SLR was identified via searching of electronic search databases and handsearching of grey literature sources (including conference proceedings, HTA submissions, clinical guidelines, reference lists, clinical trial registries, and other key international bodies). During data extraction, studies/trials with multiple publications were linked with data extracted from the primary publication and any follow-on/additional data extracted from the linked publications.

Outcome data for comparator trials included in the NMA was extracted from the primary trial publication firstly, with any additional data (not reported in the primary trial publication) extracted from linked publications (including clinical trials databases). This hierarchy was determined to prioritise inclusion of peer reviewed data in published journals for reasons of robustness and transparency.

A9. Please provide a version of Figure 22 “Baseline characteristics of the included studies.” as a table with both values of central tendency (mean, median) and

dispersion (standard deviation, interquartile range). Please also include the following baseline characteristics in these tables, with NR if they were not reported in the primary study: Type of OAB (urgency incontinence, frequency, mixed, other); Prior OAB surgery; Prior OAB drug exposure; BMI.

Response

We have provided the information on patient demographics and OAB-related baseline characteristics contained in Figure 22 in the main submission document and the additional information requested in Table 6 and Table 7 below.

Table 6 Patient demographics by treatment arm in studies included within the NMA

Study (Author and Year)	Treatment arm (n=)	Patient demographics					
		Age (years) Mean (SD) (Median [IQR])	Gender (female) N (%)	BMI kg/m2 Mean (SD) (Median [IQR])	OAB type N (%)	Prior OAB surgery N (%)	Prior OAB treatment N (%)
ARIES Nitti 2013 (9)	Mirabegron 50 mg (n=442)	59.2 (13.5)	322 (72.9)	30.0 (6.6)	Wet=135 (31.8) Mixed=156 (36.7) Other=134 (31.5) *(n=425)*	NR	NR
	Placebo (n=453)	60.1 (13.8)	345 (76.2)	30.4 (7.4) *(n=252)*	Wet=124 (28.6) Mixed=176 (40.6) Other=133 (30.7) *(n=412)*	NR	NR
CAPRICORN Herschorn 2013 (11)	Mirabegron 25 mg (n=432)	58.5 (12.9)	293 (67.8)	29.8 (6.5)	Wet=156 (38) Mixed=124 (30.2) Other=130 (31.7) *(n=410)*	NR	NR
	Mirabegron 50 mg (n=440)	60.3 (12.2)	303 (68.9)	29.5 (6.5)	Wet=164 (38.5) Mixed=148 (34.7) Other=114 (26.8) *(n=426)*	NR	NR
	Placebo (n=433)	58.2 (13.7)	301 (69.5)	29.2 (6.3)	Wet=117 (28.2) Mixed=137 (33.0) Other=161 (38.8) *(n=415)*	NR	NR
EMPOWUR Staskin 2020 (20)	Vibegron 75 mg (n=526)	60.8 (13.3) (63 [18])	449 (85.4)	31.2 (7.4)	Wet=403 (76.6) Dry=123 (23.4)	NR	77 (14.6)
	Tolterodine ER 4 mg (n=417)	59.8 (13.2) (61 [17])	352 (84.4)	31.8 (7.5)	Wet=319 (76.5) Dry=98 (23.5)	NR	51 (12.2)
	Placebo (n=520)	59.9 (13.3) (61 [16])	445 (85.6)	31.0 (6.8)	Wet=405 (77.9) Dry=115 (22.1)	NR	85 (16.3)
	Vibegron 75 mg (n=273)	61.0 (12.9)	213 (78.0)	30.6 (6.7) (29.5)	Wet=217 (79.5) Dry=56 (20.5)	NR	NR

EMPOWUR (Extension) Staskin 2021 (22)	Tolterodine ER 4 mg (n=232)	61.2 (12.7)	182 (78.4)	30.5 (6.2) (29.7) (n=218)	Wet=178 (76.7) Dry=54 (23.3)	NR	NR
Kuo 2015 Kuo 2015 (23)	Mirabegron 50 mg (n=338)	54.3 (14.2)	228 (67.5)	NR	Mixed=67 (19.8)	NR	NR
	Tolterodine ER 4 mg (n=333)	53.9 (14.5)	213 (64.0)	NR	Mixed=58 (17.4)	NR	NR
	Placebo (n=323)	55.3 (13.6)	225 (69.7)	NR	Mixed=56 (17.3)	NR	NR
Moussa 2021 Moussa 2021 (24)	Mirabegron 50 mg (n=53)	NR	23 (43.4)	NR	NR	NR	44 (83.0)
	Placebo (n=42)	NR	33 (78.6)	NR	NR	NR	35 (83.3)
SCORPIO Khullar 2013 (10)	Mirabegron 50 mg (n=493)	59.1 (12.4)	357 (72.4)	27.5 (4.9)	Mixed=108 (22.8)* Other=365 (77.2)* *(n=473)*	33 (7)	240 (50.7)
	Tolterodine ER 4 mg (n=495)	59.1 (12.9)	361 (72.9)	27.8 (5.0)	Mixed=105 (22.1)* Other=370 (77.9)* *(n=375)*	17 (3.6)	231 (48.6)
	Placebo (n=494)	59.2 (12.3)	356 (72.1)	27.8 (5.0) (n=493)	Mixed=102 (21.3)* Other=378 (78.7)* *(n=480)*	22 (4.6)	238 (49.6)
SYNERGY Herschorn 2017 (12)	Mirabegron 50 mg (n=422)	56.7 (13.3)	323 (76.5)	28.3 (6.0)*	Mixed=154 (36.5) Other=268 (63.5)	NR	195 (46.2)
	Mirabegron 25 mg (n=423)	56.9 (13.6)	327 (77.3)	28.2 (6.8)*	Mixed=156 (36.9) Other=267 (63.1)	NR	196 (46.3)
	Placebo (n=429)	57.9 (13.0)	327 (76.2)	28.7 (6.1)*	Mixed=144 (33.6) Other=285 (66.4)	NR	205 (47.8)
TAURUS	Mirabegron 50 mg (n=812)	59.2 (12.6)	602 (74.1)	NR	Wet=296 (36.5) Mixed=232 (28.6)	NR	446 (54.9)

Chapple 2013 (16)					Other=284 (35.0)		
	Tolterodine ER 4 mg (n=812)	59.6 (12.5)	600 (73.9)	NR	Wet=317 (39.0) Mixed=210 (25.9) Other=285 (35.1)	NR	447 (55.0)
Yamaguchi 2014 Yamaguchi 2014 (15)	Mirabegron 50 mg (n=369)	58.3 (13.9)	311 (84.3)	NR	Wet=230 (62.3) Dry=31 (8.4) Mixed=108 (29.3)	NR	233 (63.1)
	Tolterodine IR 4 mg (n=368)	58.3 (13.7)	304 (82.6)	NR	Wet=235 (63.9) Dry=39 (10.6) Mixed=94 (25.5)	NR	240 (65.2)
	Placebo (n=368)	58.2 (14.2)	310 (84.2)	NR	Wet=236 (64.1) Dry=39 (10.6) Mixed=93 (25.3)	NR	240 (65.2)

Abbreviations: ER, extended release; IQR, interquartile range; IR, immediate release; NR, not reported; OAB, overactive bladder; SD, standard deviation; UUI, urinary urge incontinence
*Data taken from clinicaltrials.gov posted results (not reported in primary trial publication)
NB: Where sample sizes used to assess outcomes differed from the sample size for the whole treatment arm, this has been indicated below the data point

Table 7 OAB-related baseline characteristics by treatment arm in studies included within the NMA

Study (Author and Year)	**Treatment arm (n=)**	**OAB related baseline characteristics**					
		Number of incontinence episodes/day Mean (SD) (Median [IQR])	**Number of micturitions/day Mean (SD) (Median [IQR])**	**Number of urgency episodes/day (any grade) Mean (SD) (Median [IQR])**	**Number of urgency episodes/day (grade 3-4) Mean (SD) (Median [IQR])**	**Number of UUI episodes Mean (SD) (Median [IQR])**	**Voided volume per micturition Mean (SD) (Median [IQR])**
ARIES Nitti 2013 (9)	Mirabegron 50 mg (n=442)	NR	11.8 (3.4)*	NR	5.9 (3.8)*	NR	155.2 (58.7)*
	Placebo (n=453)	NR	11.5 (3.3)*	NR	5.6 (3.3)*	2.9 (3.3)	157.2 (60.2)*

Study (Author and Year)	Treatment arm (n=)	OAB related baseline characteristics					
		Number of incontinence episodes/day Mean (SD) (Median [IQR])	**Number of micturitions/day Mean (SD) (Median [IQR])**	**Number of urgency episodes/day (any grade) Mean (SD) (Median [IQR])**	**Number of urgency episodes/day (grade 3-4) Mean (SD) (Median [IQR])**	**Number of UUI episodes Mean (SD) (Median [IQR])**	**Voided volume per micturition Mean (SD) (Median [IQR])**
CAPRICORN Herschorn 2013 (11)	Mirabegron 25 mg (n=432)	NR	165.4 (57.2)*	NR	5.5 (3.6)*	NR	165.4 (57.2)*
	Mirabegron 50 mg (n=440)	NR	158.4 (52.2)*	NR	5.8 (3.6)*	NR	158.4 (52.2)*
	Placebo (n=433)	NR	163.5 (56.4)*	NR	5.4 (3.3)*	NR	163.5 (56.4)*
EMPOWUR Staskin 2020 (20)	Vibegron 75 mg (n=526)	3.3 (3.6) (2.1)	11.3 (3.4) (10.4 [3.6])	8.1 (4.4) (7.75 [6.21])	NR	2.8 (3.1)* (2 [2.9]) (n=544)	155.4 (63.1) (150 [80.6]) (n=524)
	Tolterodine ER 4 mg (n=417)	3.2 (3.1) (2.3)	11.5 (3.2) (10.7 [3.7])	7.9 (3.9) (8 [5.47])	NR	2.7 (2.6)* (2 [2.6]) (n=430)	147.0 (60.8) (143.3 [73.5]) (n=415)
	Placebo (n=520)	3.4 (3.7) (2.3)	11.8 (4.0) (10.4 [4.0])	8.1 (4.7) (8 [5.91])	NR	2.8 (3.0)* (2 [2.6]) (n=537)	148.3 (60.7) (141.7 [76.8]) (n=514)
EMPOWUR (Extension) Staskin 2021 (22)	Vibegron 75 mg (n=266)	3.1 (3.3) (2.0)	11.6 (3.6) (10.6)	8.2 (4.7) (7.6)	NR	2.7 (2.8) (1.7)	154.5 (61.9) (150.0) (n=258)
	Tolterodine ER 4 mg (n=219)	2.8 (2.7) (2.1)	11.3 (3.2) (10.4)	7.9 (3.7) (7.8)	NR	2.3 (2.2) (1.9)	148.6 (58.6) (142.7) (n=211)
Kuo 2015	Mirabegron 50 mg (n=338)	2.4 (2.5)	12.1 (4.1)	5.2 (4.6)	NR	1.9 (2.3)	147.8 (52.7)

Study (Author and Year)	Treatment arm (n=)	OAB related baseline characteristics					
		Number of incontinence episodes/day Mean (SD) (Median [IQR])	**Number of micturitions/day Mean (SD) (Median [IQR])**	**Number of urgency episodes/day (any grade) Mean (SD) (Median [IQR])**	**Number of urgency episodes/day (grade 3-4) Mean (SD) (Median [IQR])**	**Number of UUI episodes Mean (SD) (Median [IQR])**	**Voided volume per micturition Mean (SD) (Median [IQR])**
Kuo 2015 (23)							
	Tolterodine ER 4 mg (n=333)	2.3 (2.8)	12.1 (3.7)	5.4 (4.3)	NR	2.1 (2.7)	150.2 (57.2)
	Placebo (n=323)	2.4 (2.7)	12.6 (4.9)	5.6 (5.3)	NR	1.8 (1.8)	152.6 (55.0)
Moussa 2021 Moussa 2021 (24)	Mirabegron 50 mg (n=53)	NR	11.0 (1.2)	2.4 (1.1)	NR	NR	122.1 (16.0)
	Placebo (n=42)	NR	10.4 (1.0)	2.4 (0.8)	NR	NR	112.0 (19.7)
SCORPIO Khullar 2013 (10)	Mirabegron 50 mg (n=493)	NR	11.7 (3.0)* *(n=473)*	NR	5.7 (3.7)*	NR	160.3 (57.9)*
	Tolterodine ER 4 mg (n=495)	NR	11.6 (2.8)* *(n=475)*	NR	5.8 (3.5)*	NR	157.4 (54.2)*
	Placebo (n=494)	NR	11.7 (3.1)* *(n=480)*	NR	5.7 (4.0)*	NR	156.8 (52.7)*
SYNERGY Herschorn 2017 (12)	Mirabegron 50 mg (n=422)	3.2 (3.5)	11.2 (3.3)	NR	6.46 (4.9)*	3 (3.1)	155.3 (60.8)
	Mirabegron 25 mg (n=423)	3.4 (3.4)	10.8 (2.6)	NR	6.22 (3.9)*	3.1 (3.2)	152.5 (61.0)

Study (Author and Year)	Treatment arm (n=)	OAB related baseline characteristics					
		Number of incontinence episodes/day Mean (SD) (Median [IQR])	**Number of micturitions/day Mean (SD) (Median [IQR])**	**Number of urgency episodes/day (any grade) Mean (SD) (Median [IQR])**	**Number of urgency episodes/day (grade 3-4) Mean (SD) (Median [IQR])**	**Number of UUI episodes Mean (SD) (Median [IQR])**	**Voided volume per micturition Mean (SD) (Median [IQR])**
	Placebo (n=429)	3.4 (3.4)	11.0 (2.9)	NR	6.52 (4.1)*	1.7 (1.6)	157.9 (58.8)
TAURUS Chapple 2013 (16)	Mirabegron 50 mg (n=812)	NR	11.1 (2.8)*	NR	5.7 (3.6)*	NR	160.4 (58.8)*
	Tolterodine ER 4 mg (n=812)	NR	10.9 (2.7)*	NR	5.4 (3.5)*	NR	160.8 (57.0)*
Yamaguchi 2014 Yamaguchi 2014 (15)	Mirabegron 50 mg (n=369)	2.0 (2.1)	11.2 (2.7)	4.3 (2.8)	NR	1.7 (1.6)	149.6 (46.4)
	Tolterodine IR 4 mg (n=368)	1.9 (1.8)	11.1 (2.6)	4.1 (2.8)	NR	1.7 (1.4)	145.9 (46.9)
	Placebo (n=368)	1.9 (1.8)	11.3 (2.7)	4.4 (3.0)	NR	NR	146.8 (44.2)

Abbreviations: ER, extended release; IQR, interquartile range; IR, immediate release; NR, not reported; OAB, overactive bladder; SD, standard deviation; UUI, urinary urge incontinence
*Data taken from clinicaltrials.gov posted results (not reported in primary trial publication)
NB: Where sample sizes used to assess outcomes differed from the sample size for the whole treatment arm, this has been indicated below the data point

A10. Risk of bias assessments were only provided for studies of vibegron using the RoB-2 tool, although Appendix D also indicates risk of bias assessments may have been performed for all studies included in the SLR, i.e., for studies of mirabegron also, using the “seven-criteria checklist provided in section 2.5 of the NICE single technology appraisal (STA) user guide”. Please either:

a) Provide the risk of bias assessments already completed for the mirabegron studies included in the NMAs; or
b) Using the RoB-2 checklist, complete risk of bias assessments for the mirabegron studies included in the NMA.

Response

Risk of bias assessment using the seven-criteria checklist for assessment of risk of bias provided in section 2.5 of the NICE STA guide (25) for the eight mirabegron trials included in the NMAs is provided below in Table 8 to Table 15.

Table 8 NICE STA seven-criteria checklist for risk of bias appraisal of ARIES trial (Nitti et al. 2013) (9)

Bias Domain	Signalling Question	Response options			Evidence for response
		Lower ROB	Higher ROB	Other	
Selection Bias	Was the randomisation method adequate?	Y			Patients meeting the baseline inclusion/exclusion criteria were randomly assigned in a 1:1:1 ratio to 50mg mirabegron, 100 mg mirabegron or matching placebo using a computer generated randomization scheme.
	Was the allocation adequately concealed?	Y			
	Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Y			Baseline characteristics were well balanced across treatment groups.
Performance Bias	Were the participants and care providers, blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias e.g. apart from assigned intervention, were the groups treated equally e.g. similar amount of attention, ancillary treatment and diagnostic investigations?	Y			Double-blind study
Detection Bias	Were the outcome assessors blind to treatment allocation? If not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	Y			Double-blind study
Attrition Bias	Were there unexpected imbalances in drop-outs between groups? If so, were reasons explained?	N			Overall discontinuation was well balanced between the groups. Details of reasons for discontinuations per arm 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?			Unclear	There is no statement as to whether ITT analysis was conducted.
Selective reporting	Is there any evidence to suggest that the authors measured more outcomes than they reported?	N			All prespecified outcomes were reported.
Conflict of interest	Did authors of the study publication declared conflicts of interest?	Y			Declared

Key: Y=yes; PY=probably yes; N=no
Abbreviations:, ITT, intention to treat; ROB, risk of bias;

Table 9 NICE STA seven-criteria checklist for risk of bias appraisal of CAPRICORN trial (Herschorn et al. 2013) (11)

Bias Domain	Signalling Question	Response options			Evidence for response
		Lower ROB	Higher ROB	Other	
Selection Bias	Was the randomisation method adequate?			Unclear	The method of generating the sequence of randomisation was not reported
	Was the allocation adequately concealed?			Unclear	
	Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Y			Baseline characteristics were well balanced across treatment groups.
Performance Bias	Were the participants and care providers, blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias e.g. apart from assigned intervention, were the groups treated equally e.g. similar amount of attention, ancillary treatment and diagnostic investigations?	Y			Double-blind study
Detection Bias	Were the outcome assessors blind to treatment allocation? If not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	Y			Double-blind study
Attrition Bias	Were there unexpected imbalances in drop-outs between groups? If so, were reasons explained?	N			Overall discontinuation was well balanced between the groups. Details of reasons for discontinuations per arm 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?			Unclear	There is no statement as to whether ITT analysis was conducted.
Selective reporting	Is there any evidence to suggest that the authors measured more outcomes than they reported?	N			All prespecified outcomes were reported.
Conflict of interest	Did authors of the study publication declared conflicts of interest?	Y			Declared. The study and medical writing support were funded by Astellas.

Key: Y=yes; PY=probably yes; N=no; NA=not applicable
Abbreviations:, FAS, full analysis set; ITT, intention to treat; ROB, risk of bias.

Table 10 NICE STA seven-criteria checklist for risk of bias appraisal of Kuo et al. 2015 (23)

Bias Domain	Signalling Question	Response options			Evidence for response
		Lower ROB	Higher ROB	Other	
Selection Bias	Was the randomisation method adequate?	Y			Randomization was accomplished using a computer-generated randomization scheme (Cenduit GmbH, Allschwil, Switzerland) with stratification by site.
	Was the allocation adequately concealed?			Unclear	Method of allocation concealment not reported
	Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Y			Inclusion in each analysis set and demographic characteristics were similar across treatment groups
Performance Bias	Were the participants and care providers, blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias e.g. apart from assigned intervention, were the groups treated equally e.g. similar amount of attention, ancillary treatment and diagnostic investigations?	Y			Double blind
Detection Bias	Were the outcome assessors blind to treatment allocation? If not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	Y			Double blind
Attrition Bias	Were there unexpected imbalances in drop-outs between groups? If so, were reasons explained?	N			Overall discontinuation was similar, and details of discontinuations reported for each arm
	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Y			FAS - a modified ITT analysis
Selective reporting	Is there any evidence to suggest that the authors measured more outcomes than they reported?	N			All prespecified outcomes were reported.
Conflict of interest	Did authors of the study publication declared conflicts of interest?	Y			Declared - Potential Conflicts of Interest: This study was funded by Astellas Inc. Hann- Chorng Kuo has acted as a consultant for Astellas; has received speaker honoraria and research grants from

					Astellas, Pfizer, GSK and Allergan; and has conducted clinical trials for Astellas and Allergan. Kyu-Sung Lee has acted as a consultant for Astellas and Pfizer; has conducted clinical trials for Astellas, Pfizer, GSK and Allergan; and has received speaker honoraria from Astellas, Pfizer, GSK and MSD. Shigeru Nakaji, Yosuke Kubota and Kentarou Kuroishi are employees of the study sponsor. Rajeev Sood and Yanqun Na have no conflicts of interest to declare. Grant sponsor: Astellas
Key: Y=yes; PY=probably yes; N=no; NA=not applicable **Abbreviations:**, FAS, full analysis set; ITT, intention to treat; ROB, risk of bias.					

Table 11 NICE STA seven-criteria checklist for risk of bias appraisal of Moussa et al. 2021 (24)

Bias Domain	Signalling Question	Response options			Evidence for response
		Lower ROB	Higher ROB	Other	
Selection Bias	Was the randomisation method adequate?	Y			Randomly assigned to one of the two groups by a computer generated lottery
	Was the allocation adequately concealed?	Y			All the medications were previously prepared by our clinical pharmacists who did not participate in the study enrollment All medications were given by the clinical pharmacist giving the appropriate study treatment as indicated by the computer system.
	Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?		N		There were more males in the treatment group than placebo group (57% vs 21%)
Performance Bias	Were the participants and care providers, blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias e.g. apart from assigned intervention, were the groups treated equally e.g. similar amount of attention, ancillary treatment and diagnostic investigations?	Y			Double blind. Both the medical team (urologists and neurologists) and the patients were blinded to the treatment assignments until the end of the trial.

Detection Bias	Were the outcome assessors blind to treatment allocation? If not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	Y			Double blind. Both the medical team (urologists and neurologists) and the patients were blinded to the treatment assignments until the end of the trial.
Attrition Bias	Were there unexpected imbalances in drop-outs between groups? If so, were reasons explained?	N			Overall discontinuation was similar
	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		N		ITT/FAS was not reported. Analysis appears to be per protocol, but this was not specified
Selective reporting	Is there any evidence to suggest that the authors measured more outcomes than they reported?	N			All prespecified outcomes were reported.
Conflict of interest	Did authors of the study publication declared conflicts of interest?	Y			Declared - No potential conflict of interest was reported by the author(s).
Key: Y=yes; PY=probably yes; N=no; NA=not applicable **Abbreviations:**, FAS, full analysis set; ITT, intention to treat; ROB, risk of bias.					

Table 12 NICE STA seven-criteria checklist for risk of bias appraisal of SCORPIO trial (Khullar et al. 2013) (10)

Bias Domain	Signalling Question	Response options			Evidence for response
		Lower ROB	Higher ROB	Other	
Selection Bias	Was the randomisation method adequate?	Y			Use of computer-generated randomisation
	Was the allocation adequately concealed?	Y			Use of interactive responsive system
	Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Y			Demographic and baseline characteristics were balanced across treatment groups.
Performance Bias	Were the participants and care providers, blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias e.g. apart from assigned intervention, were the groups treated equally e.g. similar amount of attention, ancillary treatment and diagnostic investigations?	Y			Double-blind study: during the double-blind treatment, both patients and investigators were blinded to the identity of the randomised drug assignment.

Detection Bias	Were the outcome assessors blind to treatment allocation? If not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	Y			Double-blind study: during the double-blind treatment, both patients and investigators were blinded to the identity of the randomised drug assignment.
Attrition Bias	Were there unexpected imbalances in drop-outs between groups? If so, were reasons explained?	N			LTFU: balanced between the groups. Details of reasons for discontinuations per arm 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?			Unclear	There is no statement as to whether ITT analysis was conducted.
Selective reporting	Is there any evidence to suggest that the authors measured more outcomes than they reported?	N			All prespecified outcomes were reported.
Conflict of interest	Did authors of the study publication declared conflicts of interest?	Y			Declared - 'See "Financial disclosures" text.
Key: Y=yes; N=no; NA=not applicable **Abbreviations:**, FAS, full analysis set; ITT, intention to treat; LTFU, Lost to follow up; ROB, risk of bias.					

Table 13 NICE STA seven-criteria checklist for risk of bias appraisal of trial SYNERGY (Herschorn et al. 2017) (12)

Bias Domain	Signalling Question	Response options			Evidence for response
		Lower ROB	Higher ROB	Other	
Selection Bias	Was the randomisation method adequate?			Unclear	Method of randomization not reported
	Was the allocation adequately concealed?			Unclear	Method of allocation concealment not reported
	Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Y			Demographic characteristics and baseline data were similar across all groups
Performance Bias	Were the participants and care providers, blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias e.g. apart from assigned intervention, were the groups treated equally e.g. similar amount of attention, ancillary treatment and diagnostic investigations?	Y			Double blind

Detection Bias	Were the outcome assessors blind to treatment allocation? If not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	Y			Double blind
Attrition Bias	Were there unexpected imbalances in drop-outs between groups? If so, were reasons explained?	N			Overall discontinuation was similar, and details of discontinuations reported for each arm.
	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Y			ITT was used in the efficacy and PROS analyses
Selective reporting	Is there any evidence to suggest that the authors measured more outcomes than they reported?	N			All prespecified outcomes were reported.
Conflict of interest	Did authors of the study publication declared conflicts of interest?	Y			Declared
Key: Y=yes; N=no; NA=not applicable **Abbreviations:**, ITT, intention to treat; PROs, Patient reported outcome measures; ROB, risk of bias.					

Table 14 NICE STA seven-criteria checklist for risk of bias appraisal of trial TAURUS (Chapple et al. 2013) (16)

Bias Domain	Signalling Question	Response options			Evidence for response
		Lower ROB	Higher ROB	Other	
Selection Bias	Was the randomisation method adequate?	Y			Patients were randomized 1:1:1 using a computer-generated randomization scheme, prepared by Pierrel Research Europe (Essen, Germany).
	Was the allocation adequately concealed?	Y			Patients were randomized 1:1:1 using a computer-generated randomization scheme.
	Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Y			Demographic characteristics were balanced across treatment groups.
Performance Bias	Were the participants and care providers, blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias e.g. apart from assigned intervention, were the groups treated equally e.g. similar amount of attention, ancillary treatment and diagnostic investigations?	Y			Double blind: the investigator, study site personnel, patients, and sponsor were blinded to treatment (including the medication received in prior trials).

Detection Bias	Were the outcome assessors blind to treatment allocation? If not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	Y			Double blind: the investigator, study site personnel, patients, and sponsor were blinded to treatment (including the medication received in prior trials).
Attrition Bias	Were there unexpected imbalances in drop-outs between groups? If so, were reasons explained?	N			LTFU: balanced between the groups. Details of reasons for discontinuations per arm 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?			Unclear	There is no statement as to whether ITT analysis was conducted.
Selective reporting	Is there any evidence to suggest that the authors measured more outcomes than they reported?	N			All prespecified outcomes were reported.
Conflict of interest	Did authors of the study publication declared conflicts of interest?	Y			Declared
Key: Y=yes; N=no; NA=not applicable **Abbreviations:**, ITT, intention to treat; LTFU, Lost to follow up; ROB, risk of bias.					

Table 15 NICE STA seven-criteria checklist for risk of bias appraisal of Yamaguchi et al. 2014 (15)

Bias Domain	**Signalling Question**	**Response options**			**Evidence for response**
		Lower ROB	Higher ROB	Other	
Selection Bias	Was the randomisation method adequate?	Y			Patients were randomized using the methods of random permuted blocks.
	Was the allocation adequately concealed?			Unclear	Method of allocation concealment not reported
	Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Y			Baseline demographic and clinical characteristics were well matched among the treatment groups.
Performance Bias	Were the participants and care providers, blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias e.g. apart from assigned intervention, were the groups treated equally e.g. similar amount of attention, ancillary treatment and diagnostic investigations?	Y			Double blind: the blinded status of patients, investigators, site monitors and the study team was maintained using a variation of the double-dummy technique.

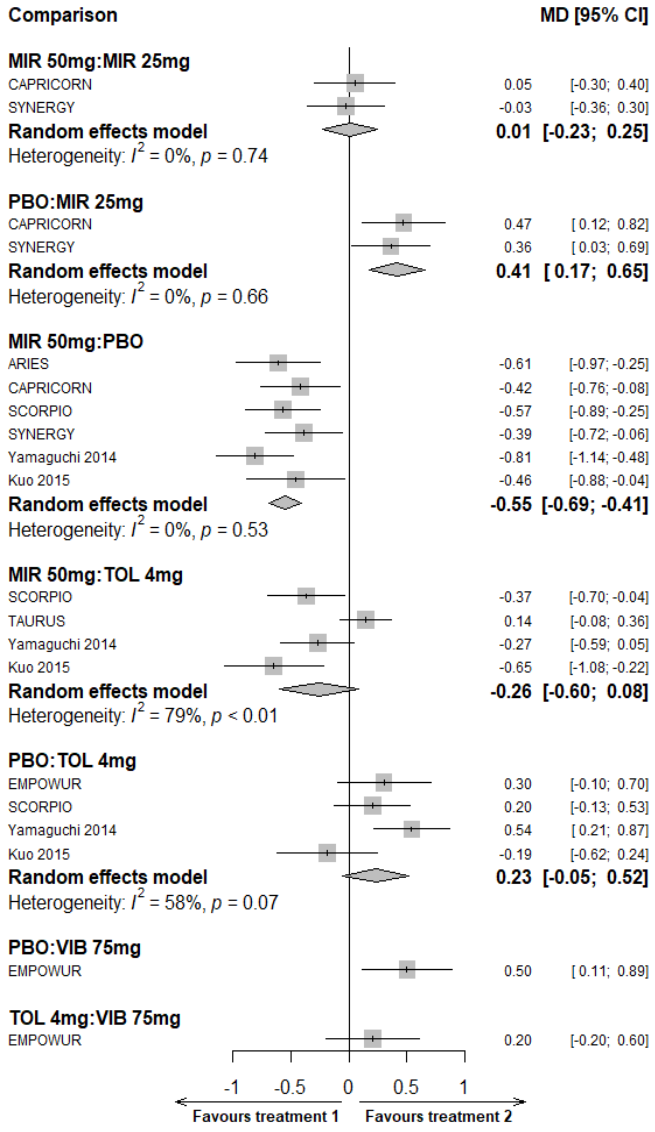
Detection Bias	Were the outcome assessors blind to treatment allocation? If not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	Y			Double blind: the blinded status of patients, investigators, site monitors and the study team was maintained using a variation of the double-dummy technique.
Attrition Bias	Were there unexpected imbalances in drop-outs between groups? If so, were reasons explained?		Y		A total of 82 patients in the oxybutynin patch group, 42 in the propiverine group and 22 in the placebo group discontinued the study prematurely.
	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Y			The evaluation of the primary efficacy parameter was employed the FAS.
Selective reporting	Is there any evidence to suggest that the authors measured more outcomes than they reported?	N			All prespecified outcomes were reported.
Conflict of interest	Did authors of the study publication declared conflicts of interest?	Y			Declared - Osamu Yamaguchi and Eiji Uchida have served as consultants to and received honoraria from Hisamitsu Pharmaceutical, the manufacturer of the oxybutynin patch. Naruhito Higo, Hidenao Minami, Shigeo Kobayashi and Hiroyuki Sato are employees of Hisamitsu Pharmaceutical.
Key: Y=yes; N=no; NA=not applicable **Abbreviations:**, FAS, full analysis set; ITT, intention to treat; ROB, risk of bias.					

A11. Using a global test, statistically significant inconsistency was detected in the key Week 12 micturition network. Please use a local method to determine which contrasts are driving this inconsistency.

Response

The TAURUS study (NCT00688688) was found to cause a significant inconsistency between data for number of micturitions at 12 weeks as shown in Figure 1 below. The relative effect of mirabegron 50mg vs tolterodine 4mg in TAURUS study differed substantially compared with other studies, i.e. it was equal to 0.14 while in other studies directly comparing mirabegron 50mg vs tolterodine 4mg the relative effect was negative (see Figure 1 below).

Figure 1 Heterogeneity analysis: Number of micturitions per day – 12 weeks

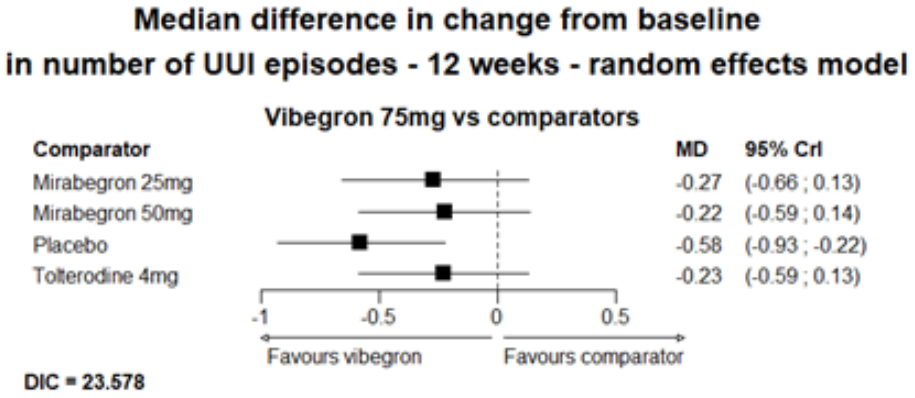


A12. In Table 10 of Appendix D, the reported standard error for Herschorn 2017 UUI outcomes is 0.100, whereas the EAG notes the values reported in the source on clinicaltrials.gov are 0.09. Please update these values accordingly and include these values in the updated NMAs.

Response

The values have been updated as requested and the results of the NMA updated with the amended SEs for Herschorn 2017 UUI outcomes (see Figure 2 below). We note that the updated SE values had minimal impact on NMA results.

Figure 2 Updated NMA plot for change in baseline in number of UUI episodes at 12 weeks



Vibegron

A13. The company submission (CS) notes that vibegron is currently subject to a black triangle and so has additional pharmacovigilance by regulatory agencies:

a) Please explain the specific safety issues identified by regulators that led to vibegron being classified with a black triangle.
b) Please outline whether there are similar safety issues associated with mirabegron to those outlined in response to part a).

Response a)

Vibegron was not classified with a black triangle because of specific identified safety issues, but because vibegron is considered as a medicinal product containing a new active substance. We would like to clarify that no specific safety issue has been identified based on the available information from the clinical studies conducted

during the development of vibegron. However, pursuant to Article 23(1) of Regulation No (EU) 726/2004, vibegron is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU. Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle. Therefore, the black triangle does not translate safety issues identified by regulators and is applied in accordance to the regulation for all new active substances.

Response b)

The black triangle is no longer applied to mirabegron. This question is not applicable. As stated above, vibegron was not classified with a black triangle because of specific identified safety issues, but because vibegron is considered as a medicinal product containing a new active substance.

EMPOWUR trial

A14. Up to 15% of participants enrolled in EMPOWUR were permitted to be male, despite the CS noting similar rates of OAB in males and females. Please provide the rationale for limiting the number of male participants in EMPOWUR to 15%.

Response

The phase 3 study protocol included this limit at 15% because comorbid conditions in male subjects such as benign prostatic hyperplasia (BPH) are commonly observed and can precipitate overflow incontinence or frequency by a mechanism other than OAB. Thus the proportion of men was limited to 15% of the trial population in order not to confound trial outcomes.

The respective mirabegron SCORPIO, ARIES and CAPRICORN trials are not dissimilar with male populations representing 18%, 15.2% and 21.5% of the study population respectively.

A15. Participants who completed the full 12-week treatment period in EMPOWUR were eligible to participate in the EMPOWUR extension study. Please:

a) Provide the number of participants who were eligible to participate in the EMPOWUR extension study but did not; and
b) Provide the reasons, if available, that participants did not continue on into the extension study.

Response a)

According to the EMPOWUR extension study protocol, to the Statistical Analysis plan approximately 500 men and women with OAB who completed 12 weeks in EMPOWUR study were planned for enrolment in this extension study. This sample size was sufficient to characterize the long-term safety profile of vibegron, which was the primary objective of the EMPOWUR-Ext study and to satisfy the ICH guideline for 1-year exposure.

Among the total number of eligible patients:

- [redacted] subjects were screened and randomized for the study, [redacted] of whom were treated with at least 1 dose of double-blind study drug. The study population was enrolled from a total of 109 sites.

- [redacted] subjects did not participate in the EMPOWUR extension study

(For further clarification the subject disposition in EMPOWUR-Ext is as follows:

- *Patients screened* [redacted]
- *Patients treated (Safety Set Extension (SAF-Ext)):* [redacted]
- *Full Analysis set extension (FAS-Ext):* [redacted]

Response b)

Recruitment stopped as soon as the planned number of subjects was obtained. This is the reason why not all eligible subjects from the EMPOWUR Study were included in the EMPOWUR EXT study.

A16. In the CS, the company infers a non-inferiority margin based on the between-group difference used in the power calculations for the EMPOWUR trial, namely a difference of 0.60 for daily micturitions and a difference of 0.51 for UUI episodes. Please:

a) Clarify how these pre-specified effect sizes were chosen for the EMPOWUR power analysis; and
b) Clarify whether the company considers these values to appropriately reflect the minimum clinically important differences for daily micturitions and UUI episodes for people with OAB.

Response a)

According to EMPOWUR study protocol (section 9.7), the sample size was determined to detect a between-group treatment difference of 0.6 in change from baseline in micturition and 0.51 in urinary urge incontinence. Variability estimations are based on the phase IIb 008 study results (2). Size effects estimation was based on vibegron Phase IIb studies and on the results observed with another beta agonist mirabegron in OAB patients. In addition, such expected size effects were consistent with those observed with pharmacologic approved treatments for OAB including antimuscarinics and beta 3 agonists and supported in recommendations by guideline committees in OAB treatment (2).

Response b)

The co-primary endpoint analyses demonstrated statistical superiority of vibegron 75 mg once-daily treatment compared with placebo at Week 12 for the reduction in daily micturitions ($p < 0.001$) and reduction in daily urge urinary incontinence episodes ($p < 0.0001$). The difference from placebo was statistically significant as early as Week 2, the earliest timepoint measured following baseline, for both micturitions and UUI episodes ($p < 0.001$ and $p < 0.0001$, respectively). Further, statistically significant efficacy was maintained at all timepoints measured through the end of the study for both co-primary endpoints.

Even if no direct comparison was conducted versus tolterodine that is marketed, the study showed that vibegron achieved numerically greater improvements than tolterodine.

Clinically meaningful improvements in OAB symptoms were demonstrated by the statistically significant improvements observed for vibegron over placebo in the three key secondary responder analyses as well as in additional secondary efficacy endpoints that assessed severity and overall control over bladder symptoms based on Patient Global Impression (PGI-Severity and PGI-Control).

A17. Please provide an updated version of Table 13 including the active difference between interventions and placebo for change in daily episodes of UUI. Please also comment on the consistency of the active difference reported in Table 13, which appears likely to numerically favour placebo over vibegron in the male subgroup, and Figure 17B, which numerically favours vibegron over placebo in the same subgroup.

Response

Apologies for this error. The UUI section in the male/female subgroup table was mistakenly derived from the descriptive dataset reported in the CSR, when it should have been derived from the mixed model for repeated measures (MMRM) dataset. This has been done now (Table 16, this document) with confidence levels reported and the active difference also reported. You will observe that there is no longer a numerical difference in favour of placebo and the data are now consistent with the Forest plot (Figure 17A, submission document).

Table 16. Subgroup MMRM analysis of the co-primary outcomes at 12 weeks by sex (male or female) from EMPOWUR study.

Sex	Outcome	Placebo	Vibegron	Tolterodine
Change in daily micturitions				
Male	Mean change from baseline (95% CI)	-1.1 (-1.7 to -0.5) n=69	-1.7 (-3.3 to -1.2) n=75	-1.0 (-1.6 to -0.4) n=65
	Active difference*		-0.6 (-1.4 to 0.1)	0.1 (-0.7 to 0.9)
Female	Mean change from baseline (95% CI)	-1.4 (-1.7 to -1.1) n=406	-1.9 (-2.2 to -1.6) n=417	-1.7 (-2.0 to -1.5) n=318
	Active difference*		-0.5 (-0.8 to -0.2)	-0.3 (-0.7 to 0.0)
Change in daily episodes of UUI (FAS-I dataset)				
Male	Mean change from baseline (SD)	-1.60 (-2.2 to -0.9) n=38	-1.60 (-2.2 to -1.0) n=42	-2.0 (2.7 to -1.3) n=33
	Active difference*		-0.1 (-0.9 to 0.8)	-0.5 (-1.4 to 0.4)
Female	Change from baseline (SD)	-1.4 (-1.6 to -1.2) n=334	-2.1 (2.3 to -1.8) n=341	-1.8 (-0.7 to -0.1) n=253
	Active difference*		-0.7 (-1.0 to -0.4)	-0.4 (-0.7 to -0.2)

Abbreviations: CI, confidence intervals, FAS, full analysis set; FAS-I full analysis set in people with incontinence (wet OAB); MMRM, mixed model repeated measures.
* Difference between intervention and placebo.

EMPOWUR extension study

A18. Table 10 presented the LS mean change from baseline to Week 52 for efficacy endpoints among patients receiving either vibegron or tolterodine in the EMPOWUR EXT study. Please provide the outcome data for the subgroup of participants who were re-randomised from placebo to vibegron or tolterodine at Week 12, i.e., the change from Week 12 to Week 52 for re-randomised participants.

Response

As requested, please find the outcome data for the daily number of micturitions (Table 17), daily number of UUI episodes (Table 18), daily number of urgency episodes (Table 19) and number of total incontinence episodes (Table 20) for the subgroup of participants who were re-randomized from placebo to vibegron or tolterodine at Week 12 and the change from Week 12 to Week 52 (40 weeks) for these participants.

(Note: in the tables below, Week 12 of EMPOWUR study is considered as the Baseline of EMPOWUR-Ext study).

Table 17. Study EMPOWUR-Ext - Change from W12-Baseline in Average Daily Number of Micturitions (MMRM) - Subset of patients re-randomised from Placebo to Vibegron or Tolterodine [FAS Ext subset]

	40-weeks Vibegron 75mg	40-weeks Tolterodine ER 4mg
Baseline (W12)		
N		
Mean (SD)		
Week 52		
N		
Mean (SD)		
Change from Week 12 to Week 52		
N		
LS means (standard error [SE])		
95% CI		

Table 18. Study EMPOWUR-Ext- Change from W12-Baseline in Average Daily Number of UUI Episodes (MMRM) - Subset of patients re-randomised from Placebo to Vibegron or Tolterodine [FAS-I Ext subset]

	40-weeks Vibegron 75mg	40-weeks Tolterodine ER 4mg
Baseline (W12)		
N		
Mean (SD)		
Week 52		
N		
Mean (SD)		
Change from Week 12 to Week 52		
N		
LS means (standard error [SE])		
95% CI		

Table 19. Study EMPOWUR-Ext - Change from W12-Baseline in Average Daily Number of Urgency Episodes (MMRM) - Subset of patients re-randomised from Placebo to Vibegron or Tolterodine [FAS Ext subset]

	40-weeks Vibegron 75mg	40-weeks Tolterodine ER 4mg
Baseline (W12)		
N		
Mean (SD)		
Week 52		
N		
Mean (SD)		
Change from Week 12 to Week 52		
N		
LS means (standard error [SE])		
95% CI		

Table 20. Study EMPOWUR-Ext - Change from W12-Baseline in Average Daily Number of Total Incontinence Episodes (MMRM) - Subset of patients re-randomised from Placebo to Vibegron or Tolterodine [FAS-I Ext subset]

	40-weeks Vibegron 75mg	40-weeks Tolterodine ER 4mg
Baseline (W12)		
N		
Mean (SD)		
Week 52		
N		
Mean (SD)		
Change from Week 12 to Week 52		
N		
LS means (standard error [SE])		
95% CI		

A19. Priority question. Please provide a comparison of the change from baseline in micturition frequency, UUI episodes and total UI episodes at Week 12 in EMPOWUR between: i) those who continued onto the EMPOWUR extension study and ii) those who were eligible to continue onto the EMPOWUR extension study but did not continue. Using these results, please discuss the likely impact of any selection bias on the Week 52 results from any patients opting to continue into the EMPOWUR extension study.

Response

As requested, please find the comparison of the change from baseline in micturition frequency, UUI episodes and total UI episodes at Week 12 in EMPOWUR between: i) those who continued into the EMPOWUR extension study (respectively Table 21,

Table 23, and Table 25) and ii) those who were eligible to continue into the EMPOWUR extension study but did not continue (respectively Table 22, Table 24, and Table 26).

Although no formal statistical comparison between these cohorts were planned, the results on the three efficacy outcomes do not indicate the presence of selection bias. The three treatment groups present consistent baseline characteristics and the differences compared with placebo do not indicate a greater effect in the cohort that participate to EMPOWUR extension.

Table 21 Study Empowur - Change from Baseline in Average Daily Number of Micturitions (MMRM) - Subset of patients who continued into the extension study [FAS Ext]

	Placebo	Vibegron 75 mg	Tolterodine ER 4 mg
Baseline			
N			
Mean (SD)			
Week 12			
N			
Mean (SD)			
Change from Baseline at Week 12			
N			
LS means (standard error [SE])			
95% CI			
Active - Placebo			
LS means difference (SE)			
95% CI			
P-value			

Table 22 Study Empowur - Change from Baseline in Average Daily Number of Micturitions (MMRM) - Subset of patients eligible to continue onto the extension study but did not continue [FAS subset]

	Placebo	Vibegron 75 mg	Tolterodine ER 4 mg
Baseline			
N			
Mean (SD)			
Week 12			
N			
Mean (SD)			
Change from Baseline at Week 12			
N			
LS means (standard error [SE])			
95% CI			
Active - Placebo			
LS means difference (SE)			
95% CI			
P-value			

Table 23 Study Empowur - Change from Baseline in Average Daily Number of UUI Episodes (MMRM) - Subset of patients who continued onto the extension study [FAS-I Ext]

	Placebo	Vibegron 75 mg	Tolterodine ER 4 mg
Baseline			
N			
Mean (SD)			
Week 12			
N			
Mean (SD)			
Change from Baseline at Week 12			
N			
LS means (standard error [SE])			
95% CI			
Active - Placebo			
LS means difference (SE)			
95% CI			
P-value			

Table 24 Study Empowur - Change from Baseline in Average Daily Number of UUI Episodes (MMRM) - Subset of patients eligible to continue onto the extension study but did not continue [FAS-I subset]

	Placebo	Vibegron 75 mg	Tolterodine ER 4 mg
Baseline			
N			
Mean (SD)			
Week 12			
N			
Mean (SD)			
Change from Baseline at Week 12			
N			
LS means (standard error [SE])			
95% CI			
Active - Placebo			
LS means difference (SE)			
95% CI			
P-value			

Table 25 Study Empowur - Change from Baseline in Average Daily Number of Total Incontinence Episodes (MMRM) - Subset of patients who continued onto the extension study [FAS-I Ext]

	Placebo	Vibegron 75 mg	Tolterodine ER 4 mg
Baseline			
N			
Mean (SD)			
Week 12			
N			
Mean (SD)			
Change from Baseline at Week 12			
N			
LS means (standard error [SE])			
95% CI			

	Placebo	Vibegron 75 mg	Tolterodine ER 4 mg
Active - Placebo			
LS means difference (SE)		[redacted]	[redacted]
95% CI			
P-value			

Table 26 Study Empowur - Change from Baseline in Average Daily Number of Total Incontinence Episodes (MMRM) - Subset of patients eligible to continue onto the extension study but did not continue [FAS-I subset]

	Placebo	Vibegron 75 mg	Tolterodine ER 4 mg
Baseline			
N	[redacted]	[redacted]	[redacted]
Mean (SD)			
Week 12			
N	[redacted]	[redacted]	[redacted]
Mean (SD)			
Change from Baseline at Week 12			
N	[redacted]	[redacted]	[redacted]
LS means (standard error [SE])			
95% CI			
Active - Placebo			
LS means difference (SE)		[redacted]	[redacted]
95% CI			
P-value			

Section B: Textual clarification and additional points

B1. Page 92 of the CS states that: “This value of 0.6 was within the upper CrI of the NMA, indicating non-inferiority, giving reassurance that there were no important differences between the drugs in terms of reduction in daily micturitions.” Please clarify if this should read: “This value of 0.6 was **outside** the upper CrI of the NMA, indicating non-inferiority”?

Response

Yes, this is correct, this should read “outside”.

B2. Please clarify if CS page 83: “Vibegron was statistically superior compared with mirabegron (50 mg) at 52 weeks, with a median of -0.82 (95% CrI -1.38 to -0.26) (**see Appendix D.3.2, Figure 18D**).” should instead read “(**see Appendix D1.2.3.2, Figure 19D**).”

Response

Apologies for the error, yes, this is correct, the relevant figure is 19D in Appendix D1.2.3.2.

References

1. Yoshida M, Kakizaki H, Takahashi S, Nagai S, Kurose T. Long-term safety and efficacy of the novel β(3) -adrenoreceptor agonist vibegron in Japanese patients with overactive bladder: A phase III prospective study. Int J Urol. 2018;25(7):668-75.
2. Mitcheson HD, Samanta S, Muldowney K, Pinto CA, Rocha BA, Green S, et al. Vibegron (RVT-901/MK-4618/KRP-114V) Administered Once Daily as Monotherapy or Concomitantly with Tolterodine in Patients with an Overactive Bladder: A Multicenter, Phase IIb, Randomized, Double-blind, Controlled Trial. Eur Urol. 2019;75(2):274-82.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison Appraisal

Vibegron for treating symptoms of overactive bladder ID 6300

Clarification questions

May 2024

File name	Version	Contains confidential information	Date
ID6300 vibegron for treating symptoms of OAB additional clarification questions 16.05.2024_V1.3_CONSOLIDATED_NoCON	1.3	No	16.05.2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

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Section A: Clarification on effectiveness data

Discontinuation

A20. Priority. The EAG notes that a formal comparison of all-cause discontinuations has not yet been performed comparing vibegron with mirabegron. Please

a) **Update Table 2 from the clarification response document ("Information on the reasons for patients discontinuing participation in the studies included in the NMA.") to include the discontinuation rates from the placebo arms of each trial; and**
b) **Provide an NMA of the odds of discontinuation by Week 12 for mirabegron 25 mg, mirabegron 50 mg, placebo, tolterodine 4 mg and vibegron 75 mg. Please provide this using the company's preferred network, and the EAG's sensitivity analysis as requested in question A21.**

Response a)

We have updated the table reporting on the reasons for discontinuation in the included studies, including data on comparator arms (including placebo) in Table 1. Rows are stratified by study and intervention (e.g. yellow cells are placebo).

Table 1. Information on the reasons for patients discontinuing participation in the studies included in the NMA.

Study	Author and Year	Country	Treatment arm	Discontinuation, n (%)			Reason for Discontinuation Stratified by Occurrence Frequency, n (%)
				12 weeks	40 weeks	52 weeks	
ARIES	Nitti 2013 (1)	United States, Canada	Mirabegron 50mg (n=442)	59 (13.3%)	NA	NA	• Withdrew consent: 22 (5.0%) • Lost to follow-up: 9 (2.0%) • AE: 18 (4.1%) • Other: 5 (1.1%) • Protocol violation: 4 (0.9%) • Efficacy: 1 (0.2%)
			Mirabegron 100mg (n=433)	53 (12.2%)	NA	NA	• AE: 19 (4.4%) • Withdrew consent: 16 (3.7%) • Efficacy: 5 (1.2%) • Protocol violation: 5 (1.2%) • Other: 4 (0.9%) • Lost to follow-up: 3 (0.7%) • Eligibility criterion not met: 1 (0.2%)
CAPRICORN	Herschorn 2013 (2)	United States, Canada, Czechia, Denmark, Finland, Germany, Hungary, Norway, Slovakia Spain, Sweden	Mirabegron 25mg (n=433)	46 (10.6%)	NA	NA	• Withdrew consent: 12 (2.8%) • AE: 17 (3.9%) • Other: 5 (1.2%) • Efficacy: 4 (0.9%) • Protocol violation: 3 (0.7%) • Lost to follow-up: 3 (0.7%) • Did not take study drug: 1 (0.2%) • Eligibility criterion not met: 1 (0.2%)
			Mirabegron 50mg (n=440)	54 (12.3%)	NA	NA	• Withdrew consent: 18 (4.1%) • AE: 12 (2.7%) • Other: 10 (2.3%)

							• Protocol violation: 8 (1.8%) • Efficacy: 3 (0.7%) • Lost to follow-up: 3 (0.7%)
Kuo 2015	Kuo 2015 (3)	Taiwan, Korea, China, India	Mirabegron 50mg (n=372)	61 (16.4%)	NA	NA	• Withdrew consent: 21 (5.6%) • Eligibility criterion not met: 18 (4.8%) • AE: 9 (2.4%) • Efficacy: 4 (1.0%) • Protocol violation: 4 (1.0%) • Lost to follow-up: 3 (0.8%) • Other: 2 (0.05%)
Moussa 2021	Moussa 2021 (4)	Lebanon	Mirabegron 50mg (n=63)	10 (15.9%)	NA	NA	• Lost to follow-up: 4 (6.3%) • Withdrew consent: 3 (4.8%) • Protocol violation: 3 (4.8%)
SCORPIO	Khullar 2013 (5)	Australia, Austria, Belarus, Belgium, Bulgaria, Czechia, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Switzerland, Ukraine, United Kingdom	Mirabegron 50mg (n=497)	57 (11.5%)	NA	NA	• AE: 25 (5.0%) • Withdrew consent: 9 (1.8%) • Eligibility criterion not met: 8 (1.6%) • Efficacy: 6 (1.2%) • Lost to follow-up: 3 (0.6%) • Protocol violation: 3 (0.6%) • Other: 2 (0.4%) • Did not take study drug: 1 (0.2%)
			Mirabegron 100mg (n=498)	45 (9.0%)	NA	NA	• Withdrew consent: 17 (3.4%) • AE:16 (3.2%) • Protocol violation: 5 (1.0%) • Efficacy: 2 (0.4%) • Other: 2 (0.4%) • Lost to follow-up: 2 (0.4%) • Did not take study drug: 1 (0.2%)
TAURUS	Chapple 2013 (6)	United States, Australia, Austria, Belarus, Belgium, Canada, Czechia, Denmark, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Latvia,	Mirabegron 50mg (n=815)	NA	NA	186 (22.8%)	• Withdrew consent: 65 (8.0%) • AE: 52 (6.4%) • Efficacy: 34 (4.2%) • Lost to follow-up: 14 (1.7%) • Eligibility criterion not met: 7 (0.9%) • Other: 7 (0.9%) • Protocol violation: 6 (0.7%) • Did not take study drug: 1 (0.1%)

		Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Switzerland, Ukraine, United Kingdom	Mirabegron 100mg (n=824)	NA	NA	179 (21.7%)	• Withdrew consent: 75 (9.1%) • AE: 49 (5.9%) • Efficacy: 25 (3.0%) • Protocol violation: 9 (1.1%) • Lost to follow-up: 7 (0.8%) • Other: 7 (0.8%) • Eligibility criterion not met: 7 (0.8%)
Yamaguchi 2014	Yamaguchi 2014 (7)	Japan	Mirabegron 50mg (n = 380)	31 (8.2%)	NA	NA	• Adverse events: 15 (3.9%) • Withdrew consent: 8 (2.1%) • Inadequate efficacy: 4 (1.1%) • Protocol deviations: 3 (0.8%) • Other: 1 (0.3%)
SYNERGY	Herschorn 2017 (8)	USA, Argentina, Australia, Belgium, Bulgaria, Canada, China, Columbia, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Italy, Republic of Korea, Latvia, Lithuania, Malaysia, Mexico, Netherlands, New Zealand, Norway, Peru, Philippines, Poland, Romania, Russia, Singapore, Slovakia, Slovenia, South Africa, Spain, Sweeden, Taiwan, Thailand, Turkey, Ukraine, United Kingdom	Mirabegron 25mg (n = 441)	44 (10.0%)	NA	NA	• No study group: 5 (1.1%) • Protocol violation: 2 (0.5%) • Lost to follow-up: 2 (0.5%) • AE: 8 (1.8%) • Withdrew consent: 27 (6.1%)
			Mirabegron 50mg (n = 437)	50 (11.4%)	NA	NA	• No study group: 4 (0.9%) • Protocol violation: 3 (0.7%) • Lost to follow-up: 4 (0.9%) • AE: 12 (2.7%) • Withdrew consent: 23 (5.3%) • Other: 4 (0.9%)

EMPOWUR	Staskin 2020 (9)	United States, Canada, Hungary, Latvia, Lithuania, Poland	Vibegron 75mg (n=547)	45 (8.2%)	NA	NA	• Lost to follow-up: 15 (2.7%) • Withdrew consent: 14 (2.6%) • AE: 8 (1.5%) • Other: 6 (1.1%) • Protocol violation: 2 (0.4%)
EMPOWUR (Extension)	Staskin 2021 (10)	United States	Vibegron 75mg (n=92)	NA	13 (14.1%)	NA	• Withdrew consent: 6 (6.5%) • Lost to follow-up: 4 (4.3%) • AE: 1 (1.1%) • Death: 1 (1.1%) • Other: 1 (1.1%)
			Vibegron 75mg (n=181)	NA	NA	26 (14.3%)	• Withdrew consent: 11 (6.0%) • Lost to follow-up: 6 (3.3%) • AE: 3 (1.6%) • Withdrawn by investigator: 1 (0.5%) • Efficacy: 1 (0.5%) • Protocol violation: 1 (0.5%) • Other: 3 (1.6%)
EMPOWUR	Staskin 2020 (9)	United States, Canada, Hungary, Latvia, Lithuania, Poland	Tolterodine ER 4mg (n=431)	46 (10.7%)	NA	NA	• Withdrew consent: 13 (3.0%) • AE: 13 (3.0%) • Lost to follow-up: 10 (2.3%) • Withdrawn by investigator: 3 0.7%) • Other: 3 (0.7%) • Efficacy: 1 (0.2%) • Protocol violation: 1 (0.2%) • Withdrawn by Sponsor: 1 (0.2%) • Death: 1 (0.2%)
EMPOWUR (Extension)	Staskin 2021 (10)	United States	Tolterodine ER 4mg (n=91)	NA	19 (20.9%)	NA	• Withdrew consent: 7 (7.7%) • AE: 4 (4.4%) • Lost to follow-up: 3 (3.3%) • Withdrawn by investigator: 1 (1.1%) • Other: 4 (4.4%)
			Tolterodine ER 4mg (n=141)	NA	NA	18 (12.8%)	• Withdrew consent: 8 (5.7%) • AE: 4 (2.8%) • Lost to follow-up: 2 (1.4%) • Withdrawn by investigator: 1 (0.7%) • Withdrawn by Sponsor: 1 (0.7%)

							• Efficacy: 1 (0.7%) • Other: 1 (0.7%)
Kuo 2015	Kuo 2015 (3)	Taiwan, Korea, China, India	Tolterodine ER 4mg (n=377)	67 (17.8%)	NA	NA	• Withdrew consent: 24 (6.4%) • Eligibility criterion not met: 17 (4.5%) • AE: 15 (4.0%) • Lost to follow-up: 7 (1.9%) • Efficacy: 2 (0.5%) • Other: 2 (0.5%) • Protocol violation: 0 (0.0%)
SCORPIO	Khullar 2013 (5)	Australia, Austria, Belarus, Belgium, Bulgaria, Czechia, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Switzerland, Ukraine, United Kingdom	Tolterodine ER 4mg (n=495)	50 (10.1%)	NA	NA	• AE: 24 (4.8%) • Withdrew consent: 9 (1.8%) • Lost to follow-up: 5 (1.0%) • Eligibility criterion not met: 4 (0.8%) • Efficacy: 3 (0.6%) • Protocol violation: 3 (0.6%) • Other: 2 (0.4%)
TAURUS	Chapple 2013 (6)	United States, Australia, Austria, Belarus, Belgium, Canada, Czechia, Denmark, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, Slovakia,	Tolterodine ER 4mg (n=813)	NA	NA	192 (23.6%)	• Withdrew consent: 64 (7.9%) • AE: 49 (6.0%) • Lack of efficacy: 45 (5.5%) • Protocol violation: 11 (1.4%) • Eligibility criterion not met: 10 (1.2%) • Lost to follow-up: 7 (0.9%) • Other: 6 (0.7%)

		South Africa, Spain, Sweden, Switzerland, Ukraine, United Kingdom					
Yamaguchi 2014	Yamaguchi 2014 (7)	Japan	Tolterodine 4mg (n = 378)	23 (6.1%)	NA	NA	• Adverse events: 13 (3.4%) • Other: 5 (1.3%) • Inadequate efficacy: 2 (0.5%) • Protocol deviations: 2 (0.5%) • Withdrew consent: 1 (0.3%)
EMPOWUR	Staskin 2020 (9)	United States, Canada, Hungary, Latvia, Lithuania, Poland	Placebo (n=540)	54 (10%)	NA	NA	• Withdrew consent: 21 (3.9%) • Lost to follow-up: 14 (2.6%) • Other: 8 (1.5%) • AE: 6 (1.1%) • Lack of efficacy: 3 (0.6%) • Withdrawn by investigator: 1 (0.2%) • Withdrawn by Sponsor: 1 (0.2%)
CAPRICORN	Herschorn 2013 (2)	United States, Canada, Czechia, Denmark, Finland, Germany, Hungary, Norway, Slovakia Spain, Sweden	Placebo (n=433)	66 (15.2%)	NA	NA	• Withdrew consent: 20 (4.6%) • AE: 15 (3.5%) • Efficacy: 11 (2.5%) • Protocol violation: 5 (1.2%) • Lost to follow-up: 4 (0.9%) • Eligibility criterion not met: 1 (0.2%)
ARIES	Nitti 2013 (1)	United States, Canada	Placebo (n=454)	69 (15.2%)	NA	NA	• Withdrew consent: 29 (6.4%) • AE: 17 (3.7%) • Efficacy: 9 (2.0%) • Protocol violation: 7 (1.5%) • Other: 4 (0.9%) • Lost to follow-up: 2 (0.4%) • Did not take study drug: 1 (0.2%)
Kuo 2015	Kuo 2015 (3)	Taiwan, Korea, China, India	Placebo (n=377)	77 (20.4%)	NA	NA	• Eligibility criterion not met: 23 (6.1%) • Withdrew consent: 21 (5.6%) • AE:14 (3.7%) • Lost to follow-up: 6 (1.6%) • Other: 4 (1.1%) • Protocol violation: 2 (0.5%)

Moussa 2021	Moussa 2021 (4)	Lebanon	Placebo (n=47)	5 (10.6%)	NA	NA	• Lost to follow-up: 3 (6.4%) • Withdrew consent: 2 (4.3%)
SCORPIO	Khullar 2013 (5)	Australia, Austria, Belarus, Belgium, Bulgaria, Czechia, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Switzerland, Ukraine, United Kingdom	Placebo (n=497)	44 (8.9%)	NA	NA	• AE:13 (2.6%) • Withdrew consent: 11 (2.2%) • Eligibility criterion not met: 5 (1.0%) • Efficacy: 5 (1.0%) • Lost to follow-up: 4 (0.8%) • Protocol violation: 2 (0.4%) • Other: 2 (0.4%) • Did not take study drug: 2 (0.4%)
SYNERGY	Herschorn 2017 (8)	USA, Argentina, Australia, Belgium, Bulgaria, Canada, China, Columbia, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Italy, Republic of Korea, Latvia, Lithuania, Malaysia, Mexico, Netherlands, New Zealand, Norway, Peru, Philippines, Poland, Romania, Russia, Singapore, Slovakia, Slovenia, South Africa, Spain, Sweeden, Taiwan,	Placebo (n=447)	43 (9.6%)	NA	NA	• No study group: 2 (0.4%) • Efficacy: 1 (0.2%) • Protocol violation: 2 (0.4%) • Lost to follow-up: 4 (0.9%) • AE: 13 (2.9%) • Withdrew consent: 21 (4.7%)

		Thailand, Turkey, Ukraine, United Kingdom					
Yamaguchi 2014	Yamaguchi 2014 (7)	Japan	Placebo (n=381)	31 (8.1%)	NA	NA	• Withdrew consent: 12 (3.1%) • Adverse events: 9 (2.4%) • Protocol deviations: 5 (1.3%) • Inadequate efficacy: 3 (0.8%) • Other: 2 (0.5%)
Abbreviations: AE, Adverse Events; ER, extended release; NA, not applicable **Key:** Blue: Mirabegron; Orange: Vibegron; Grey: Tolterodine; Yellow: Placebo							

Response b)

We have provided an NMA of all cause discontinuations at 12 weeks using our favoured network (base case) and the random effects model (to account for study heterogeneity). This is illustrated in the Forest plot in Figure 1, with raw data from the trials reported in Table 2 and the comparison table reported in Table 3.

The NMA favours vibegron numerically against all comparators, although these differences are not statistically significant.

Figure 1. Forest plot showing all discontinuations at 12 weeks.

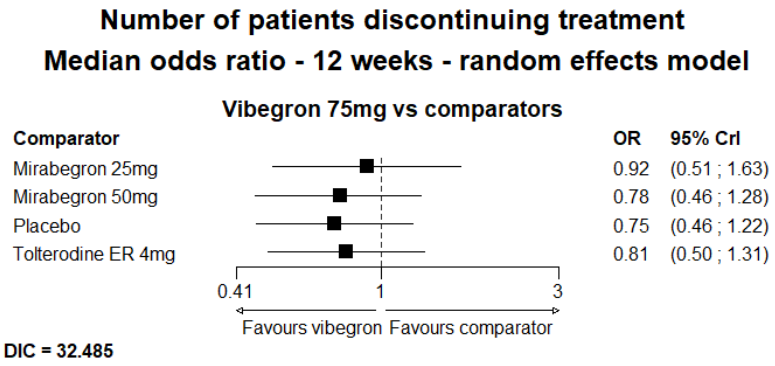


Table 2. Input data table for the number of patients discontinuing treatment

Number of patients discontinuing treatment - 12 weeks				
Author year	**Study**	**Treatment**	**n**	**N**
Nitti 2013 (1)	ARIES	Mirabegron 50mg	59	442
		Placebo	69	454
Herschorn 2013 (2)	CAPRICORN	Mirabegron 25mg	46	433
		Mirabegron 50mg	54	440
		Placebo	66	433
Staskin 2020 (9)	EMPOWUR	Vibegron 75mg	45	547
		Tolterodine ER 4mg	46	431
		Placebo	54	540
Kuo 2015 (3)	Kuo 2015	Mirabegron 50mg	61	372
		Tolterodine ER 4mg	67	377
		Placebo	77	377
Khullar 2013 (5)	SCORPIO	Mirabegron 50mg	57	497
		Tolterodine ER 4mg	50	495
		Placebo	44	497
Herschorn 2017 (8)	SYNERGY	Mirabegron 50mg	50	437
		Mirabegron 25mg	44	441
		Placebo	43	447
Yamaguchi 2014 (7)	Yamaguchi 2014	Mirabegron 50mg	31	380
		Tolterodine ER 4mg	23	378
		Placebo	31	381

Table 3. Comparison for the number of patients discontinuing treatment at 12 weeks "each vs each"

Mirabegron 25mg	Mirabegron 50mg	Placebo	Tolterodine ER 4mg	Vibegron 75mg
Mirabegron 25mg	1.184 (0.838, 1.665)	1.229 (0.868, 1.717)	1.143 (0.759, 1.704)	0.922 (0.512, 1.634)
0.845 (0.601, 1.193)	Mirabegron 50mg	1.037 (0.837, 1.277)	0.967 (0.73, 1.265)	0.779 (0.46, 1.285)
0.814 (0.583, 1.153)	0.964 (0.783, 1.194)	Placebo	0.932 (0.721, 1.199)	0.751 (0.463, 1.221)
0.875 (0.587, 1.317)	1.035 (0.791, 1.369)	1.073 (0.834, 1.387)	Tolterodine ER 4mg	0.806 (0.497, 1.309)
1.085 (0.612, 1.951)	1.284 (0.778, 2.175)	1.332 (0.819, 2.161)	1.24 (0.764, 2.014)	Vibegron 75mg

Sensitivity analyses

We have performed the NMA analysis (random effects model) with the addition of two phase 2 trials and the exclusion of the TAURUS trial (see response to question A21a). The NMA favours vibegron numerically against all comparators, although these differences are not statistically significant (Figure 2,Table 4 and Table 5).

Figure 2. Forest plot showing all discontinuations at 12 weeks (sensitivity analysis).

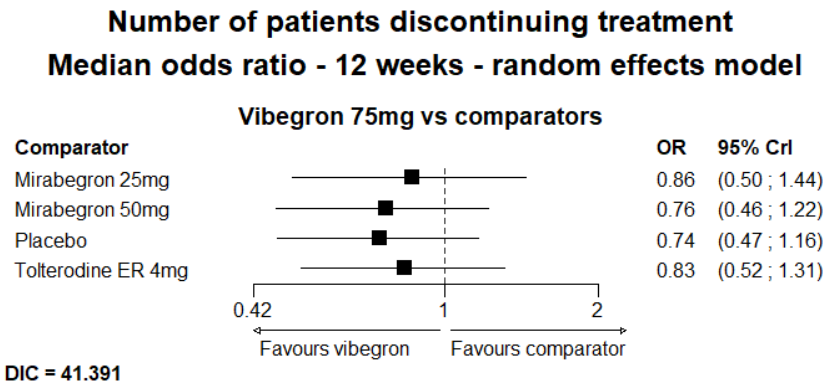


Table 4. Input data table for the number of patients discontinuing treatment at 12 weeks (sensitivity analysis)

Number of patients discontinuing treatment - 12 weeks				
Author year	**Study**	**Treatment**	**n**	**N**
Nitti 2013	ARIES	Mirabegron 50mg	59	442
		Placebo	69	454
Herschorn 2013	CAPRICORN	Mirabegron 25mg	46	433
		Mirabegron 50mg	54	440
		Placebo	66	433
Staskin 2020	EMPOWUR	Vibegron 75mg	45	547
		Tolterodine ER 4mg	46	431
		Placebo	54	540
Kuo 2015	Kuo 2015	Mirabegron 50mg	61	372
		Tolterodine ER 4mg	67	377
		Placebo	77	377
Khullar 2013	SCORPIO	Mirabegron 50mg	57	497
		Tolterodine ER 4mg	50	495
		Placebo	44	497

Herschorn 2017	SYNERGY	Mirabegron 50mg	50	437
		Mirabegron 25mg	44	441
		Placebo	43	447
Yamaguchi 2014	Yamaguchi 2014	Mirabegron 50mg	31	380
		Tolterodine 4mg	23	378
		Placebo	31	381
Chapple 2013	DRAGON	Mirabegron 25mg	16	169
		Mirabegron 50mg	16	169
		Placebo	12	169
		Tolterodine 4mg	3	85
Yamaguchi 2015	Yamaguchi 2015	Mirabegron 25mg	11	211
		Mirabegron 50mg	13	208
		Placebo	16	214

Table 5. Comparison for the number of patients discontinuing treatment at 12 weeks "each vs each" (sensitivity analysis).

Mirabegron 25mg	Mirabegron 50mg	Placebo	Tolterodine ER 4mg	Vibegron 75mg
Mirabegron 25mg	1.125 (0.849, 1.495)	1.154 (0.869, 1.527)	1.038 (0.722, 1.455)	0.86 (0.501, 1.441)
0.889 (0.669, 1.178)	**Mirabegron 50mg**	1.027 (0.845, 1.235)	0.922 (0.708, 1.173)	0.765 (0.465, 1.217)
0.866 (0.655, 1.15)	0.974 (0.809, 1.184)	**Placebo**	0.898 (0.699, 1.136)	0.745 (0.468, 1.161)
0.964 (0.687, 1.384)	1.085 (0.852, 1.413)	1.114 (0.88, 1.43)	**Tolterodine ER 4mg**	0.831 (0.521, 1.307)
1.163 (0.694, 1.997)	1.307 (0.822, 2.148)	1.343 (0.861, 2.136)	1.204 (0.765, 1.919)	**Vibegron 75mg**

Network meta-analyses

A21. Priority. The EAG notes that Phase 2 RCTs were not included in the company's NMA, but they do provide information relevant to the decision problem and were considered in TA290. The EAG also notes that participants from TAURUS may also have participated in previous Phase III trials of mirabegron (Khullar 2013 and Nitti 2013), and as such may contribute data twice to the current NMAs. Please:

a) **Provide a NMA sensitivity analyses at Week 12, including the Phase 2 DRAGON (NCT00337090) and Yamaguchi 2015 (NCT00527033) studies, but excluding TAURUS. Please provide these for the following NMAs: i) average daily number of micturitions, ii) UUI episodes, iii) total incontinence episodes, and iv) all presented AE analyses.**

The EAG notes another Phase 2 study of mirabegron, SYMPHONY (Abrams 2015) was not included in the company NMAs based on study phase. The EAG also notes that in this study only 21.5% of the FAS population reported one incontinence episode or more at baseline, i.e., different to the majority of patients in all other trials. As such, the EAG does not consider SYMPHONY should be included in the requested NMA sensitivity analysis.

Response a)

Information on contributing studies to sensitivity analyses

TAURUS trial

We have reviewed the TAURUS trial, published in *European Urology* by Chapple *et al.* (2013) (6), and the trial protocol on clinicaltrials.gov (NCT00688688) (11). These studies stated that whilst prior participation in studies on mirabegron was not an exclusion criterion for TAURUS, participants had to undergo a minimum of 30 days washout (6). That is, TAURUS was not an extension trial. For this reason, we considered that participants in TAURUS were enrolled and randomised independently in a manner that was acceptable for inclusion in the NMA, and, as this study provided valuable information, our preferred analysis is to retain this study. However, we do note from the Evidence Review Group (ERG) report of TA290 (12) that patients enrolled in TAURUS included those who participated in the SCORPIO (5) and ARIES trials (1), so for this sensitivity analyses we have removed the TAURUS study as requested.

Additional phase 2 trials

An *a priori* requirement for inclusion into the NMA was that the trials should be phase 3 or above. The reasons for this were to maximise the quality of evidence informing the NMA and to reduce the contributary risk of bias from the informing studies. Phase 2 trials typically have smaller sample sizes, have less follow up, and are often "dose finding", meaning they feature more treatment arms at different, often unlicensed, doses of the intervention drug, and consequently smaller sizes in the treatment arms. In other studies, dose escalation is used, further confounding analysis. These features make phase 2 trials less suitable for HTA and incorporation into an NMA. Additionally, there is empirical evidence that phase 2 trials tend to overestimate efficacy results compared with phase 3 trials (13), so restricting analysis to phase 3 trials is a conservative approach.

Nevertheless, we have reviewed all the studies that were excluded from the NMA on the basis of trial phase. These studies are reported in Table 6. We have concluded from this review that only the studies by Chapple *et al*. (2013) (14) (DRAGON

STUDY, NCT00337090) and the study by Yamaguchi et al. (2015) (15) (NCT00527033) are suitable for inclusion in the NMA.

Table 6. Phase 2 studies identified in literature search and suitability for inclusion into the NMA (sensitivity analyses).

Study Author year	**Treatment**	**Original reason for exclusion from NMA**	**Clarified reason for exclusion from NMA (if appropriate)**
DRAGON Chapple 2013 (14)	•Mirabegron 25mg •Mirabegron 50mg •Mirabegron 100mg •Mirabegron 200mg •Tolterodine ER 4mg •Placebo	Inadequate study phase (phase 2)	This study has been included in the updated NMA analysis. The company maintains reservations about the phase of this study but accepts the data from the placebo, 25 mg and 50 mg mirabegron arms can be used to inform the NMA.
Kinjo 2023 (16)	•Mirabegron 50mg •Vibegron 50mg	Unknown phase Not relevant comparator Postmenopausal women with treatment-naïve OAB	Kinjo (2013) is reported fully in the submission. The authors reported an open-label trial comparing vibegron directly with mirabegron. However, the dose of vibegron used is unlicensed in the UK.
Kuo 2023 (17)	•Mirabegron 25mg •Mirabegron 50mg •Solifenacin 5mg •Mirabegron 25mg plus solifenacin 5mg	Open-label study	The study by Kuo (2023) was small and open label. All patients initially received mirabegron at a dose of 25 mg before randomisation to other treatments. There was no placebo control group or other active comparator suitable for inclusion in the network.
MK-4618-008 Mitcheson 2019 (18)	•Vibegron 3mg •Vibegron 15mg •Vibegron 50mg •Vibegron 100mg •Tolterodine ER 4mg •Vibegron 50mg plus tolterodine ER 4mg (4 wks)/ Vibegron 50mg (4 wks) •Placebo	Inadequate study phase (phase 2)	Mitcheson (2019) reported on a phase 2 trial which is fully reported in the submission. The authors compared difference doses of vibegron and combinations of the drug with tolterodine and placebo. However, none of the doses were 75 mg allowing for integration into the NMA.
PILLAR Wagg 2020 (19)	•Mirabegron 25mg or 50mg •Placebo	Inadequate study phase	The PILLAR trial was a phase 2 trial comparing mirabegron 25 mg with placebo. However, following randomisation to one of these treatment arms, patients on mirabegron were allowed to up-titrate to 50 mg at the clinician discretion, thus breaking randomisation. We also had additional concerns with the consistency of this study. For instance, the higher dose of mirabegron (50 mg) was reported as not having a significant impact on daily micturitions compared with placebo, in contrast to the lower dose (25 mg). This could be related to patient selection, but adds uncertainty to the analysis.

SYMPHONY Abrams 2015 (20)	•Mirabegron 25mg •Mirabegron 50mg •Solifenacin 2.5mg •Solifenacin 5mg •Solifenacin 10mg •Solifenacin 2.5mg+Mirabegron 25mg •Solifenacin 2.5mg+Mirabegron 50mg •Solifenacin 5mg+Mirabegron 25mg •Solifenacin 5mg+Mirabegron 50mg •Solifenacin 10mg+Mirabegron 25mg •Solifenacin 10mg+Mirabegron 50mg •Placebo	Inadequate study phase (phase 2)	The EAG has highlighted that the symphony trial enrolled a fewer proportion of patients with incontinence compared with other trials in the NMA. SYMPHONY was mainly focussed on combinations of treatment that do not usefully inform the decision problem.
Yamaguchi 2015 (15)	•Mirabegron 25mg •Mirabegron 50mg •Mirabegron 100mg •Placebo	Inadequate study phase (phase 2)	This study has been included in the updated NMA analysis. The company maintains reservations about the phase of this study but accepts the data from the placebo, 25 mg and 50 mg mirabegron arms can be used to inform the NMA.
Yoshida 2018 (21)	•Vibegron 50mg •Vibegron 100mg •Placebo •Imidafenacin 0.1mg	Not relevant comparators	The study by Yoshida (2018) is fully reported in the submission but does not form part of the NMA. This is because the doses of vibegron used (50 and 100 mg) are not licensed in the UK.
Abbreviations: NMA, network meta-analysis. **Key:** Orange studies are excluded from the NMA, green studies have been included in the updated NMA (sensitivity analyses).			

Sensitivity analyses

In this section, we have run sensitivity analyses excluding the TAURUS study (6) and included the DRAGON study by Chapple et al. (2013) (14) and the study by Yamaguchi et al. (2015) (15). We have done this on the primary efficacy outcomes reported at 12 weeks using the random effects model (due to potential study heterogeneity), providing Forest plots and data tables as appropriate. We have also reported full data for the global (aggregated adverse events). For specific adverse events, only Forest plots are reported.

Number of daily micturitions

The sensitivity analysis of the number of daily number of micturitions reported there were no significant differences between mirabegron and any active intervention (Figure 3, Table 7 and Table 8). Vibegron was statistically superior compared with placebo (mean difference [MD] -0.49, 95% confidence intervals [CI] -0.89 to -0.08).

Figure 3. Forest plot showing daily micturitions at 12 weeks (sensitivity analysis).

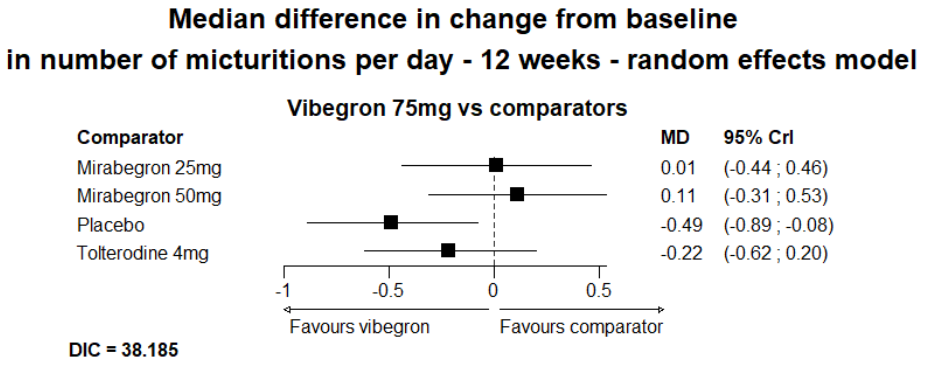


Table 7. Input data table for the number of daily micturitions at 12 weeks (sensitivity analysis).

Number of micturitions per day - 12 weeks					
Author year	**Study**	**Treatment**	**Comparator**	**Mean**	**SE**
Nitti 2014	ARIES	Mirabegron 50mg		-1.66	0.130
		Placebo		-1.05	0.130
Herschorn 2013	CAPRICORN	Mirabegron 25mg		-1.65	0.130
		Mirabegron 50mg		-1.6	0.120
		Placebo		-1.18	0.124
Staskin 2020	EMPOWUR	Vibegron 75mg		-1.8	0.140
		Tolterodine ER 4mg		-1.6	0.150
		Placebo		-1.3	0.140
Khullar 2013	SCORPIO	Mirabegron 50mg		-1.94	0.116
		Tolterodine ER 4mg		-1.57	0.123
		Placebo		-1.37	0.115
Herschorn 2017	SYNERGY	Mirabegron 50mg		-2.03	0.120
		Mirabegron 25mg		-2	0.120
		Placebo		-1.64	0.120
Yamaguchi 2014	Yamaguchi 2014	Mirabegron 50mg		-1.67	0.115
		Tolterodine 4mg		-1.4	0.113
		Placebo		-0.86	0.123
Yamaguchi 2015	Yamaguchi 2015	Mirabegron 25mg		-1.94	0.149
		Mirabegron 50mg		-2.12	0.165
		Placebo		-1.18	0.148
Kuo 2015	Kuo 2015	Mirabegron 50mg	Placebo	-0.46	0.217
		Tolterodine ER 4mg	Placebo	0.19	0.219
		Placebo			0.162

Number of micturitions per day - 12 weeks					
Author year	**Study**	**Treatment**	**Comparator**	**Mean**	**SE**
Chapple 2013	DRAGON	Mirabegron 25mg	Placebo	-0.45	0.278
		Mirabegron 50mg	Placebo	-0.64	0.278
		Tolterodine ER 4mg	Placebo	-0.52	0.278
		Placebo			0.216

Table 8. Comparison for the number of daily micturitions at 12 weeks "each vs each" (sensitivity analysis).

Mirabegron 25mg	**Mirabegron 50mg**	**Placebo**	**Tolterodine 4mg**	**Vibegron 75mg**
Mirabegron 25mg	-0.1 (-0.31, 0.11)	0.5 (0.29, 0.71)	0.23 (-0.03, 0.48)	0.01 (-0.44, 0.46)
0.1 (-0.11, 0.31)	Mirabegron 50mg	0.6 (0.44, 0.75)	0.32 (0.13, 0.52)	0.11 (-0.31, 0.53)
-0.5 (-0.71, -0.29)	-0.6 (-0.75, -0.44)	Placebo	-0.27 (-0.46, -0.08)	-0.49 (-0.89, -0.08)
-0.23 (-0.48, 0.03)	-0.32 (-0.52, -0.13)	0.27 (0.08, 0.46)	Tolterodine 4mg	-0.22 (-0.62, 0.2)
-0.01 (-0.46, 0.44)	-0.11 (-0.53, 0.31)	0.49 (0.08, 0.89)	0.22 (-0.2, 0.62)	Vibegron 75mg

Number of episodes of UUI

The data reporting the sensitivity analysis on the numbers of episodes of UUI are reported in Figure 4, Table 9 and Table 10. There were no statistically significant differences between vibegron and the active interventions, although the data favoured vibegron in all of these. Vibegron was statistically superior compared with placebo, reducing episodes by -0.56 (95% CI -0.91 to -0.21).

Figure 4. Forest plot showing episodes of UUI at 12 weeks (sensitivity analysis).

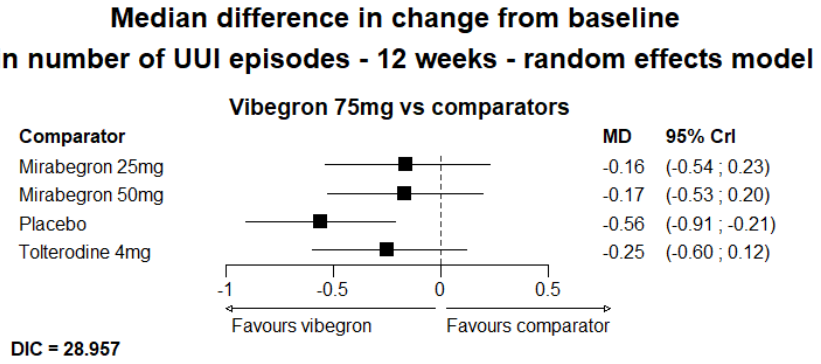


Table 9. Input data table for the episodes of UUI at 12 weeks (sensitivity analysis).

Number of UUI episodes - 12 weeks					
Author year	**Study**	**Treatment**	**Comparator**	**Mean**	**SE**
Nitti 2014	ARIES	Mirabegron 50mg		-1.32	0.100
		Placebo		-0.89	0.100
Herschorn 2013	CAPRICORN	Mirabegron 25mg		-1.31	0.112
		Mirabegron 50mg		-1.33	0.111
		Placebo		-0.95	0.110
Staskin 2020	EMPOWUR	Vibegron 75mg		-2	0.130
		Tolterodine ER 4mg		-1.8	0.140
		Placebo		-1.4	0.130
Herschorn 2017	SYNERGY	Mirabegron 50mg		-1.62	0.090
		Mirabegron 25mg		-1.58	0.090
		Placebo		-1.33	0.090
Yamaguchi 2014	Yamaguchi 2014	Mirabegron 50mg		-1.01	0.084
		Tolterodine 4mg		-0.95	0.104

Number of UUI episodes - 12 weeks					
Author year	**Study**	**Treatment**	**Comparator**	**Mean**	**SE**
		Placebo		-0.6	0.109
Yamaguchi 2015	Yamaguchi 2015	Mirabegron 25mg		-1.14	0.096
		Mirabegron 50mg		-1.09	0.115
		Placebo		-0.68	0.118
Kuo 2015	Kuo 2015	Mirabegron 50mg	Placebo	-0.16	0.242
		Tolterodine ER 4mg	Placebo	-0.2	0.237
		Placebo			0.180
Chapple 2013a	DRAGON	Mirabegron 25mg	Placebo	-0.86	0.263
		Mirabegron 50mg	Placebo	-0.69	0.253
		Tolterodine ER 4mg	Placebo	-0.31	0.311
		Placebo			0.184

Table 10. Comparison for the episodes of UUI at 12 weeks "each vs each" (sensitivity analysis).

Mirabegron 25mg	**Mirabegron 50mg**	**Placebo**	**Tolterodine 4mg**	**Vibegron 75mg**
Mirabegron 25mg	0.02 (-0.14, 0.18)	0.4 (0.24, 0.57)	0.09 (-0.15, 0.33)	-0.16 (-0.54, 0.23)
-0.02 (-0.18, 0.14)	Mirabegron 50mg	0.39 (0.26, 0.52)	0.07 (-0.12, 0.28)	-0.17 (-0.53, 0.2)
-0.4 (-0.57, -0.24)	-0.39 (-0.52, -0.26)	Placebo	-0.32 (-0.51, -0.11)	-0.56 (-0.91, -0.21)
-0.09 (-0.33, 0.15)	-0.07 (-0.28, 0.12)	0.32 (0.11, 0.51)	Tolterodine 4mg	-0.25 (-0.6, 0.12)
0.16 (-0.23, 0.54)	0.17 (-0.2, 0.53)	0.56 (0.21, 0.91)	0.25 (-0.12, 0.6)	Vibegron 75mg

Number of total incontinence episodes

The data reporting the sensitivity analysis on the total number of episodes of incontinence are reported in Figure 5, Table 11 and Table 12. There were no statistically significant differences between vibegron and mirabegron at either dose, although the point estimates favoured vibegron. Vibegron was statistically superior compared with placebo, reducing episodes by -0.62 (95% CI -1.02 to -0.23) and superior to tolterodine (MD -0.39, 95% CI -0.80 to -0.01).

Figure 5. Forest plot showing total episodes of incontinence at 12 weeks (sensitivity analysis).

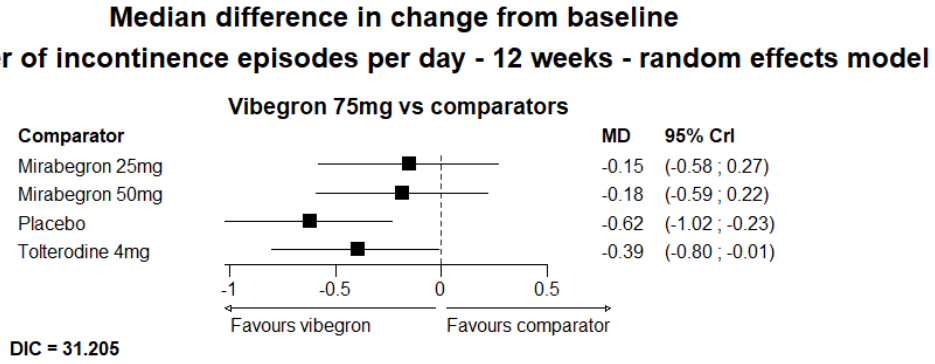


Table 11. Input data table for the total episodes of incontinence at 12 weeks (sensitivity analysis).

Number of incontinence episodes per day - 12 weeks					
Author year	**Study**	**Treatment**	**Comparator**	**Mean**	**SE**
Nitti 2014	ARIES	Mirabegron 50mg		-1.47	0.110
		Placebo		-1.13	0.110
Herschorn 2013	CAPRICORN	Mirabegron 25mg		-1.36	0.120
		Mirabegron 50mg		-1.38	0.120
		Placebo		-0.96	0.122
Staskin 2020	EMPOWUR	Vibegron 75mg		-2.3	0.150

Number of incontinence episodes per day - 12 weeks					
Author year	**Study**	**Treatment**	**Comparator**	**Mean**	**SE**
		Tolterodine ER 4mg		-2	0.160
		Placebo		-1.6	0.150
Khullar 2013	SCORPIO	Mirabegron 50mg		-1.62	0.137
		Tolterodine ER 4mg		-1.21	0.137
		Placebo		-1.13	0.126
Herschorn 2017	SYNERGY	Mirabegron 50mg		-1.76	0.100
		Mirabegron 25mg		-1.7	0.100
		Placebo		-1.34	0.100
Yamaguchi 2014	Yamaguchi 2014	Mirabegron 50mg		-1.12	0.090
		Tolterodine 4mg		-0.97	0.104
		Placebo		-0.66	0.115
Yamaguchi 2015	Yamaguchi 2015	Mirabegron 25mg		-1.29	0.167
		Mirabegron 50mg		-1.2	0.121
		Placebo		-0.64	0.115
Kuo 2015	Kuo 2015	Mirabegron 50mg	Placebo	-0.13	0.250
		Tolterodine ER 4mg	Placebo	-0.01	0.245
		Placebo			0.185
Chapple 2013	DRAGON	Mirabegron 25mg	Placebo	-0.84	0.311
		Mirabegron 50mg	Placebo	-0.62	0.306
		Tolterodine ER 4mg	Placebo	-0.28	0.372
		Placebo			0.204

Table 12. Comparison for the total episodes of incontinence at 12 weeks "each vs each" (sensitivity analysis).

Mirabegron 25mg	Mirabegron 50mg	Placebo	Tolterodine 4mg	Vibegron 75mg
Mirabegron 25mg	0.03 (-0.15, 0.21)	0.46 (0.28, 0.65)	0.24 (0, 0.49)	-0.15 (-0.58, 0.27)
-0.03 (-0.21, 0.15)	Mirabegron 50mg	0.44 (0.31, 0.57)	0.21 (0.03, 0.4)	-0.18 (-0.59, 0.22)
-0.46 (-0.65, -0.28)	-0.44 (-0.57, -0.31)	Placebo	-0.22 (-0.4, -0.04)	-0.62 (-1.02, -0.23)
-0.24 (-0.49, 0)	-0.21 (-0.4, -0.03)	0.22 (0.04, 0.4)	Tolterodine 4mg	-0.39 (-0.8, -0.01)
0.15 (-0.27, 0.58)	0.18 (-0.22, 0.59)	0.62 (0.23, 1.02)	0.39 (0.01, 0.8)	Vibegron 75mg

Any adverse events

The data reporting the sensitivity analysis on the total number of adverse events are reported in Figure 6, Table 11, and Table 12. There were no statistically significant differences between vibegron or any of its comparators.

We would reiterate for all the safety analyses, there are constraints on how these can be compared and interpreted between interventions and studies. These limitations are discussed in Section B.3.9.5 of the original submission.

Figure 6. Forest plot showing total number of adverse events at 12 weeks (sensitivity analysis)

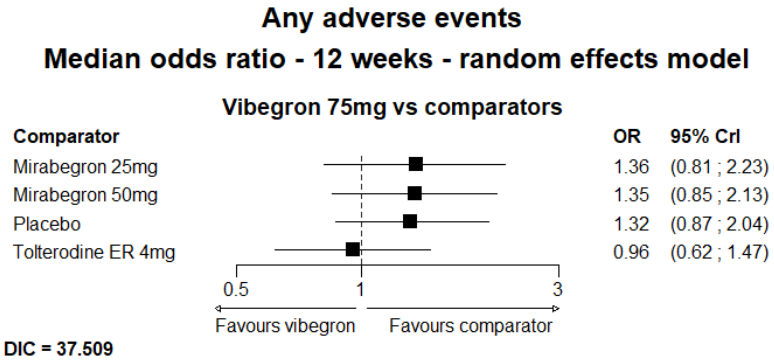


Table 13. Input data table for the total number of adverse events at 12 weeks (sensitivity analysis).

Any AEs - 12 weeks				
Author year	**Study**	**Treatment**	**n**	**N**
Nitti 2014	ARIES	Mirabegron 50mg	38	442
		Placebo	39	453
Staskin 2020	EMPOWUR	Vibegron 75mg	211	545
		Tolterodine ER 4mg	166	430
		Placebo	180	540
Khullar 2013	SCORPIO	Mirabegron 50mg	211	493
		Tolterodine ER 4mg	231	495
		Placebo	214	494
Herschorn 2013	CAPRICORN	Mirabegron 25mg	210	432
		Mirabegron 50mg	208	440
		Placebo	217	433
Herschorn 2017	SYNERGY	Mirabegron 50mg	147	422
		Mirabegron 25mg	135	423

Any AEs - 12 weeks				
Author year	**Study**	**Treatment**	**n**	**N**
		Placebo	145	429
Kuo 2015	Kuo 2015	Mirabegron 50mg	191	366
		Tolterodine ER 4mg	260	371
		Placebo	214	366
Yamaguchi 2015	Yamaguchi 2015	Mirabegron 25mg	169	210
		Mirabegron 50mg	171	208
		Placebo	157	212

Table 14. Comparison for the total number of adverse events at 12 weeks "each vs each" (sensitivity analysis).

Mirabegron 25mg	**Mirabegron 50mg**	**Placebo**	**Tolterodine ER 4mg**	**Vibegron 75mg**
Mirabegron 25mg	1.003 (0.757, 1.321)	1.029 (0.768, 1.341)	1.414 (0.981, 2.027)	1.356 (0.813, 2.233)
0.997 (0.757, 1.321)	Mirabegron 50mg	1.026 (0.823, 1.247)	1.41 (1.062, 1.876)	1.352 (0.85, 2.134)
0.972 (0.746, 1.303)	0.975 (0.802, 1.215)	Placebo	1.375 (1.07, 1.822)	1.317 (0.867, 2.039)
0.707 (0.493, 1.019)	0.709 (0.533, 0.942)	0.728 (0.549, 0.935)	Tolterodine ER 4mg	0.958 (0.618, 1.469)
0.738 (0.448, 1.23)	0.74 (0.468, 1.177)	0.759 (0.49, 1.154)	1.044 (0.681, 1.617)	Vibegron 75mg

Serious adverse events

The data reporting the sensitivity analysis on the number of serious adverse events are reported in Figure 7, Table 11 and Table 12. There were no statistically significant differences between vibegron or any of its comparators.

Figure 7. Forest plot showing number of serious adverse events at 12 weeks (sensitivity analysis)

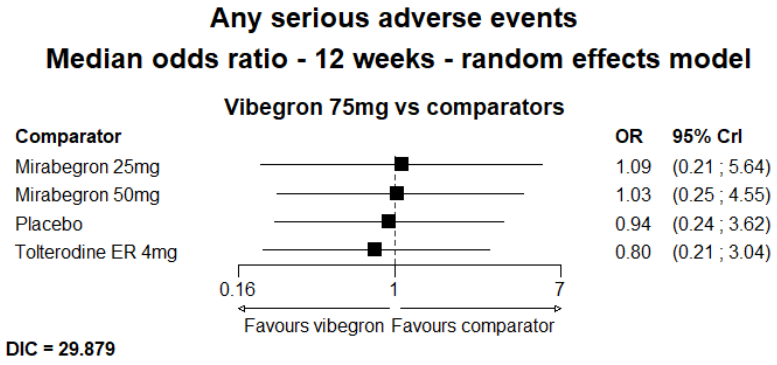


Table 15. Input data table for the number of serious adverse events at 12 weeks (sensitivity analysis). Any SAEs - 12 weeks

Author year	Study	Treatment	n	N
Nitti 2014	ARIES	Mirabegron 50mg	11	442
		Placebo	9	453
Herschorn 2013	CAPRICORN	Mirabegron 25mg	7	432
		Mirabegron 50mg	4	440
		Placebo	12	433
Staskin 2020	EMPOWUR	Vibegron 75mg	8	545
		Tolterodine ER 4mg	10	430
		Placebo	6	540
Herschorn 2017	SYNERGY	Mirabegron 50mg	5	422
		Mirabegron 25mg	6	423
		Placebo	8	429
Khullar 2013	SCORPIO	Mirabegron 50mg	14	493
		Tolterodine ER 4mg	11	495
		Placebo	8	494
Kuo 2015	Kuo 2015	Mirabegron 50mg	5	366

Table 15. Input data table for the number of serious adverse events at 12 weeks (sensitivity analysis). ***Any SAEs - 12 weeks***				
Author year	**Study**	**Treatment**	**n**	**N**
		Tolterodine ER 4mg	6	371
		Placebo	7	366

Table 16. Comparison for the number of serious adverse events at 12 weeks "each vs each" (sensitivity analysis).

Mirabegron 25mg	**Mirabegron 50mg**	**Placebo**	**Tolterodine ER 4mg**	**Vibegron 75mg**
Mirabegron 25mg	1.052 (0.376, 2.84)	1.16 (0.429, 3.088)	1.363 (0.405, 4.532)	1.089 (0.207, 5.636)
0.951 (0.352, 2.66)	Mirabegron 50mg	1.097 (0.594, 2.183)	1.287 (0.557, 3.181)	1.032 (0.251, 4.555)
0.862 (0.324, 2.332)	0.911 (0.458, 1.684)	Placebo	1.172 (0.527, 2.593)	0.942 (0.242, 3.617)
0.734 (0.221, 2.471)	0.777 (0.314, 1.797)	0.853 (0.386, 1.896)	Tolterodine ER 4mg	0.799 (0.211, 3.038)
0.918 (0.177, 4.83)	0.969 (0.22, 3.989)	1.062 (0.277, 4.126)	1.251 (0.329, 4.739)	Vibegron 75mg

Adverse events leading to treatment discontinuation

The data reporting the sensitivity analysis on the number of discontinuations due to adverse events are reported in Figure 8, Table 17 and Table 18. There were no statistically significant differences between vibegron or any of its comparators, although all the outcomes favoured vibegron numerically.

Figure 8. Forest plot showing discontinuation due to adverse events at 12 weeks (sensitivity analysis)

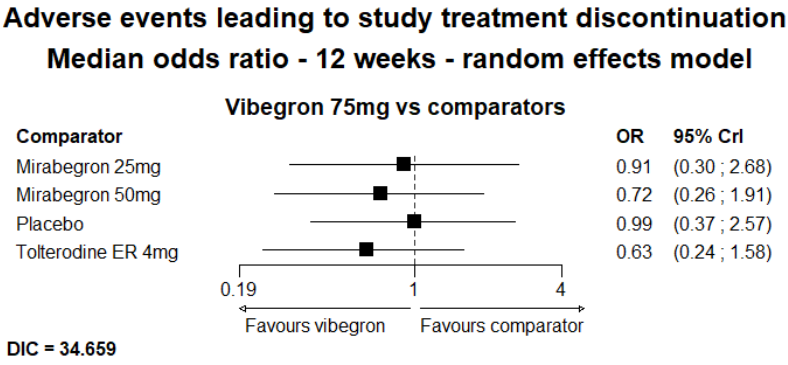


Table 17. Input data table for the number of discontinuations due to adverse events at 12 weeks (sensitivity analysis).

AEs leading to study treatment discontinuation - 12 weeks				
Author year	**Study**	**Treatment**	**n**	**N**
Nitti 2014	ARIES	Mirabegron 50mg	18	442
		Placebo	17	453
Staskin 2020	EMPOWUR	Vibegron 75mg	9	545
		Tolterodine ER 4mg	14	430
		Placebo	6	540
Khullar 2013	SCORPIO	Mirabegron 50mg	24	493
		Tolterodine ER 4mg	22	495
		Placebo	13	494
Herschorn 2013	CAPRICORN	Mirabegron 25mg	17	433
		Mirabegron 50mg	12	440
		Placebo	15	433
Herschorn 2017	SYNERGY	Mirabegron 50mg	10	422

AEs leading to study treatment discontinuation - 12 weeks				
Author year	**Study**	**Treatment**	**n**	**N**
		Mirabegron 25mg	7	423
		Placebo	9	429
Kuo 2015	Kuo 2015	Mirabegron 50mg	9	366
		Tolterodine ER 4mg	11	371
		Placebo	8	366
Yamaguchi 2014	Yamaguchi 2014	Mirabegron 50mg	15	379
		Tolterodine ER 4mg	13	375
		Placebo	9	379
Yamaguchi 2015	Yamaguchi 2015	Mirabegron 25mg	6	210
		Mirabegron 50mg	12	208
		Placebo	6	212

Table 18. Comparison for the number of discontinuations due to adverse events at 12 weeks "each vs each" (sensitivity analysis).

Mirabegron 25mg	**Mirabegron 50mg**	**Placebo**	**Tolterodine ER 4mg**	**Vibegron 75mg**
Mirabegron 25mg	1.26 (0.733, 2.173)	0.919 (0.535, 1.596)	1.438 (0.757, 2.858)	0.906 (0.305, 2.679)
0.794 (0.46, 1.365)	Mirabegron 50mg	0.731 (0.508, 1.035)	1.146 (0.736, 1.818)	0.72 (0.264, 1.91)
1.088 (0.627, 1.869)	1.369 (0.966, 1.968)	Placebo	1.571 (1.01, 2.483)	0.991 (0.372, 2.569)
0.695 (0.35, 1.32)	0.872 (0.55, 1.359)	0.637 (0.403, 0.99)	Tolterodine ER 4mg	0.63 (0.237, 1.58)
1.103 (0.373, 3.284)	1.389 (0.524, 3.795)	1.009 (0.389, 2.688)	1.588 (0.633, 4.221)	Vibegron 75mg

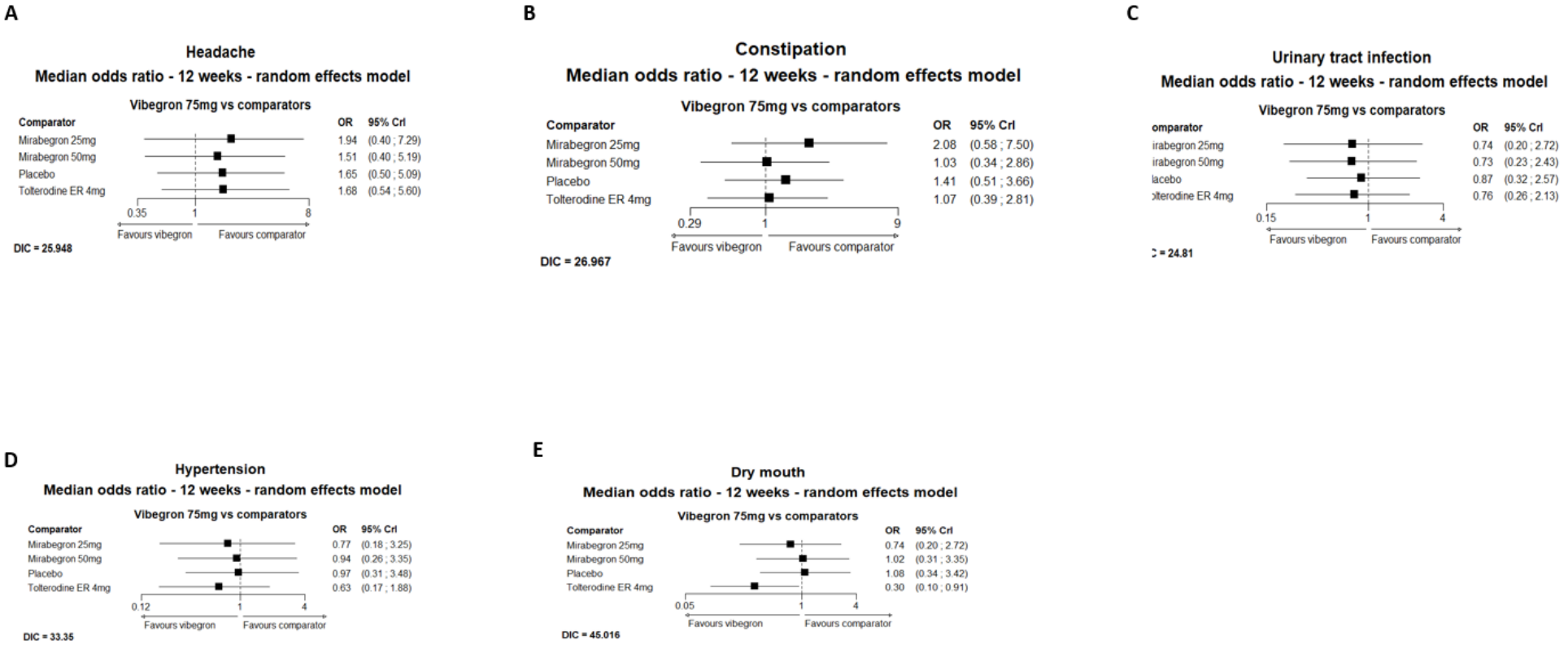
Specific adverse events

Forest plots of the individual adverse events of interest are reported in Figure 9.

There were no statistically significant differences observed between vibegron and

any of its comparators for any adverse event. The sole exception to this was for dry mouth compared with tolterodine, where fewer incidences were observed with vibegron (odds ratio [OR] 0.30, 95% CI 0.10 to 0.91).

Figure 9. Forest plots reporting the comparative safety of vibegron compared with mirabegron (25 or 50 mg), tolterodine (4 mg ER) or placebo for: A) headache; B) constipation C) urinary tract infection; D) hypertension; E) dry mouth.



b) **Please provide the full text for Yamaguchi 2015:**

Yamaguchi O, Marui E, Igawa Y, Takeda M, Nishizawa O, Ikeda Y, Ohkawa S. Efficacy and Safety of the Selective β3-Adrenoceptor Agonist Mirabegron in Japanese Patients with Overactive Bladder: A Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study. LUTS: Lower Urinary Tract Symptoms. 2015 May;7(2):84-92.

A copy of the above reference is provided alongside this response.

Adverse effects

A22. Priority. For the any serious adverse effects NMA, the EAG notes data from several mirabegron studies were not included (including CAPRICORN, SCORPIO, and AIRES). The EAG notes these data are not included in the trial primary publications but are published on the clinical trial registry records, and also in the company submission and assessment report of TA290. Please:

A) **Clarify whether these data should have been identified and included in the NMA, or whether there was a reason for not including these data.**

B) **If these data should have been included in the NMA, please provide an updated database with these records included, and updated NMAs. Please ensure the relevant records have been checked and updated for each safety NMA.**

Response A)

Thank you. We typically do not extract comparator data that is not available in the peer-reviewed journal. However, in this case we agree it is appropriate to include these data and we have implemented the analysis into the original NMA and sensitivity analysis.

Response B)

The incidence of serious adverse events of the comparator interventions compared with vibegron (75 mg) in the preferred analysis set is reported in Figure 10. Data supporting these graphical analyses are provided in Table 19 and Table 20. There were no statistically significant differences identified between vibegron and the interventions, including placebo, which numerically slightly favoured vibegron (OR 0.94, 95% CI 0.24 to 3.63). The equivalent data for the sensitivity analysis dataset is reported in Figure 7, Table 15 and Table 16.

Figure 10. Forest plot showing serious adverse events at 12 weeks (preferred analysis).

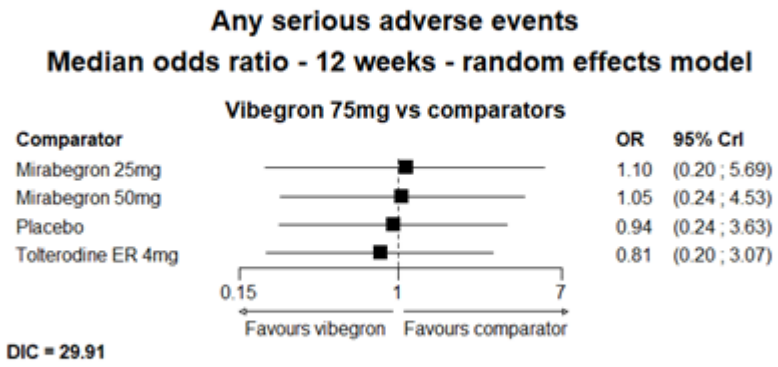


Table 19. Input data table for the number of discontinuations due to adverse events at 12 weeks (preferred analysis).

Any SAEs - 12 weeks				
Author year	**Study**	**Treatment**	**n**	**N**
Nitti 2013 (1)	ARIES	Mirabegron 50mg	11	442
		Placebo	9	453
Herschorn 2013 (2)	CAPRICORN	Mirabegron 25mg	7	432
		Mirabegron 50mg	4	440
		Placebo	12	433
Staskin 2020 (9)	EMPOWUR	Vibegron 75mg	8	545
		Tolterodine ER 4mg	10	430
		Placebo	6	540
Herschorn 2017 (8)	SYNERGY	Mirabegron 50mg	5	422
		Mirabegron 25mg	6	423

		Placebo	8	429
Khullar 2013 (5)	SCORPIO	Mirabegron 50mg	14	493
		Tolterodine ER 4mg	11	495
		Placebo	8	494
Kuo 2015 (3)	Kuo 2015	Mirabegron 50mg	5	366
		Tolterodine ER 4mg	6	371
		Placebo	7	366

Table 20.Comparison of serious adverse events at 12 weeks "each vs each" (preferred analysis).

Mirabegron 25mg	Mirabegron 50mg	Placebo	Tolterodine ER 4mg	Vibegron 75mg
Mirabegron 25mg	1.051 (0.369, 2.828)	1.158 (0.426, 3.147)	1.358 (0.396, 4.605)	1.098 (0.203, 5.689)
0.951 (0.354, 2.712)	Mirabegron 50mg	1.101 (0.589, 2.209)	1.295 (0.55, 3.19)	1.046 (0.243, 4.533)
0.864 (0.318, 2.349)	0.908 (0.453, 1.699)	Placebo	1.172 (0.52, 2.627)	0.942 (0.239, 3.632)
0.736 (0.217, 2.523)	0.772 (0.313, 1.818)	0.853 (0.381, 1.924)	Tolterodine ER 4mg	0.811 (0.205, 3.071)
0.911 (0.176, 4.933)	0.956 (0.221, 4.114)	1.062 (0.275, 4.176)	1.233 (0.326, 4.872)	Vibegron 75mg

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Vibegron for treating symptoms of overactive bladder [ID6300]

NICE medicines optimisation briefing

December 2023

Advice

A full single technology appraisal of vibegron for treating symptoms of overactive bladder in adults is unlikely to add value. A fast-track appraisal with a cost comparison comparing vibegron with mirabegron is appropriate.

Rationale

Vibegron is likely to be used in the same population and at the same point in the treatment pathway as another NICE-approved oral beta-3 adrenergic agonist, mirabegron (TA290, June 2013). Mirabegron is recommended as an option for treating symptoms of overactive bladder only for people in whom antimuscarinics are contraindicated or clinically ineffective, or have unacceptable side effects.

Vibegron appears to show similar modest reductions in average daily micturition frequency and in urinary incontinence episodes as mirabegron in people with overactive bladder. However, this is based on short-term, placebo-controlled phase 3 trials. There are no published head-to-head randomised controlled trials designed to compare vibegron with mirabegron.

It is unclear whether blood pressure monitoring (as is recommended for mirabegron) will be required for vibegron.

Technology overview

Vibegron is an oral selective beta-3 adrenergic agonist, which is licensed in the US for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults at a dosage of 75 mg orally once daily (FDA Drug approval package Gemtesa: printed labelling). It is not yet known if the marketing authorisation will be the same in the UK. Beta-3 adrenergic agonists activate beta-3-adrenoceptors causing the bladder to relax, which helps it to fill and also to store urine (TA290).

Context

Management of overactive bladder is covered by several NICE guidelines (NG210, NG123, CG148 and CG97). Bladder training and lifestyle advice are offered as first-line treatments. An antimuscarinic (also known as an anticholinergic) with the lowest acquisition cost is offered second-line. If the first antimuscarinic treatment is not effective or well-tolerated, another antimuscarinic with a low acquisition cost may be offered (NG123).

The efficacy of antimuscarinics is modest and they are also limited by their lack of bladder specificity and, therefore, side effects such as dry mouth, constipation and dizziness (Staskin et al. 2020). Antimuscarinic burden is also associated with increased cognitive impairment (NG97).

NICE has assessed mirabegron, another oral selective beta-3 adrenergic agonist. It is recommended as an option for treating symptoms of overactive bladder only for people in whom antimuscarinics are contraindicated or clinically ineffective, or have unacceptable side effects (TA290). Mirabegron is the only licensed beta-3 adrenergic agonist to treat symptoms of overactive bladder available in the UK.

For people with overactive bladder that has not responded to non-surgical management or pharmacological treatment, more invasive

procedures may be considered (NG123 and CG97). Several further pieces of NICE guidance cover specific aspects of invasive management (MTG50, IPG362, IPG326 and IPG64).

Table 1: Characteristics of vibegron compared with mirabegron and antimuscarinics

	Vibegron	Mirabegron	Antimuscarinics
Mechanism of action	Selective beta-3 adrenergic agonist	Selective beta-3 adrenergic agonist	Muscarinic acetylcholine receptor antagonist
Indication	Symptomatic treatment of overactive bladder (details to be confirmed when the marketing authorisation is granted)	Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adults with overactive bladder syndrome (Mirabegron SPC)	Symptomatic treatment of overactive bladder. See licensed indications for exact wording for each medicine
Dosage and route of administration	75 mg orally once daily (dosages to be confirmed when the marketing authorisation is granted)	50 mg orally once daily	Most antimuscarinics are taken orally. Oral dosages vary from once to four times a day
Resource impact	Oral treatment: convenient and non-invasive	Oral treatment: convenient and non-invasive	Oral treatment: convenient and non-invasive

Current practice

Oral medicines for overactive bladder (antimuscarinics or mirabegron) are usually prescribed in primary care. System intelligence from NICE associates indicates that local treatment pathways for the initial management of overactive bladder follow NICE guidance (see Context section).

Vibegron will likely fit into the treatment pathway as an alternative to mirabegron; that is for people in whom antimuscarinics are contraindicated, clinically ineffective, or have unacceptable side effects. However, clinicians who care for older people are keen to have additional options available early in the treatment pathway to reduce the need for antimuscarinics because of the risk of side effects, such as cognitive impairment. This might include use after non-pharmacological management in people who are at high risk of side effects from antimuscarinics.

Further oral treatment options to antimuscarinics, such as mirabegron or vibegron, could avoid invasive treatment, such as botulinum toxin, which may have significant side effects (for example, urinary retention needing catheterisation).

Factors for decision making

Effectiveness

Staskin et al. (2020) conducted a phase 3, randomised, double-blind, placebo and active controlled trial (EMPOWUR) of oral vibegron 75 mg (n=547), placebo (n=540) and extended-release tolterodine 4 mg (n=431) once daily in adults with symptoms of overactive bladder.

The people included in the trial (median age 61 to 63 years across treatment groups) had a history of overactive bladder for 3 months or more and an average of 8 or more micturitions per day (mean at baseline in the full analysis set was 11.5). They also had either 1 or more urge urinary incontinence episodes per day for wet overactive bladder (mean at baseline 3.5), or 3 or more urgency episodes per day for dry overactive bladder. At baseline, 85% of participants were female, 43% were 65 years or older and 77% had wet overactive bladder. People with a urine volume output of more than 3 litres per day were excluded.

At week 12, there were statistically significant improvements from baseline with vibegron compared with placebo for the average daily number of micturitions (least squares mean change from baseline, -1.8 versus -1.3; P<0.001) and urge urinary incontinence episodes in those with wet overactive bladder (-2.0 versus -1.4; P<0.0001). These were the 2 primary endpoints. The respective differences from baseline for tolterodine, which was not part of the formal efficacy analysis, were -1.6 and -1.8.

Three randomised controlled trials are currently underway in Japan, comparing vibegron with mirabegron, but results have not yet been published; 1 comparative study (UMIN000038288) and 2 cross-over studies (UMIN000034720 and UMIN000035525).

Safety

In the 12-week EMPOWUR study, 9 people (1.7%) in the vibegron group, 6 (1.1%) in the placebo group and 14 (3.3%) in the tolterodine group discontinued treatment because of adverse events. At the end of a 40-week extension study, people who completed 12 weeks of vibegron or tolterodine were continued on the same treatment and those who completed 12 weeks of placebo were randomised 1:1 to either vibegron or tolterodine. Discontinuation due to adverse events was 1.5% in the vibegron group and 3.4% in the tolterodine group (Staskin et al. 2021).

As has been seen with mirabegron, a lower incidence of dry mouth was reported with vibegron than with tolterodine (12-week study: tolterodine 6.5%, vibegron 1.7%, placebo 0.9%; extension study: tolterodine 5.2%, vibegron 1.8%).

As has also been reported with mirabegron, urinary tract infection was the most common adverse event in the vibegron group (vibegron 5.0%, placebo 6.1%, tolterodine 5.8%). Tachycardia, which has been reported

commonly with mirabegron (SPC mirabegron), was not reported with vibegron in the 12-week study.

Following an MHRA warning for mirabegron on the risk of severe hypertension and associated cerebrovascular and cardiac events, mirabegron is contraindicated in severe uncontrolled hypertension. The US product information for vibegron does not list hypertension as a contraindication (FDA Drug approval package Gemtesa: printed labelling). Neither does it recommend that blood pressure is monitored before and during vibegron treatment (another requirement with mirabegron). However, hypertension was the most common adverse event reported in the 40-week extension study (vibegron 8.8%, tolterodine 8.6%, no placebo group). It is not yet known whether similar contraindications and monitoring will be required for vibegron when it is licensed for use in the UK.

Serious adverse events considered by the investigator to be possibly or probably related to vibegron were pneumonia and non-cardiac chest pain (2 people) in the 12-week study and moderate collagenous colitis (1 person) in the extension study.

Patient centred factors

Vibegron and mirabegron are both oral tablets that are taken once daily. Therefore, patient acceptability of each treatment option is unlikely to differ. Antimuscarinics are also usually given orally. Many antimuscarinics can be given orally once daily, but this can vary from once daily to four times a day, depending on the preparation chosen. Vibegron may be another option before trying invasive treatment, such as botulinum toxin, which may have significant side effects and needs to be given in an outpatient clinic under local anaesthetic.

Health inequalities

The prevalence of overactive bladder increases with increasing age. Incontinence could also disproportionately affect people on a low income, because of the need to purchase incontinence pads and other related products (TA290).

Limitations of the evidence

A strength of the placebo-controlled, phase 3, 12-week EMPOWUR study was its double-blind design and large sample size (n=1,518 randomised). However, while it was an international study, there were no UK participants; about 90% of participants were from the US where management of overactive bladder may be different from UK clinical practice. Nevertheless, 43% of people were aged 65 years or over, which reflects the increasing frequency of overactive bladder in an ageing population.

Another limitation of EMPOWUR was that its duration was only 12 weeks. The smaller (n=506), 40-week extension study provides useful safety data on vibegron treatment for up to 1 year. However, while it suggested efficacy was consistent with the 12-week study, the extension study was not powered to look at efficacy (the primary outcome was safety) and it did not include a placebo group.

When considering how vibegron might compare with antimuscarinics in people with overactive bladder, it is helpful that both EMPOWUR and the 40-week extension study included an active control group with tolterodine. However, in the formal efficacy analysis, only comparisons of vibegron with placebo were included. Efficacy endpoints including comparisons of tolterodine with placebo were only considered supportive and statistical significance could not be confirmed. No formal statistical comparisons were prespecified in the extension study.

An important limitation of the evidence to date is that there are no published head-to-head randomised controlled trials designed to

directly compare vibegron with an active treatment, particularly with mirabegron, in people with overactive bladder. The EMPOWUR study included a similar population to mirabegron studies, and vibegron compared with placebo appears to show similar modest reductions in average daily reductions in micturitions and in urinary incontinence episodes as mirabegron. This apparent similarity needs to be interpreted with caution because it is not from a head-to-head study. It is also unclear how much the modest changes in micturition seen with these medicines matter to people.

Data are not available in people in whom antimuscarinics are contraindicated, clinically ineffective, or have unacceptable side effects (when mirabegron is recommended). In EMPOWUR, fewer than 15% of people in the full analysis set had previously taken an antimuscarinic at baseline.

BMJ TAG

Vibegron for treating symptoms of overactive bladder [ID6300]

Cost-Comparison Technology Appraisal

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This report was commissioned by the NIHR Evidence Synthesis Programme as project number 166390.

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Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.
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Contribution of authors:

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Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence
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All authors read and commented on draft versions of the EAG report.

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List of Abbreviations

AE	Adverse event
ANCOVA	Analysis of covariance
β3-AR	Beta-3 adrenergic receptor
CCA	Cost-comparison appraisal
CFB	Change from baseline
CI	Confidence interval
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
DSA	Deterministic sensitivity analysis
ER	Extended release
EAG	External Assessment Group
EMA	European Medicines Agency
FAS	Full analysis set
FAS-ext	Full analysis set extension
FAS-I	Full analysis set for incontinent participants
FTA	Fast track appraisal
HRQoL	Health-related quality of life
ICS	International Continence Society
ITC	Indirect treatment comparison
ITT	Intention to treat
IQR	Inter-quartile range
LS	Least squares
MCID	Minimal clinically important difference
MeSH	Medical subject headings
MMRM	Mixed model for repeated measures
N/A	Not applicable
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
OAB	Overactive bladder
OABSS	Overactive bladder symptom score
OAB-q	OAB questionnaire
OR	Odds ratio
PBO	Placebo
QoL	Quality of life
RCT	Randomised controlled trial
RoB-2	Cochrane risk of bias tool 2
SAE	Serious adverse event

SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
STA	Single technology appraisal
TEAE	Treatment emergent adverse event
UTI	Urinary tract infection
UUI	Urgency urinary incontinence
VAS	Visual analogue scale

1 Summary of EAG's view of the company's CCA case

A cost-comparison analysis was developed by the company to assess vibegron 75 mg compared with mirabegron 50 mg and 25 mg for the symptomatic treatment of adult patients with overactive bladder (OAB) syndrome in whom antimuscarinic drugs are contraindicated or clinically ineffective, or who have unacceptable side effects. To be considered for a cost-comparison technology appraisal, the National Institute for Health and Care Excellence (NICE) requires the intervention under review to be clinically similar to one treatment that NICE has previously recommended in technology appraisal guidance for the same indication. Mirabegron has previously been recommended by NICE as an option for as an option for treating the symptoms of overactive bladder only for people in whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects (TA290).

Generally, the External Assessment Group (EAG) considers that, based on the clinical and cost-effectiveness evidence presented by the company for vibegron, the assumption of clinical similarity with mirabegron is reasonably appropriate and it is likely that vibegron is cost-saving compared with mirabegron.

The EAG believes none of the issues discussed below would preclude a cost-comparison appraisal from being appropriate but highlights them as limitations or factors for the committee to be aware of:

- There was a low rate of prior anticholinergic use (14.6%) in the EMPOWUR clinical trial, which is the main source of clinical evidence in the submission. This is in contrast to the population vibegron 75 mg is being positioned for: people with OAB in whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects;
    - The EAG notes, however, that prior anticholinergic use is not expected to be a large treatment effect modifier for vibegron or mirabegron;
- There are limited subgroup data available for males in the pivotal vibegron 75 mg trial, with only 14.8% of EMPOWUR participants being male;
- No formal indirect comparison was possible at Week 52 for discontinuation between vibegron 75 mg and mirabegron 50 mg;
- No indirect comparisons were possible at Week 52 between vibegron 75 mg and mirabegron 25 mg due to a lack of 52-week data for mirabegron 25 mg;
- At Week 52, vibegron 75 mg had a higher rate of any AEs compared to mirabegron 50 mg, with the 95% CrI of the indirect comparison odds ratio not crossing 1. However, the rates of

serious AEs, i.e., those most likely to incur cost, and the AEs included in TA290, dry mouth and constipation, were similar between vibegron 75 mg and mirabegron 50 mg.

The company's economic analysis only considered one-year drug acquisition costs for vibegron and mirabegron as it was assumed that there will be no other cost differences between the two drugs. The EAG considers the company has likely been conservative in their approach to the cost-comparison analysis. Notably, the EAG's clinical experts highlighted that monitoring costs may be lower for vibegron compared with mirabegron, as patients on the latter drug might require additional blood pressure monitoring, and dose adjustments are required for patients with renal or hepatic impairment. Therefore, under the company's assumptions of all else being equal, the EAG considers that vibegron is likely to be cost-saving compared with mirabegron.

2 Background

Overactive bladder (OAB) can be defined as, "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology" (International Urogynecological Association/International Continence Society joint report, 2010).[1] Section B.1.3 of the company submission (CS) provided an overview of OAB, its diagnosis, disease burden and current management strategies in English clinical practice. Based on discussion with its clinical experts, the EAG considers this overview to represent an appropriate summary of OAB and its current management in England.

Vibegron 75 mg is being considered in a cost-comparison appraisal (CCA) with mirabegron 50 mg and mirabegron 25 mg. Mirabegron 50 mg and mirabegron 25 mg were recommended by the National Institute for Health and Care Excellence (NICE) in 2013 as an option for treating the symptoms of OAB only for people in whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects (TA290).[2] This is the same population as the company is positioning vibegron 75 mg in the CS, but is narrower than the anticipated marketing authorisation of vibegron 75 mg: vibegron is scheduled to be indicated for the symptomatic treatment of adult patients with OAB (draft summary of product characteristics, CS Appendix C).

Vibegron is a selective beta-3 adrenergic receptor (β3-AR) agonist.[3, 4] In the bladder, β3-AR activation reduces the contraction of the detrusor smooth muscles, which can relieve symptoms of OAB through increasing bladder capacity and reducing the frequency of muscle contractions. Like vibegron, mirabegron is also a selective β3-AR agonist, and as such vibegron and mirabegron share a common mechanism of action in treating symptoms of OAB.[3, 5]

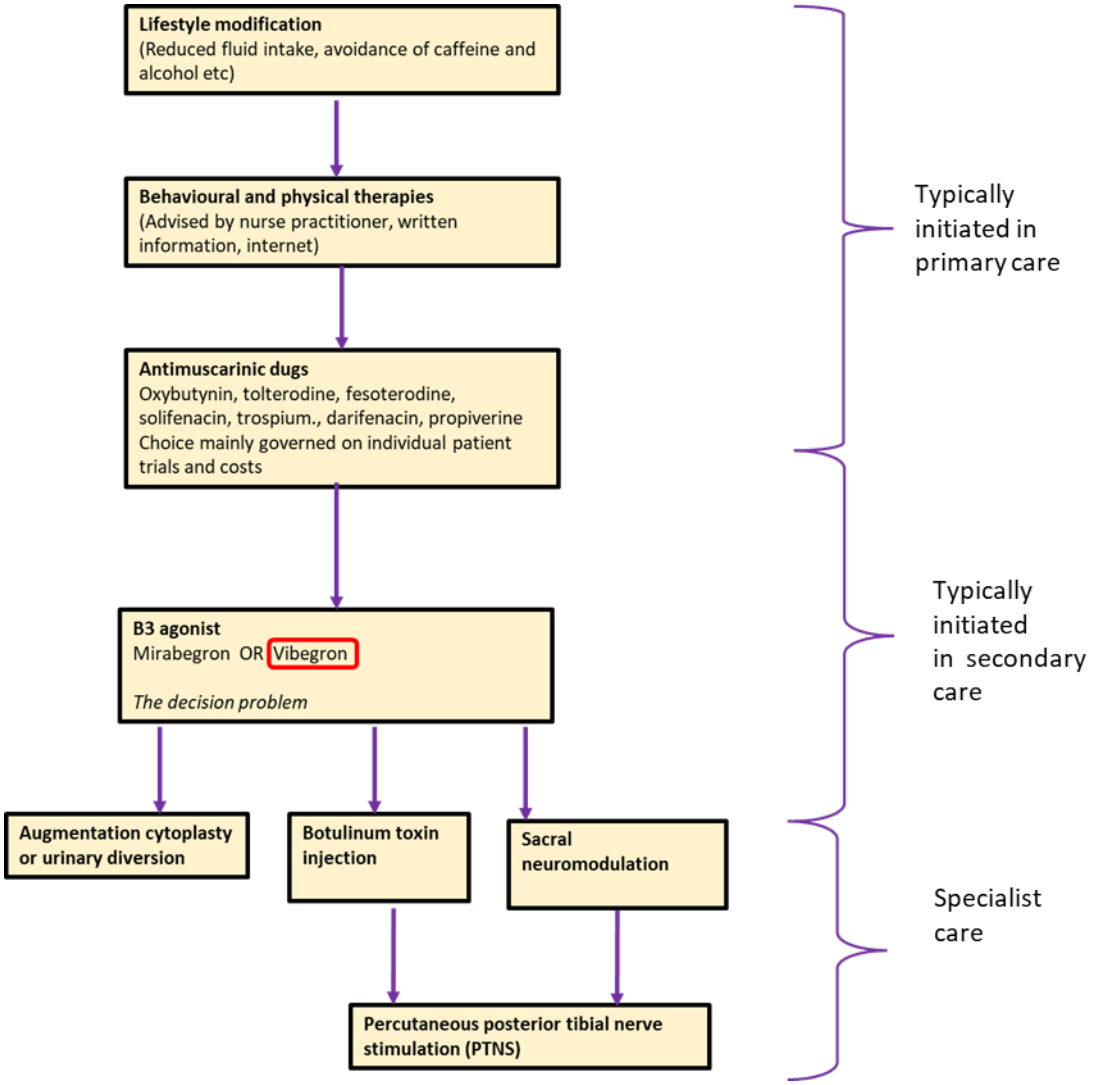
The current treatment pathway for OAB in England, and the proposed positioning of vibegron, was presented by the company in Figure 4 of the CS, and is reproduced in Figure 1 below. The EAG's clinical experts agreed that the pathway outlined in Figure 1 reasonably reflects the treatment pathway used for OAB in English practice, and also that recommended by NICE guideline NG123 (Urinary incontinence and pelvic organ prolapse in women: management).[6] The EAG's clinical experts clarified that:

- In addition to lifestyle modification outlined in Figure 1, weight loss and containment products are recommended;
- Behavioural and physical therapies include pelvic floor muscle training and bladder training;

- Some centres may in practice trial antimuscarinics in combination with mirabegron prior to moving to surgical management of OAB; and
- Percutaneous sacral nerve stimulation may be offered after non-response to botulinum toxin type A or if the patients is not prepared to accept the risks of needing catheterisation associated with botulinum toxin type A, in line with NG123.

Two experts also noted that some centres may initiate mirabegron as a first-line drug therapy instead of antimuscarinic drugs. The EAG notes that such use is outside of the NICE recommendation for the routine use of mirabegron and the company's positioning of vibegron, unless the patient is contraindicated to antimuscarinics.[2]

Figure 1. Company's proposed position of vibegron in OAB treatment pathway. Reproduced from CS Figure 4.



3 Critique of the decision problem in the company's submission

The company provided a summary of the final scope issued by the National Institute for Health and Care Excellence (NICE),[7] together with the rationale for any deviation from the decision problem. As mentioned previously, the company's decision problem covers only part of the anticipated marketing authorisation for vibegron: vibegron is expected to be indicated in symptomatic treatment of adult patients with overactive bladder (OAB) syndrome (company submission [CS] Appendix C). However, the cost-comparison case in the CS is made against mirabegron in people with OAB in whom antimuscarinic drugs are contraindicated or clinically ineffective or have unacceptable side effects. The EAG notes this is the same population in which mirabegron was recommended in TA290, and therefore considers it appropriate and in line with NICE guidance, to focus on this subpopulation of vibegron's anticipated marketing authorisation for a cost-comparison with mirabegron. A summary of the final scope issued by NICE, the decision problem addressed in the CS and the EAG's critique of this is provided in Table 1.

Table 1. Summary of decision problem as outlined in the company submission

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the scope	EAG comment
Population	Adults with symptoms of overactive bladder	No change	N/A	The company have submitted evidence specifically for the population with symptoms of overactive bladder in whom antimuscarinic drugs are contraindicated, clinically ineffective, or have unacceptable side effects. This is narrower than the final scope issued by NICE but matches the population in which mirabegron was recommended in TA290.[2]
Intervention	Vibegron	Vibegron 75 mg once daily.	Clarification of dose based on SmPC (Appendix C)	N/A
Comparator(s)	For people who have not had previous treatment for symptoms of overactive bladder: • Bladder training and lifestyle advice • For people who have not achieved satisfactory benefit from bladder training and lifestyle advice: Antimuscarinic treatments, including:	Mirabegron	Vibegron will be positioned for people in whom antimuscarinic drugs are contraindicated, clinically ineffective, or have unacceptable side effects. Therefore, mirabegron will be considered as the comparator. Antimuscarinic drugs, including all those	The company have submitted evidence supporting the cost-effectiveness of vibegron compared to mirabegron specifically for the population with symptoms of overactive bladder in whom antimuscarinic drugs are contraindicated, clinically

	• oxybutynin (including modified-release preparations) • tolterodine • fesoterodine • solifenacin • trospium • darifenacin • propiverine For people in whom antimuscarinic drugs are contraindicated, clinically ineffective, or have unacceptable side effects: Mirabegron		listed, would be prescribed before mirabegron. Mirabegron is positioned in the treatment pathway as an option for treating the symptoms of overactive bladder only for people in whom antimuscarinic drugs are contraindicated or clinically ineffective or have unacceptable side effects (Section B.1.3.4). The evidence base used to support vibegron in this submission is consistent with that used in TA290 (Section B.2) with no evidence of difference detected between treatment naïve and prior treatment groups (Section B.3.7.2)	ineffective, or have unacceptable side effects.
Outcomes	The outcome measures to be considered include: • symptoms of urgency • urinary frequency • frequency of urge urinary incontinence • nocturia • adverse effects of treatment • health-related quality of life.	No Change	N/A	The company have submitted evidence of the clinical effectiveness of vibegron for each of the outcomes specified in the NICE final scope. However, the comparative evidence submitted comparing vibegron to mirabegron has focused on the outcomes included in the economic model of TA290,[2] namely: • Total urinary incontinence episodes;

				• Micturition frequency; and • Adverse effects of treatment. In addition to total urinary incontinence episodes, and in line with the final scope issued by NICE, the company also presents urge urinary incontinence (UUI) episodes as a key clinical outcome. UUI episodes are a subset of total incontinence episodes, along with stress incontinence. However, treatments for OAB aim to reduce UUI episode frequency in particular, and therefore the EAG agrees with the additional focus of the company placed on UUI episodes.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out.	The economic analysis will be a *de novo* cost comparison in line with NICE fast track methodology. This means that incremental benefits, i.e. quality-adjusted life-years, are not relevant to this submission.	This is consistent with the FTA programme of NICE.	Appropriate.

	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 compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.			
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • men and women • previously untreated and previously treated overactive bladder	No change	N/A	Subgroup data for men and women and prior OAB treatment were presented from the pivotal EMPOWUR trial for vibegron, but were not considered in the comparative evidence presented between vibegron and mirabegron. The EAG notes there to be no clear mechanism by which the treatment effectiveness of vibegron or mirabegron would differ between men and women, nor are there reasons to anticipate

				the effects of prior therapy would differentially impact the effectiveness of vibegron or mirabegron.
Special considerations, including issues related to equity or equality	None mentioned	None mentioned	N/A	None identified

Abbreviations: CS, company submission; EAG, external assessment group; FTA, fast-track appraisal; NICE, National Institute for Health and Care Excellence; OAB, overactive bladder; SmPC, summary of product characteristics

3.1 Population

Alignment to NICE final scope and population in England

As noted in Section 3, the company has restricted the decision problem to focus on the population of people with OAB in whom antimuscarinic drugs are contraindicated, clinically ineffective, or have unacceptable side effects. This population is narrower than the NICE final scope, but in line with the population for which mirabegron, the comparator, which was recommended in TA290.[2]

The EAG's clinical experts noted that the subpopulation of interest will consist mainly of patients who have started and discontinued one or more antimuscarinic drugs, estimating that:

- Around 10% of patients are contraindicated to antimuscarinic drugs;
- Around 40% of patients will discontinue antimuscarinic drugs due to lack of effectiveness; and
- Around 20% of patients will discontinue antimuscarinic drugs due to unacceptable side effects.

However, in the pivotal trial supporting this appraisal, EMPOWUR, only 215 of 1463 (14.6%) of participants reported previous anticholinergic drug use,[8] and the number of participants who were contraindicated to anticholinergic drugs was not reported. While this limits the representativeness of the EMPOWUR trial population to the predominantly treatment-experienced patients who would receive mirabegron through routine commissioning in England, the EAG notes that:

- A subgroup analysis of EMPOWUR by prior treatment experience was reported in Section B.3.7.2 of the CS, in which the vibegron treatment effect compared to placebo and tolterodine was similar, albeit numerically larger, in the prior anticholinergic use subgroup; and
- The EAG's clinical experts did not expect prior anticholinergic use to be a large or differential treatment effect modifier for either mirabegron or vibegron, providing patients have been appropriately diagnosed with OAB.

The EAG asked its clinical experts about the relevance of several inclusion criteria of the EMPOWUR clinical trial to the patients they would see with OAB in clinical practice in England, specifically:

Inclusion criteria

- OAB was defined as urgency, with or without UUI, usually associated with frequency and nocturia. Urodynamic evaluation was not required;
- Up to 15% of subjects could be male;
- Up to 25% of subjects could meet OAB dry criteria;
- Met either the OAB Wet or OAB Dry criteria:
    - Wet OAB
        - An average of ≥ 8.0 micturitions per Diary Day;
        - An average of ≥ 1.0 UUI episodes per Diary Day;
        - If stress urinary incontinence was present, the total number of UUI episodes must have been greater than the total number of stress urinary incontinence episodes from the previous visit diary.
    - Dry OAB
        - An average of ≥ 8.0 micturitions per Diary Day;
        - An average of ≥ 3.0 urgency episodes per Diary Day;
        - An average of < 1.0 UUI episodes per diary day.

Exclusion criteria

- Had lower urinary tract pathology that could, in the opinion of the investigator, be responsible for urgency, frequency, or incontinence.

The EAG's clinical experts considered the EMPOWUR inclusion and exclusion criteria to reasonably reflect most patients with symptomatic OAB that they would see in clinical practice. Specifically, they noted that:

- The requirement for an average ≥ 8.0 micturitions per Diary Day and either an average of ≥ 1.0 UUI episodes per Diary Day (wet OAB) or an average of ≥ 3.0 urgency episodes per Diary Day represents the patients who are most likely to seek support for OAB;
- A 25:75 split between patients with dry and wet OAB reasonably reflects the numbers of patients who seek support for OAB in clinical practice;
- While OAB is more common in females than males, it is unclear why the EMPOWUR trial limited the number of males to 15% of all participants. However, the prevalence of benign prostatic hyperplasia in males may limit the ability of clinical trials of OAB to recruit a large number of males.

In summary, the EAG considers the data presented within the CS to be representative of patients with OAB in England who would be eligible for vibegron, should it be made available through routine commissioning. However, the pivotal EMPOWUR clinical trial recruited a predominantly

antimuscarinic naïve population, whereas most patients who would be eligible for vibegron – should it be approved for routine commissioning under the company's positioning – would have had prior exposure to antimuscarinics. The EAG does not consider this to threaten the case of clinical similarity between vibegron and mirabegron in the current appraisal, as outlined in Sections 4.3.3 (Subgroup analysis) and 4.4 (Indirect treatment comparisons) of the Assessment Report.

3.2 Intervention

Vibegron (brand name: Obgemsa™, Pierre Fabre, Castres, France) does not currently have marketing authorisation in the UK, but marketing authorisation is expected in July 2024. The expected indication for vibegron is for the symptomatic treatment of adult patients with OAB. syndrome (Vibegron draft summary of product characteristics [SmPC], CS Appendix C). Vibegron is taken orally at a recommended dose of 75 mg once daily.

As outlined in the draft SmPC (Appendix C page 7): "Vibegron is a selective and potent human beta-3 adrenergic receptor (β3-AR) agonist over β1-AR and β2-AR. Activation of the beta-3 adrenergic receptor located in the bladder detrusor muscle increases bladder capacity by relaxing the detrusor smooth muscle during bladder filling."

3.3 Comparators

Mirabegron (brand name: Betmiga™, Astellas Pharma Limited, Addlestone, UK) is the sole comparator presented in the CS. Mirabegron is indicated for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with OAB syndrome.[9] Mirabegron is taken orally at a recommended dose of 50 mg once daily, or 25 mg once daily for people with moderate hepatic impairment or severe renal impairment, or for people with mild or moderate renal impairment and/or mild hepatic impairment in the presence of strong CYP3A inhibitors. People with severe controlled hypertension, defined as systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg, are contraindicated to mirabegron.

Like vibegron, mirabegron is a selective β3-AR agonist, and as such shares a similar mechanism of action. Unlike vibegron, mirabegron also has interactions with CYP3A.[9]

In England, mirabegron is recommended within its marketing authorisation as an option for treating the symptoms of overactive bladder only for people in whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects (TA290).[2] The EAG's clinical experts confirmed that mirabegron is currently the only drug available for people with OAB

who are contraindicated to antimuscarinics or who have discontinued antimuscarinics due to clinically ineffectiveness or side effects. The EAG therefore agrees that mirabegron is an appropriate comparator for a cost-comparison appraisal (CCA).

3.4 Outcomes

The outcomes included in the CS match the outcomes described in the final scope as issued by NICE. All outcomes included from the NICE final scope were presented for the pivotal EMPOWUR trial of vibegron 75 mg, with the exception of nocturia, which was not an endpoint in EMPOWUR. Indirect treatment comparisons between vibegron 75 mg and mirabegron 50 mg were only conducted for the outcomes included in the cost-effectiveness model of TA290 and several adverse event categories (CS, Section B.3.9).

Table 2 provides a comparisons of the outcomes included in the NICE final scope,[7] the CS and those included in the cost-effectiveness modelling in TA290.[2]

Table 2. Comparisons of outcomes included in the NICE final scope, Company submission and TA290.

Outcome included in NICE final scope	Key source of evidence (defined by company)	Outcome presented from EMPOWUR	Outcome included in TA290 cost-effectiveness model	Comparison made between vibegron 75 mg and mirabegron 50 mg or 25 mg in CS
Symptoms of urgency	EMPOWUR study [10] Section B.3.6.1.2 Section B.3.9 (ITC)	• Frequency of micturitions (trial co-primary endpoint, CS B.3.6.1.2) • Urgency episodes • Volume voided • OAB-q Coping score • Responder analyses	• Frequency of micturitions	NMA of frequency of micturitions (CS Section B.3.9)
Urinary frequency	EMPOWUR study [10] Section B.3.6.1.2 Section B.3.9 (ITC)	• Total incontinence episodes	• Total UI frequency	NMA of total UI frequency (CS Section B.3.9)
Frequency of urge urinary incontinence	EMPOWUR study [10] Section B.3.6.1.3	• UUI episode frequency (trial co-primary endpoint, CS B.3.6.1.2)	• Not included in CE model (subset of total UI)	NMA of UUI episode frequency (CS Section B.3.9)
Nocturia	Yoshida et al. (2018) [11] Shin et al. (2023) [12] Section B.3.6.2.2	• Not an outcome	• Not included in CE model	No comparison performed
Adverse effects of treatment	EMPOWUR study [10] Section B.3.10.1 Section B.3.9 (ITC)	• AEs reported by ≥2% of patients in the vibegron, tolterodine, or placebo arms	• Constipation • Dry mouth	NMAs of: • AEs due to any cause • SAEs • AEs leading to treatment discontinuation

				• Headache • Hypertension • Urinary tract infection • Dry mouth • Constipation (CS Section B.3.9)
Health-related quality of life	EMPOWUR study [10] Yoshida et al. (2018) [11] Shin et al. (2023) [12] Section B.3.6.1.3 Section B.3.6.2.1	• OAB-q score • EQ-5D VAS • EQ-5D index	• EQ-5D index scores, with scenarios using OAB-q scores	No comparisons performed

Abbreviations: AE, adverse event; CS, company submission; EQ-5D, EuroQol 5 Dimensions; NMA, network meta-analysis; OAB, overactive bladder; OAB-q, overactive bladder questionnaire; SAE, serious adverse event; UI, urinary incontinence; UUI, urge urinary incontinence; VAS, visual analogue scale

4 Summary of the EAG's critique of clinical effectiveness evidence submitted

4.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify randomised controlled trials (RCTs) of vibegron, mirabegron and antimuscarinic drugs for treating the symptoms of overactive bladder (OAB). Only RCTs of vibegron 75 mg and mirabegron 50 mg and 25 mg that shared a common comparator arm were subsequently included in the network meta-analyses (NMA). The EAG considers the SLR methods used by the company to be robust, and the methods were reported in Appendix D of the company submission (CS). Table 3 contains the EAG's assessment of the SLR methods used by the company.

Table 3. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix D.1.1.1.1	**Appropriate**. The following databases were searched on 13 October 2023: • EMBASE; • MEDLINE®, MEDLINE® In Process & Other Non-Indexed Citations and MEDLINE® Epub Ahead of Print and MEDLINE® Daily; and • Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials. The following trial registries were searched: • US National Institute of Health Database (ClinicalTrials.gov); • EU Clinical Trials Register; • WHO International Clinical Trials Registry Platform; and • ISRTCN Registry. In addition, the company searched: i) the abstracts of six relevant conferences from 2019 to April 2023, ii) six HTA agency websites, iii) five clinical guidelines and iv) five relevant websites. Full details of these searches are provided in CS Appendix D1.1.1.1
Search strategies	Appendix D.1.1.1.2	**Appropriate**. The search terms included an appropriate range of free text key words and MeSH and EMTREE terms. The search was broadly restricted by indication (OAB) study design (RCTs) and interventions (vibegron, mirabegron and antimuscarinics).

		The EAG notes the searches were date restricted to records published since 2013, coinciding with the publication of two key Phase II proof-of-concept and dose ranging studies of mirabegron.[13, 14] Records published up to March 2023 were language restricted to English language studies, whereas no restriction was placed on records from March 2023 to November 2023.
Inclusion criteria	Appendix D.1.1.2	**Appropriate**. The inclusion criteria included but were not limited to each outcome used in the economic model of TA290.[2]
Screening	Appendix D.1.1.2	**Appropriate**. Two independent reviewers were used at both title and abstract review and at full text review
Data extraction	Appendix D.1.1.2.1	**Appropriate**. Data extraction was performed by a single reviewer and verified by another.
Quality assessment of included study or studies	Appendix D.1.1.2.2	**Appropriate**. RCTs of vibegron identified in the SLR were appraised at the study level using the Cochrane risk-of-bias 2 (RoB-2) checklist,[15] with free-text justification provided for each decision. At clarification the company also provided risk of bias assessments using the NICE seven-criteria checklist for RCTs of mirabegron included in the network meta-analyses,[16] again providing free-text justification for each decision.

Abbreviations: CS, company submission; EAG, External Assessment Group; MeSH, medical subject headings; NICE, National Institute for Health and Care Excellence; SLR, systematic literature review; RoB-2, Cochrane risk-of-bias tool 2.

In the initial SLR, 6,384 records were identified from searches conducted on 22 March 2023. Of these 2,307 were removed as duplicates, leaving 4,077 records for title and abstract review. At title and abstract review, 430 records were included and entered full-text screening. Of these, 128 records were included in the SLR, corresponding to 110 unique RCTs. An SLR update was performed in November 2023, which ultimately included 8 new RCTs, leading to a total of 136 records corresponding to 118 RCTs included in the SLR. Full details of the study flow across the initial SLR and update are presented in CS Appendix D1.1.1.3. Of the 118 RCTs included in the SLR:

- Eight were RCTs including vibegron, including two RCTs comparing vibegron 50 mg with mirabegron 50 mg;
- Twenty-one were RCTs including mirabegron; and
- The other 89 RCRs were of antimuscarinic drugs that did not include a vibegron or mirabegron arm.

4.2 Critique of trials of the technology of interest, the company's analysis and interpretation

The eight RCTs including a vibegron arm that were included in the company's SLR are summarised in Table 4 below. Only one RCT, EMPOWUR and the associated EMPOWUR extension study, included a vibegron arm at the anticipated licensed dose in the UK, 75 mg daily.

Table 4. RCTs of vibegron included in the CS.

Reference	Intervention	Comparator	Population	Location	Blinding	Efficacy follow-up duration	Primary endpoint(s)
RCTs of vibegron 75 mg							
EMPOWUR[10]	vibegron 75 mg	• placebo • tolterodine 4 mg	People with OAB	International (United States, Poland, Hungary, Canada, Latvia, Lithuania)	Double-blind	12 weeks	Change from baseline in: • Average number of daily micturitions • Average number of UUI episodes
EMPOWUR extension[17]	vibegron 75 mg	tolterodine 4 mg	People with OAB	International (United States, Poland, Hungary, Canada, Latvia, Lithuania)	Double-blind	52 weeks	Incidence of any treatment-emergent adverse event by system organ class and preferred term
RCTs of vibegron 50 mg vs mirabegron 50 mg							
Kinjo 2023[18]	vibegron 50 mg (n=97)	mirabegron 50 mg (n=102)	Postmenopausal women with treatment naïve OAB	Japan	Open label	12 weeks	Change from baseline in total overactive bladder symptom score (OABSS)
Sato 2023[19]	vibegron 50 mg (n=44)	mirabegron 50 mg (n=45)	Postmenopausal women with treatment naïve OAB	Japan	Open label	12 weeks	Change from baseline in total OABSS

Wada 2024[20]	vibegron 50 mg (total n=83, crossover trial)	mirabegron 50 mg total (n=83, crossover trial)	Women ≥ 50 years with treatment naïve OAB	Japan	No blinding reported	Period 1: 8 weeks Period 2: 8 weeks	Change from baseline in total OABSS
Other vibegron RCTs							
Yoshida 2018[11]	• vibegron 50 mg (n=370) • vibegron 100 mg (n=368)	• imidafencin 0.1 mg twice daily (n=117) • placebo (n=339)	People with OAB	Japan	Double-blind	12 weeks	Change from baseline in mean number of daily micturitions
Shin 2023[12]	vibegron 50 mg (n=106)	placebo (n=104)	People with OAB	South Korea	Double-blind	12 weeks	Change from baseline in mean number of daily micturitions
Mitcheson 2019 Part 1[21]	• vibegron 3 mg (n=144) • vibegron 15 mg (n=134) • vibegron 50 mg (n=150) • vibegron 100 mg (n=149) • vibegron 50 mg + tolterodine 4 mg (4 weeks) followed by vibegron 50 mg (n=134)	• tolterodine 4 mg (n=135) • placebo (n=141)	People with OAB	International (18 countries, specific countries NR)	Double-blind	8 Weeks	Change from baseline in mean number of daily micturitions
Mitcheson 2019 Part 2[21]	• vibegron 100 mg (n=112) • vibegron 100 mg + tolterodine 4 mg (n=110)	• tolterodine 4 mg (n=122) • placebo (n=64)	People with OAB	International (18 countries, specific countries NR)	Double-blind	4 Weeks	NR

Abbreviations: CS, company submission; mg, milligram; NR, not reported; OAB, overactive bladder; OABSS, overactive bladder symptom score; RCT, randomised controlled trial' UUI, urge urinary incontinence

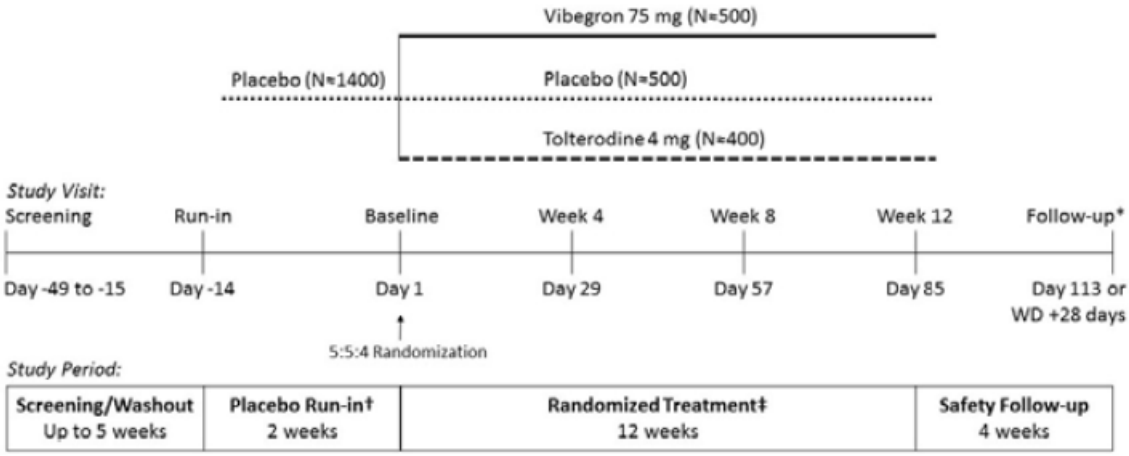
4.2.1 EMPOWUR

EMPOWUR was a Phase 3 double-blind, international RCT comparing vibegron 75 mg with tolterodine 4 mg and placebo over a 12-week efficacy period. At Week 12, participants from the first phase of the trial were eligible to enrol in the EMPOWUR 52-week extension study, and participants who did not enrol had a safety follow-up visit around Week 16. The co-primary endpoints of EMPOWUR were the change from baseline at Week 12 in the:

- Average number of daily micturitions; and
- Average number of UUI episodes.

Figure 2 displays the trial design of EMPOWUR, which is described further in CS Sections B.3.3.1 and B.4.4.1.

Figure 2. Trial design of EMPOWUR study. Reproduced from CS Figure 9.



*The Follow-up visit occurred at Day 113 for subjects who completed the Week 12 visit but did not enroll in the optional 40-week extension study (RVT-901-3004) or at 28 days after withdrawal (WD) for subjects who withdraw early from the study; †Single-blind (subjects did not know they were receiving placebo); ‡Double-blind.

Table 5 presents the EAG's quality assessment of the EMPOWUR clinical trial. Overall, the EAG considers EMPOWUR to be a high-quality clinical trial at low risk of bias for the assessment of the co-primary endpoints of daily micturitions and UUI episodes at Week 12. This is in-line with the company's quality assessment of EMPOWUR, which was presented in CS Appendix D.1.3.

Table 5. EAG quality assessment of the EMPOWUR clinical trial

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	Appendix D.1.3.1	**Appropriate** Patients were randomised 5:5:4 to either vibegron 75 mg, placebo or tolterodine ER 4 mg using a central, web based interactive response system.
Eligibility criteria	CS Table 6	**Appropriate** The EAG's clinical experts noted that the inclusion criteria of the EMPOWUR trial were reflective of patients seeking clinical support for symptomatic OAB in UK clinical practice, and appropriately excluded patients with other causes of urinary incontinence.
Blinding and masking	Appendix D.1.3.1, EMPOWUR CSR	**Appropriate** EMPOWUR was a double-blind/masked study with treatment allocation concealed using a web based interactive response system.
Baseline characteristics	CS Table 7	**Some concerns** The EAG's clinical experts agreed that the age of participants and severity of OAB at baseline in EMPOWUR was reasonably reflective of patients seeking clinical support for symptomatic OAB in UK clinical practice. However, the proportion of patients with prior anticholinergic drug use (14.6%) is substantially lower than the proportion of patients who would have received prior anticholinergics prior to vibegron, based on the positioning of vibegron in the CS. The EAG explores the evidence for subgroup effects in treatment experienced individuals in Section 4.3.3.
Dropouts	Appendix D.1.2.1	**Appropriate** Across the 12-week study period, the overall discontinuation rate was 9.55%, which was reasonably balanced between the placebo (10.0%), vibegron 75 mg (8.2%) and tolterodine 4 mg (10.7%) arms. The EAGs clinical experts commented that treatment discontinuation for lack of efficacy and/or side effects were relatively common for drug therapies for OAB.
Statistical analysis		
Sample size and power	CS Section B.3.4.1 EMPOWUR SAP	**Appropriate** EMPOWUR was powered to have approximately 96% power to detect both of the following differences between placebo and vibegron 5 mg for the co-primary endpoints at $p < 0.05$: • Number of daily micturitions: 0.6 and; • Number of UUI episodes: 0.51. While no formal minimum clinically important differences (MCID) are defined for daily micturitions and number of UUI episodes for OAB, the EAG's clinical experts advised that: • A halving of the number of daily micturitions above 8 would likely be considered meaningful, which for the EMPOWUR

		population would be a MCID of approximately (10.43-8)/2 = 1.2; and • A daily reduction in UUI episodes of around 0.5 would likely be meaningful for a patient group with a median baseline UUI frequency of 2. Hence, the EAG considers EMPOWUR appropriately powered to detect clinically important changes in both co-primary endpoints. The EAG notes the power calculation was calculated under the assumption of independence between the co-primary outcomes, which is a conservative assumption given the likely correlation between reductions in micturition frequency and UUI episodes.
Handling of missing data	CS Section B.3.4.1 EMPOWUR SAP EMPOWUR CSR	**Appropriate** The co-primary endpoints were tested using mixed models for repeated measures (MMRM), assuming data were missing at random. While the EAG considers it likely that data were not missing at random due to discontinuations due to lack of efficacy, the EAG notes that: • Discontinuations were reasonably balanced between groups; and • Prespecified sensitivity analyses provided in Section 14 of the EMPOWUR CSR using ANCOVAs with missing data imputed by multiple imputation or last observation carried forward provided results directly in line with the primary analyses.
Outcome assessment	CS Section B.3.3.1	**Appropriate** Participants self-reported symptoms through a voiding diary while blinded to treatment, which is a common outcome assessment tool in OAB. Participants were required to demonstrate adequate completion of the voiding diary during run in and baseline to participate in the study. Two different analysis sets were used for efficacy outcomes: • Full analysis set (FAS), prospectively defined as: "all randomised OAB patients who took at least one dose of double-blind study treatment and have at least one evaluable change from baseline micturition measurement" (EMPOWUR SAP, page 27) • Full analysis set for incontinence (FAS-I): "all randomised OAB Wet patients who took at least one dose of double-blind study treatment and have at least one evaluable change from baseline UUI measurement." (EMPOWUR SAP, page 27) The EAG notes using a FAS-I analysis set to detect changes from baseline in incontinence episodes, for people who experienced incontinence at baseline, is a common method in studies of mixed wet and dry OAB populations and was used in the analyses of mirabegron trials in TA290.[2]

Abbreviations: ANCOVA, analysis of covariance; CS, company submission; CSR, clinical study report; EAG, External Assessment Group; MCID, minimum clinically important difference; MMRM, mixed models for repeated measures; OAB, overactive bladder; SAP, statistical analysis plan; UUI, urge urinary incontinence.

4.2.2 EMPOWUR extension

A subset of participants completing the EMPOWUR study were eligible to enrol in the EMPOWUR extension study. The EMPOWUR extension study aimed to recruit around 500 participants who had ≥ 80% compliance with their study treatment during EMPOWUR. An overview of the study design of the EMPOWUR extension study is provided in Figure 3. Briefly:

- Eligible participants who completed Week 12 of EMPOWUR on vibegron 75 mg continued to receive vibegron 75 mg for 40 further weeks during the EMPOWUR extension study;
- Eligible participants who completed Week 12 of EMPOWUR on tolterodine ER 4 mg continued to receive tolterodine ER 4 mg for 40 further weeks during the EMPOWUR extension study;
- Eligible participants who completed Week 12 of EMPOWUR in the placebo arm were re-randomised 1:1 to receive either vibegron 75 mg or tolterodine ER 4 mg for 40 further weeks during the EMPOWUR extension study.

Figure 3. Study design of the EMPOWUR extension study. Reproduced from EMPOWUR Extension CSR Figure 1.

*The Follow-up visit occurred at Day 393 for subjects who completed the Week 52 visit or at 28 days after withdrawal (WD) for subjects who withdraw early from the study.

The EAG notes the following about the EMPOWUR extension study, in addition to the quality assessment provided for the parent study in Table 5:

- The primary endpoint of the EMOPWUR extension study was a safety outcome, namely the incidence of any treatment-emergent adverse events. Change from baseline in micturition frequency, number of UUI episodes and total incontinence episodes were secondary outcomes, and changes in EQ-5D was an exploratory outcome;
- No formal power analysis was conducted due to the primary objective being safety monitoring;
- The sample sizes of each treatment arm in the extension study were smaller than the parent study (e.g. 182 of 526 [34.6%] of vibegron 75 mg participants continued from the parent to the extension study). However, the EAG notes that more within trial data are available from participants completing the extension study, which may offset the loss of power associated with reducing the total sample size; and
- Despite the total sample size dropping from 1463 in EMPOWUR to 505 in EMPOWUR extension, this was a planned reduction based on the pre-specified target sample of 500 in the EMPOWUR extension study. In total, [redacted] participants were screened for the extension study and 505 were treated with at least one dose of the study drug. The EAG therefore considers the risk of selection bias when enrolling into the extension study to be low.

The baseline characteristics of participants continuing into the EMPOWUR extension study were not reported in the CS, and so the EAG has reproduced these data from the CSR in Appendix 9.1. The EAG considers the baseline characteristics to be reasonably balanced between individuals continuing on vibegron 75 mg (n=181) and individuals continuing on tolterodine 4 mg (n=141), including for baseline micturitions (FAS, vibegron 75 mg, mean [SD]: 11.32 [3.415]; tolterodine 4 mg: 11.33 [3.218]) and UUI episodes (FAS-I, vibegron 75 mg, mean [SD]: 3.18 [2.837]; tolterodine 4 mg: 3.00 [2.038]).

4.2.3 Studies of vibegron at doses other than 75 mg

The design of the three RCTs of vibegron 50 mg compared to mirabegron 50 mg, and the three other placebo or active controlled RCTs of vibegron at non-75 mg doses were described by the company in CS Section B.3.3.2, and were summarised by the EAG in Table 4.

4.3 Clinical effectiveness results

4.3.1 EMPOWUR

The company presented results of the EMPOWUR study in CS Section B.3.6.1. The EAG now summarises the results of the outcomes most relevant to the present cost-comparison appraisal. The EAG focuses on the Week 12 results, i.e., the results at the timepoint that the co-primary endpoints were tested at.

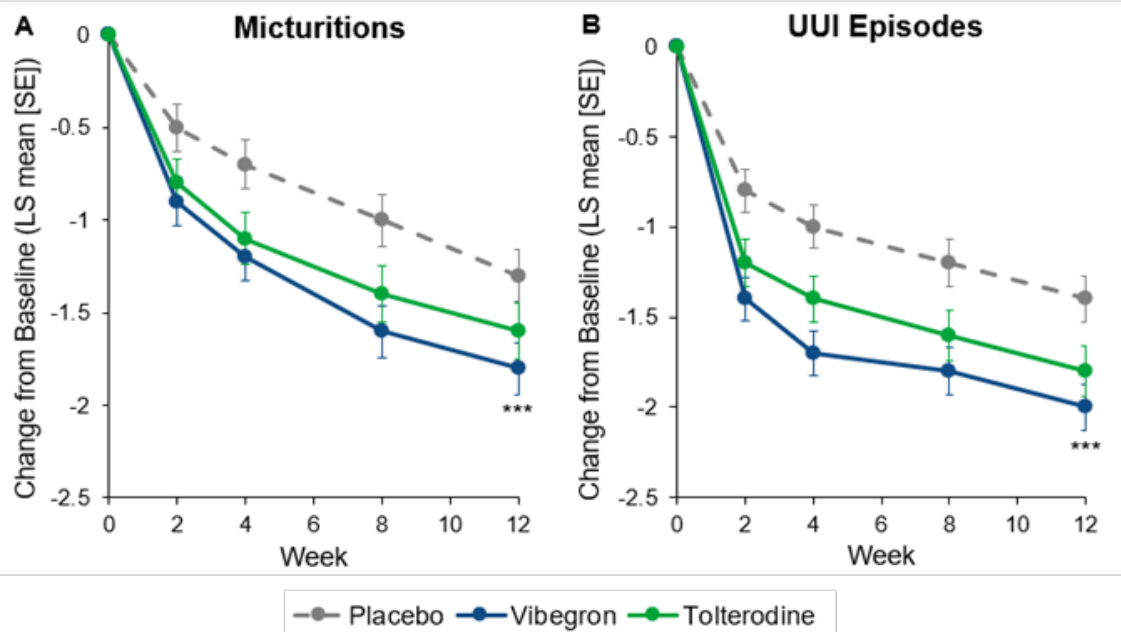
4.3.1.1 Co-primary endpoints: micturition frequency and UUI episodes

At Week 12, vibegron was associated with a statistically significant greater reduction from baseline compared versus placebo for both co-primary endpoints:

- Average number of daily micturitions: least squares mean difference of –0.5 (vibegron minus placebo, 95% confidence interval [CI]: –0.8 to –0.2, $p < 0.001$);
- Average number of daily UUI episodes: least squares mean difference of –0.6 (vibegron minus placebo, 95% CI: –0.9 to –0.3, $p < 0.001$);

At Week 12, the absolute changes from baseline for the average daily number micturitions were –1.8 (vibegron 75 mg, 95% CI: –2.1 to –1.5), –1.6 (tolterodine 4 mg, 95% CI: –1.9 to –1.3) and –1.3 (placebo, 95% CI: –1.6 to –1.0). At Week 12, the absolute changes from baseline for the average daily number of UUI episodes were –2.0 (vibegron 75 mg, 95% CI: –2.3 to –1.8), –1.8 (tolterodine 4 mg, 95% CI: –2.1 to –1.5) and –1.4 (placebo, 95% CI: –1.7 to –1.2). These data are summarised in Figure 4.

Figure 4. Least squares mean change from baseline in average daily number of (A) micturitions (FAS), (B) UUI episodes (FAS-I). Reproduced from CS Figure 11.



Abbreviations: FAS, full analysis set; FAS-I, full analysis set for incontinence; LS, least squares; SE, standard error; UUI, urge urinary incontinence.

Note: *** denotes p<0.001 for vibegron vs. placebo using a mixed model for repeated measures.

Source: CS Figure 11

The EAG notes that:

- There was a considerable reduction from baseline in the placebo arm for both outcomes. This may be attributable to a combination of effective bladder management and training encouraged by the clinical trial protocol and regression to the mean, as participants were selected at baseline based on a certain threshold of micturition frequency (all participants) and UUI episodes (wet OAB participants);
- While the absolute change from baseline in UUI frequency for vibegron (–2.0) is numerically larger than the change from baseline in micturition frequency (–1.8), which may be clinically implausible in the same patients, these analyses were conducted on different analysis sets (FAS-I for UUI episodes [wet patients only], and FAS for micturition frequency [all patients]).

4.3.1.2 Total incontinence episodes

At Week 12 in EMPOWUR, the mean placebo adjusted change from baseline in total incontinence episodes was –0.7 (95% CI: –1.0 to –0.4) for vibegron 75 mg and –0.5 for tolterodine 4 mg (95% CI: –1.0 to –0.4).

4.3.1.3 EQ-5D-5L

The change from baseline in EQ-5D-5L index (US value set) and visual analogue scores were reported as exploratory outcomes at Week 12 in EMPOWUR and are presented in Table 6. There were little differences in EQ-5D index score at Week 12 for between placebo (mean 0.16; standard deviation [SD] 0.13), vibegron 75 mg (mean 0.03, SD 0.12) and tolterodine 4 mg (mean 0.03, SD 0.11), although vibegron was numerically favoured over placebo.

Table 6. Change in EQ-5D VAS and index score between baseline and 12 weeks in EMPOWUR trial. Reproduced from CS Table 9.

	EQ-5D parameter	Placebo	Vibegron	Tolterodine
Index score[a]	Mean (SD)	0.0162 (0.12756)	0.0300 (0.11950)	0.0312 (0.11379)
	Median (IQR)	0.000 (–0.034 to 0.073)	0.000 (–0.005 to 0.090)	0.000 (–0.012 to 0.095)
VAS (mm)	Mean (SD)	1.7 (14.20)	3.4 (13.28)	2.4 (12.67)
	Median (IQR)	0.0 (–5 to 10)	0.0 (–5 to 10)	0.0 (–5 to 10)

[a]US value set used

Abbreviations: IQR, interquartile range; SD, standard deviation; VAS, visual analogue scale

4.3.2 EMPOWUR extension

For participants who received 52 weeks of either vibegron 75 mg (n=152) or tolterodine 4 mg (n=120), the change from baseline in the average number of daily micturitions, UUI episodes and total incontinence episodes are presented in Table 7. For vibegron 75 mg, the magnitude of the response observed at Week 12 was maintained up to Week 52 for micturitions (mean change –2.4, 95% CI: –2.9 to –2.0), UUI episodes (mean change –2.2, 95% CI: –2.5 to –1.9) and total incontinence episodes (mean change –2.5, 95% CI: –2.8 to –2.2).

Table 7. LS mean change from baseline to Week 52 for efficacy endpoints among patients receiving either vibegron or tolterodine, EMPOWUR EXT (FAS-Ext or FAS-I-Ext datasets). Reproduced from CS Table 10.

Endpoint	Vibegron	n	95% CI	Tolterodine	n	95% CI
Micturitions[a]	–2.4	152	–2.9 to –2.0	–2.0	120	–2.5 to –1.5
UUI Episodes[b]	–2.2	125	–2.5 to –1.9	–1.7	91	–2.0 to –1.3
Total Incontinence Episodes[b]	–2.5	125	–2.8 to –2.2	–1.9	91	–2.3 to –1.6

Note: all outcomes represent change in average daily number of episodes.

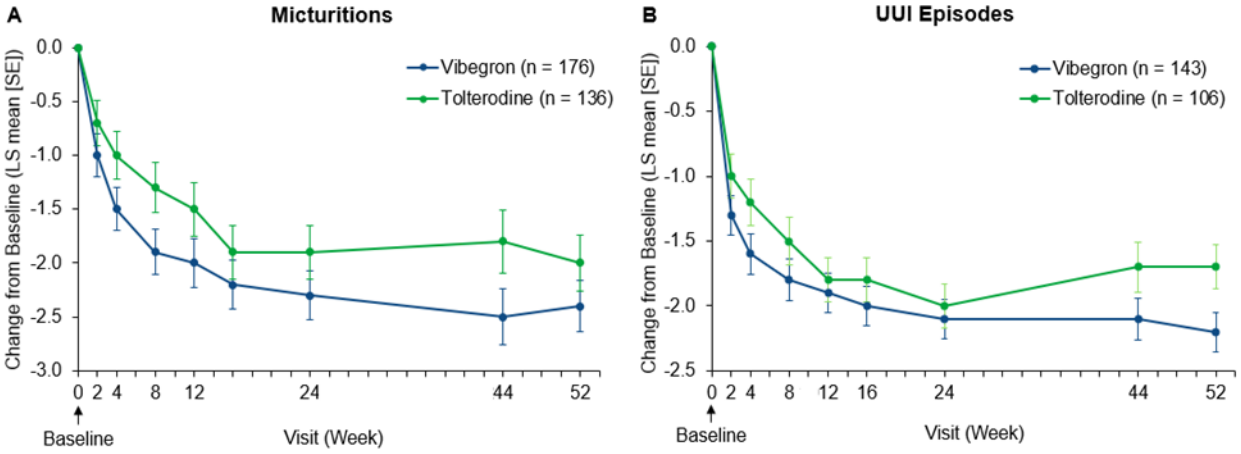
Abbreviations: CI, confidence interval; FAS-Ext, full analysis set extension; FAS-I-Ext, full analysis set extension for incontinence; LS, least squares; OAB, overactive bladder; UUI, urge urinary incontinence.

[a]Assessed in FAS-Ext. [b]Assessed in FAS-I-Ext (OAB wet patients only).

Source: CS Table 10

A comparison of the by-visit changes in micturition frequency and UUI episodes over EMPOWUR and the EMPOWUR extension study are presented in Figure 5.

Figure 5. LS mean change from baseline in average daily number of (A) micturitions (FAS-Ext) and (B) UUI episodes (FAS-I-Ext) over 52 weeks, EMPOWUR-EXT study. Reproduced from CS Figure 16.



Abbreviations: FAS-Ext, full analysis set extension; FAS-I-Ext, full analysis set for incontinence extension; LS, least squares; SE, standard error; UUI, urge urinary incontinence.
Source: CS Figure 16

The change from baseline in EQ-5D-5L index (US value set) and visual analogue scores were reported as exploratory outcomes at Week 52 in the EMPOWUR extension study and are presented in Table 8. There were little differences in EQ-5D index score at Week 52 between vibegron 75 mg (mean 0.08, SD 0.18) and tolterodine 4 mg (mean 0.06, SD 0.14), although vibegron was numerically favoured over tolterodine.

Table 8. Change in EQ-5D VAS and index score between baseline and 52 weeks in the EMPOWUR extension study.

	EQ-5D parameter	52-weeks vibegron 75 mg (n=176)	52-week tolterodine ER 4 mg (n=136)
Index score[a]	Mean (SD)	0.0774 (0.18459)	0.0553 (0.14324)
	Median (IQR)	0.000 (–0.005 to 0.139)	0.000 (0.000 to 0.124)
VAS (mm)	Mean (SD)	5.3 (13.82)	3.6 (13.03)
	Median (IQR)	4.5 (0 to 13)	2.0 (–5 to 10)

[a]US value set used
Abbreviations: ER, extended release; IQR, interquartile range; SD, standard deviation; VAS, visual analogue scale
Source: EMPOWUR extension study CSR Table 14.2.19.1

4.3.3 Subgroup analyses

In-line with the final scope issued by NICE,[7] the company presented subgroup analyses of the EMPOWUR trial co-primary endpoints for: i) men and women; and ii) previously untreated and previously treated overactive bladder, in Section B.3.7 of the CS.

4.3.3.1 Men and women

The male subgroup size was limited in the EMPOWUR trial (vibegron, n=75 FAS, n=42 FAS-I; placebo n=69 FAS, n=38 FAS-I), and the EAG notes that the EMPOWUR trial was not powered to detect effects within individual subgroups. For the change in daily micturitions (FAS), the point estimate for the placebo-adjusted difference was similar between males (–0.6, 95% CI: –1.4 to 0.1) and females –(0.5, 95% CI –0.8 to –0.2). For the change in daily episodes of UUI, the placebo-adjusted point estimate for males (–0.1, 95% CI: –0.9 to 0.8) was numerically smaller than for females (–0.7, 95% CI: –1.0 to –0.4). These data are presented in Table 9.

Table 9. Subgroup MMRM analysis of the co-primary outcomes at 12 weeks by sex (male or female) from EMPOWUR study. Reproduced from CS Table 13.

Sex	Outcome	Placebo	Vibegron	Tolterodine
Change in daily micturitions (FAS dataset)				
Male	Mean change from baseline (95% CI)	–1.1 (–1.7 to –0.5) n=69	–1.7 (–3.3 to –1.2) n=75	–1.0 (–1.6 to –0.4) n=65
	Active difference*		–0.6 (–1.4 to 0.1)	0.1 (–0.7 to 0.9)
Female	Mean change from baseline (95% CI)	–1.4 (–1.7 to –1.1) n=406	–1.9 (–2.2 to –1.6) n=417	–1.7 (–2.0 to –1.5) n=318
	Active difference*		–0.5 (–0.8 to –0.2)	–0.3 (–0.7 to 0.0)
Change in daily episodes of UUI (FAS-I dataset)				
Male	Mean change from baseline (SD)	–1.60 (–2.2 to –0.9) n=38	–1.60 (–2.2 to –1.0) n=42	–2.0 (2.7 to –1.3) n=33
	Active difference*		–0.1 (–0.9 to 0.8)	–0.5 (–1.4 to 0.4)
Female	Change from baseline (SD)	–1.4 (–1.6 to –1.2) n=334	–2.1 (2.3 to –1.8) n=341	–1.8 (–0.7 to –0.1) n=253
	Active difference*		–0.7 (–1.0 to –0.4)	–0.4 (–0.7 to –0.2)

Abbreviations: CI, confidence intervals, FAS, full analysis set; FAS-I full analysis set in people with incontinence (wet OAB); MMRM, mixed model repeated measures.

* Difference between intervention and placebo.

The EAG considers this subgroup analysis difficult to interpret due to the small number of male participants, especially within the FAS-I dataset. The EAG's clinical experts noted that, providing other causes of incontinence were adequately managed in male participants or in the absence of benign prostatic hyperplasia (BPH) and bladder outlet obstruction , there is no strong reason why the effectiveness of vibegron would differ between males and females. Hence, the EAG considers the point estimate favouring placebo over vibegron for the change in daily episodes of UUI is at high risk of being a consequence of sampling variance.

The EAG notes a large sample Phase 3 RCT of vibegron 75 mg versus placebo in men with OAB symptoms who were receiving therapy with either an alpha blocker monotherapy or an alpha blocker plus 5-alpha reductase inhibitor for BPH. In total, n=1105 men with BPH were enrolled and the following results were reported at Week 12:[22-24]

- Change in daily micturition frequency least squares mean difference (95% CI), –0.74 (–1.02 to –0.46), $p < 0.0001$:
    - Placebo: –1.30
    - Vibegron 75 mg: –2.04
- Change in average number of urge urinary incontinence episodes per day least squares mean difference (95% CI),–0.80 (−1.33 to −0.27), $p = 0.003$:
    - Placebo: –1.39
    - Vibegron 75 mg: –2.19

While these data are in a study population (males with OAB who are receiving therapy for BPH) outside of the decision problem addressed in this submission (people with OAB), the EAG consider these data to provide supporting evidence of a superiority of vibegron compared to placebo in males with OAB generally.

4.3.3.2 Previously treated

The EAG notes that previously treated vs previously untreated overactive bladder, particularly regarding those previously treated with anticholinergics, is a subgroup of high relevance to the current appraisal. In EMPOWUR, only 14.6% of participants reported prior anticholinergic use, however such patients will make up the majority of the recommended population should vibegron be recommended for routine commissioning based on the company's positioning in the CS.

The EAG has presented the results of the prior anticholinergic subgroup analyses in Table 10. While formal comparisons between vibegron and placebo were not presented, the EAG has calculated the naïve difference in point estimates below:

Change from baseline in daily number of micturitions

- Prior anticholinergic subgroup: –0.7 (vibegron minus placebo);
- No prior anticholinergic subgroup: –0.4 (vibegron minus placebo).

Change from baseline in daily episodes of UUI

- Prior anticholinergic subgroup: –0.7 (vibegron minus placebo);
- No prior anticholinergic subgroup: –0.5 (vibegron minus placebo).

Table 10. Mean (SD) change from baseline to Week 12 in co-primary outcomes prior OAB anticholinergic pharmacotherapy, EMPOWUR study (FAS and FAS-I). Adapted from CS Table 14.

Subgroup	Placebo	n	Vibegron 75 mg	n	Tolterodine 4mg	n
Co-primary outcome: daily number of micturitions (FAS dataset)						
Prior anticholinergic use	–1.3 (2.3)	79	–2.0 (2.4)	74	–1.5 (1.9)	48
No prior anticholinergic use	–1.7 (2.8)	396	–2.1 (2.6)	418	–1.8 (2.7)	330
Co-primary outcome: daily episodes of UUI (FAS-I dataset)						
Prior anticholinergic use	–0.8 (2.2)	68	–1.5 (2.2)	64	–1.0 (1.8)	39
No prior anticholinergic use	–1.6 (2.4)	304	–2.1 (2.5)	319	–1.9 (2.4)	247

Abbreviations: FAS, full analysis set; FAS-I, full analysis set for incontinence; OAB, Overactive Bladder; SD, standard deviation; UUI, urge urinary incontinence.

The point estimates of the relative treatment effect (vibegron vs placebo) are numerically larger in the prior anticholinergic subgroup than the no prior anticholinergic subgroup. The EAG notes that, despite the absence of a formal comparison with quantified uncertainty:

- It is reassuring that the magnitude of the difference in point estimates between prior and no prior anticholinergic subgroups in EMPOWUR is: i) small and; ii) numerically favours the population that is most relevant to UK clinical practice;
- It is uncertain whether prior anticholinergic exposure is a meaningful treatment effect modifier for vibegron, although the EAG's clinical experts did not consider it likely;
- If the same degree and direction of treatment modification observed in EMPOWUR for vibegron were to generalise to studies of mirabegron too (i.e., a larger relative treatment

effect in prior anticholinergic users), this would lead to conservative estimates of the relative treatment effect of vibegron in indirect treatment comparisons between vibegron and mirabegron, due to the smaller degree of prior anticholinergic drug use in EMPOWUR than key mirabegron trials (Section 4.4).

In TA290, the EAG presented a comparison of previously treated and treatment-naïve individuals for the mean number of micturitions and total incontinence episodes, reported as part of a pre-specified pooled analysis of three mirabegron trials (SCORPIO, ARIES and CAPRICORN):[25-27]

Change from baseline in daily number of micturitions

- Previously treated OAB subgroup: –0.74 (95% CI: –1.01 to –0.47, mirabegron minus placebo);
- Treatment naive subgroup: –0.33 (95% CI: –0.63 to –0.05, mirabegron minus placebo).

Change from baseline in daily incontinence episodes

- Previously treated OAB subgroup: –0.57 (95% CI: –0.81 to –0.33, mirabegron minus placebo);
- Treatment naive subgroup: –0.15 (95% CI: –0.44 to 0.14, mirabegron minus placebo).

While neither interaction *p*-value was statistically significant, these data support prior treatment as a potential treatment effect modifier for patients later treated with β3-AR agonists, with a heightened treatment effect seen in treatment experienced individuals. As noted, this is likely to favour mirabegron in the indirect treatment comparisons presented in Section 4.4.

4.3.4 Adverse effects

The adverse events (AE) included in TA290 were dry mouth and constipation – common AEs associated with anticholinergic drugs. The company presented AE data from EMPOWUR, EMPOWUR extension and other vibegron RCTs in CS Section B.3.10. Here, the EAG summaries the AE data from EMPOWUR and EMPOWUR extension, highlighting those AEs included in TA290, and the AEs for which the company presented indirect treatment comparisons for in CS Section B.3.9: all cause AEs, serious AEs, AEs leading to treatment discontinuation, headache, hypertension, urinary tract infection, dry mouth and constipation.

4.3.4.1 EMPOWUR

A summary of the AEs reported by ≥2% of patients, and constipation, in EMPOWUR is provided in Table 11.

Table 11. Global AEs and AEs reported by ≥2% of patients in the vibegron, tolterodine, or placebo groups over 12 weeks, EMPOWUR study (safety analysis set). Reproduced from CS Section B.3.10.1 and Table 18.

Endpoint	Placebo (n = 540)	Vibegron 75 mg (n = 545)	Tolterodine 4 mg (n = 430)	ITC performed?
Patients with any TEAE	33.3%	38.7%	38.6%	Yes
Patients with any serious AEs	1.1%	1.5%	2.3%	Yes
Patients with AEs leading to treatment discontinuation	1.1%	1.7%	3.3%	Yes
Specific AEs (≥2% of patients, and constipation)				
Hypertension *	1.7%	1.7%	2.6%	Yes
Urinary tract infection	6.1%	5.0%	5.8%	Yes
Headache *	2.4%	4.0%	2.6%	Yes
Nasopharyngitis	1.7%	2.8%	2.6%	No
Diarrhoea	1.1%	2.2%	2.1%	No
Nausea	1.1%	2.2%	1.2%	No
Upper respiratory infection	0.7%	2.0%	0.5%	No
Dry mouth †	0.9%	1.7%	6.5%	Yes
Constipation †	1.3%	1.7%	1.4%	Yes

* *A priori* safety end point of interest according to trial protocol.
† Included as safety endpoint of interest in TA290. Constipation occurred <2% of patients in all groups.
Abbreviations: AE, adverse event; CS, company submission; ITC, indirect treatment comparison; mg, milligram; TAEA, treatment emergent adverse event

4.3.4.1 EMPOWUR extension

A summary of the AEs reported by ≥2% of patients, and constipation, in EMPOWUR is provided in Table 12.

Table 12. Global AEs and AEs reported by ≥2% of patients in the vibegron group over 52 weeks, EMPOWUR extension study (safety analysis set). Adapted from CS Table 18.

N (%)	Vibegron 75 mg n = 273	Tolterodine 4 mg n = 232	ITC performed?
Patients with ≥1 treatment-emergent AE	171 (62.6)	126 (54.3)	Yes
Patients discontinuing study medication owing to an AE	4 (1.5)	8 (3.4)	Yes
Patients with ≥1 treatment-emergent SAE	9 (3.3)	10 (4.3)	Yes
SAEs considered treatment related by the investigator	1 (0.4)	2 (0.9)	No
AEs (>2% for vibegron)			
Hypertension	24 (8.8)	20 (8.6)	Yes
Urinary tract infection	18 (6.6)	17 (7.3)	Yes
Headache	15 (5.5)	9 (3.9)	Yes
Diarrhoea	13 (4.8)	4 (1.7)	No
Nasopharyngitis	13 (4.8)	12 (5.2)	No
Constipation	10 (3.7)	6 (2.6)	Yes
Nausea	10 (3.7)	7 (3.0)	No
Upper respiratory tract infection	10 (3.7)	1 (0.4)	No
Bronchitis	8 (2.9)	3 (1.3)	No
Anaemia	7 (2.6)	2 (0.9)	No
Hyperglycaemia	7 (2.6)	2 (0.9)	No
Residual urine volume increased	7 (2.6)	3 (1.3)	No
Back pain	6 (2.2)	3 (1.3)	No
Musculoskeletal pain	6 (2.2)	1 (0.4)	No

Abbreviations: AE, adverse event; CS, company submission; ITC, indirect treatment comparison; mg, milligram; SAE, serious adverse event; TAEA, treatment emergent adverse event

4.3.4.2 EAG comment

The overall rate of AEs was greater for vibegron 75 mg and tolterodine 4 mg compared to placebo after 12 weeks in EMPOWUR. After 52 weeks, the percentage of participants with ≥1 treatment-emergent AE was greater for vibegron 75 mg (62.6%) than tolterodine 4 mg (54.3%). However, across both the 12-week EMPOWUR study and 52-week EMPOWUR extension study, the rate of serious AEs was low across all arms, and at 52 weeks 9 of 273 (3.3%) of vibegron 75 mg patients had

reported an SAE compared to 10 of 232 (4.3%) tolterodine 4 mg patients. The EAG's clinical experts considered the AEs of hypertension, UTI, headache, constipation, dry mouth, diarrhoea and nasopharyngitis to be most likely to be treatment related.

4.3.5 Other studies

The clinical effectiveness results of the RCTs including vibegron doses other than 75 mg were presented in CS section B.3.6.2.1. The EAG notes these results were consistent with the superiority of vibegron over placebo for most outcomes of interest, and similarity in clinical outcomes between vibegron and mirabegron.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

As there were no head-to-head trials comparing vibegron 75 mg to mirabegron 50 mg or 25 mg, the company performed network meta-analyses (NMAs) for the following outcomes at 4, 8, 12 and 52 weeks:

Efficacy NMAs

- Average number of daily micturitions;
- Average number of UUI episodes;
- Average number of incontinence episodes; and
- Average volume voided.

Safety NMAs

- Adverse events due to any cause;
- Serious adverse events;
- Adverse events leading to study treatment discontinuation;
- Headache;
- Hypertension;
- Urinary tract infection;
- Dry mouth; and
- Constipation.

The following comparators were included in the NMAs:

- vibegron 75 mg;
- mirabegron 50 mg;
- mirabegron 25 mg;
- placebo; and
- tolterodine 4 mg.

The company presented the NMA methods and results across CS Section B.3.9, Appendix D1.1, Appendix D1.2 and also provided a separate ITC report, code and input data sufficient for the EAG to reproduce the NMA results. In the following sections, the EAG focuses its critique on the NMAs performed at Week 12 (the time the primary endpoint was tested for most trials) and Week 52 (the time of the longest available follow-up for vibegron 75 mg), but notes the results of the Week 4 and Week 8 NMAs were in-line with the Week 12 results.

4.4.1 Critique of trials identified and included in the NMAs

Of the 118 studies identified in the company's SLR, 18 studies were identified as trials of vibegron or mirabegron with a common comparator. Of these, 10 studies were ultimately included in the NMAs following the application of the following two criteria:

- Trial design: Phase 3, randomised and double blind; and
- Intervention: vibegron 75 mg, mirabegron 50 mg or mirabegron 25 mg, i.e., at the doses specified in the marketing authorisation or the dose expected to be specified in the marketing authorisation.

The EAG notes that of the eight studies excluded:

- Three were phase 2 RCTs of mirabegron 50 mg or 25 mg compared to placebo,[13, 28, 29] two of which contain data highly relevant to the decision problem;[13, 29]
- One was a phase 4 RCT of dose titration for patients receiving mirabegron 25 mg;[30]
- One did not include a common comparator with EMPOWUR;[31] and
- Three did not include a vibegron arm at the expected licensed dose of 75 mg.[11, 18, 21]

At clarification, the company provided a sensitivity analysis of the primary NMAs that included the Phase 2 trials of mirabegron (Section 4.4.3.1.1).

The EAG agreed with the company that the EMPOWUR study was at low risk of bias (Section 4.2), and the company provided quality assessments of each of the mirabegron studies included in the NMA in response to clarification question A10. The EAG agrees with the quality assessment performed by the company, noting that all included studies were Phase 3 double-blind RCTs. Where sufficient information was provided in the trial publications, the company assessed the risk of bias to be low for each study aside from Moussa 2021.[32] The EAG notes that Moussa 2021 was an RCT of mirabegron or placebo in a selected patient population — people with OAB and Parkinson's disease. Moussa 2021 was not included in the company's primary analyses, and the EAG agrees with this exclusion.

The study design and relevant treatment regimens of the studies included in the company's NMAs, and the two additional phase 2 trials included in the EAG sensitivity analyses, are presented in Table 13.

Table 13. Description of studies included in the company NMAs and phase 2 trials of mirabegron. Adapted from CS Table 15.

Study	Author and Year	Number of patients*	Study duration	Number of arms*	Treatment
ARIES	Nitti 2014[33]	1328 (895)	12 weeks	3 (2)	•Mirabegron 50mg •Placebo
CAPRICORN	Herschorn 2013[27]	1305	12 weeks	3	•Mirabegron 25mg •Mirabegron 50mg •Placebo
EMPOWUR	Staskin 2020[10]	1463	12 weeks	3	•Vibegron 75mg •Tolterodine ER 4mg •Placebo
EMPOWUR (Extension)	Staskin 2021[17]	505	40 weeks (52 in total)	2	•Vibegron 75mg •Tolterodine ER 4mg
Kuo 2015	Kuo 2015[34]	994	12 weeks	3	•Mirabegron 50mg •Tolterodine ER 4mg •Placebo
Moussa 2021	Moussa 2021[32]	95	12 weeks	2	•Mirabegron 50mg •Placebo
SCORPIO	Khullar 2013[35]	1978 (1482)	12 weeks	4 (3)	•Mirabegron 50mg •Tolterodine ER 4mg •Placebo
SYNERGY	Herschorn 2017[36]	3398 (1274)	12 weeks	6 (3)	•Mirabegron 25mg •Mirabegron 50mg •Placebo

TAURUS	Chapple 2013[37]	2444 (1624)	12 months	3 (2)	•Mirabegron 50mg •Tolterodine ER 4mg
Yamaguchi 2014	Yamaguchi 2014[38]	1105	12 weeks	3	•Mirabegron 50mg •Tolterodine 4mg •Placebo
DRAGON†	Chapple 2013[13]	928 (592)	12 weeks	6 (4)	•Mirabegron 25mg •Mirabegron 50mg •Tolterodine ER 4mg •Placebo
Yamaguchi 2015**	Yamaguchi 2015[29]	842 (633)	12 weeks	4 (3)	•Mirabegron 25mg •Mirabegron 50mg •Placebo

Abbreviations: ER, extended release; NMA, network meta-analysis

*Value in parenthesis regards to data included in the NMAs

†Phase 2 trial included in EAG sensitivity analyses

A comparison of the key baseline characteristics of patients included in the trials entering the NMA is provided in Table 14. The EAG notes that patient characteristics were well balanced between studies, aside from:

- EMPOWUR had the highest proportion of female participants (85%) across all trials, although the overall number of females was similar throughout the trials excluding Moussa 2021 (range: 67% to 85%). In response to clarification question A14, the company stated: *"The phase 3 study protocol [of EMPOWUR] included this limit [of the number of male participants] at 15% because comorbid conditions in male subjects such as benign prostatic hyperplasia (BPH) are commonly observed and can precipitate overflow incontinence or frequency by a mechanism other than OAB. Thus the proportion of men was limited to 15% of the trial population in order not to confound trial outcomes.";* and
- Where prior OAB treatment was reported, EMPOWUR had the lowest number of treatment experienced (11%) individuals than all other trials (range 11% to 65%, excluding Moussa 2021).

The EAG considers it plausible that sex and prior OAB treatment are potentially treatment effect modifiers (4.3.3). For sex, this would be due the presence of comorbid conditions that may limit the incontinence treatment effects that is possible without treatment of the comorbidity. The EAG notes that:

- The imbalances in sex across trials are small in magnitude, but may favour vibegron in the NMA due to EMPOWUR having the fewest number of males of included studies;
- The imbalances in prior treatment experience are larger in magnitude, and likely will favour mirabegron in the NMA, due to EMPOWUR having the lowest rate of prior treatment experience, of studies that reported this characteristic.

Hence, the EAG does not consider it likely that bias in the NMAs would systematically favour vibegron in the efficacy NMAs.

Table 14. Key baseline characteristics of trials included in the company NMAs. Adapted from company response to clarification Table 6 and Table 7.

Study (Author and Year)	Treatment arm (n=)	Patient demographics				OAB related baseline characteristics		
		Age (years) Mean (SD) (Median [IQR])	Gender (female) N (%)	BMI kg/m2 Mean (SD) (Median [IQR])	Prior OAB treatment N (%)	Number of incontinence episodes/day Mean (SD) (Median [IQR])	Number of micturitions/day Mean (SD) (Median [IQR])	Number of UUI episodes Mean (SD) (Median [IQR])
ARIES Nitti 2013 [39]	Mirabegron 50 mg (n=442)	59.2 (13.5)	322 (72.9)	30.0 (6.6)	NR	NR	11.8 (3.4)*	NR
	Placebo (n=453)	60.1 (13.8)	345 (76.2)	30.4 (7.4) *(n=252)*	NR	NR	11.5 (3.3)*	2.9 (3.3)
CAPRICORN Herschorn 2013 [27]	Mirabegron 25 mg (n=432)	58.5 (12.9)	293 (67.8)	29.8 (6.5)	NR	NR	11.66 (3.12)*	NR
	Mirabegron 50 mg (n=440)	60.3 (12.2)	303 (68.9)	29.5 (6.5)	NR	NR	11.69 (3.23)*	NR
	Placebo (n=433)	58.2 (13.7)	301 (69.5)	29.2 (6.3)	NR	NR	11.54 (2.98)*	NR
EMPOWUR Staskin 2020 [10]	Vibegron 75 mg (n=526)	60.8 (13.3) (63 [18])	449 (85.4)	31.2 (7.4)	77 (14.6)	3.3 (3.6) (2.1)	11.3 (3.4) (10.4 [3.6])	2.8 (3.1)* (2 [2.9]) (n=544)
	Tolterodine ER 4 mg (n=417)	59.8 (13.2) (61 [17])	352 (84.4)	31.8 (7.5)	51 (12.2)	3.2 (3.1) (2.3)	11.5 (3.2) (10.7 [3.7])	2.7 (2.6)* (2 [2.6]) (n=430)
	Placebo (n=520)	59.9 (13.3) (61 [16])	445 (85.6)	31.0 (6.8)	85 (16.3)	3.4 (3.7) (2.3)	11.8 (4.0) (10.4 [4.0])	2.8 (3.0)* (2 [2.6])

								(n=537)
EMPOWUR (Extension) Staskin 2021 [40]	Vibegron 75 mg (n=273)	61.0 (12.9)	213 (78.0)	30.6 (6.7)	NR	3.1 (3.3)	11.6 (3.6)	2.7 (2.8)
	Tolterodine ER 4 mg (n=232)	61.2 (12.7)	182 (78.4)	30.5 (6.2) (n=218)	NR	2.8 (2.7)	11.3 (3.2)	2.3 (2.2)
Kuo 2015 [34]	Mirabegron 50 mg (n=338)	54.3 (14.2)	228 (67.5)	NR	NR	2.4 (2.5)	12.1 (4.1)	1.9 (2.3)
	Tolterodine ER 4 mg (n=333)	53.9 (14.5)	213 (64.0)	NR	NR	2.3 (2.8)	12.1 (3.7)	2.1 (2.7)
	Placebo (n=323)	55.3 (13.6)	225 (69.7)	NR	NR	2.4 (2.7)	12.6 (4.9)	1.8 (1.8)
Moussa 2021 [41]	Mirabegron 50 mg (n=53)	NR	23 (43.4)	NR	44 (83.0)	NR	11.0 (1.2)	NR
	Placebo (n=42)	NR	33 (78.6)	NR	35 (83.3)	NR	10.4 (1.0)	NR
SCORPIO Khullar 2013 [26]	Mirabegron 50 mg (n=493)	59.1 (12.4)	357 (72.4)	27.5 (4.9)	240 (50.7)	NR	11.7 (3.0)* *(n=473)*	NR
	Tolterodine ER 4 mg (n=495)	59.1 (12.9)	361 (72.9)	27.8 (5.0)	231 (48.6)	NR	11.6 (2.8)* *(n=475)*	NR
	Placebo (n=494)	59.2 (12.3)	356 (72.1)	27.8 (5.0) (n=493)	238 (49.6)	NR	11.7 (3.1)* *(n=480)*	NR
SYNERGY Herschorn 2017 [42]	Mirabegron 50 mg (n=422)	56.7 (13.3)	323 (76.5)	28.3 (6.0)*	195 (46.2)	3.2 (3.5)	11.2 (3.3)	2.89 (3.31) †
	Mirabegron 25 mg	56.9 (13.6)	327 (77.3)	28.2 (6.8)*	196 (46.3)	3.4 (3.4)	10.8 (2.6)	3.00 (3.09) †

	(n=423)							
	Placebo (n=429)	57.9 (13.0)	327 (76.2)	28.7 (6.1)*	205 (47.8)	3.4 (3.4)	11.0 (2.9)	3.14 (3.23)†
TAURUS Chapple 2013[37]	Mirabegron 50 mg (n=812)	59.2 (12.6)	602 (74.1)	NR	446 (54.9)	NR	11.1 (2.8)*	NR
	Tolterodine ER 4 mg (n=812)	59.6 (12.5)	600 (73.9)	NR	447 (55.0)	NR	10.9 (2.7)*	NR
Yamaguchi 2014[38]	Mirabegron 50 mg (n=369)	58.3 (13.9)	311 (84.3)	NR	233 (63.1)	2.0 (2.1)	11.2 (2.7)	1.7 (1.6)
	Tolterodine ER 4 mg†† (n=368)	58.3 (13.7)	304 (82.6)	NR	240 (65.2)	1.9 (1.8)	11.1 (2.6)	1.7 (1.4)
	Placebo (n=368)	58.2 (14.2)	310 (84.2)	NR	240 (65.2)	1.9 (1.8)	11.3 (2.7)	NR

Abbreviations: ER, extended release; IQR, interquartile range; IR, immediate release; NR, not reported; OAB, overactive bladder; SD, standard deviation; UUI, urinary urge incontinence

*Data taken from clinicaltrials.gov posted results (not reported in primary trial publication)

†Value corrected by EAG based on trial primary publication

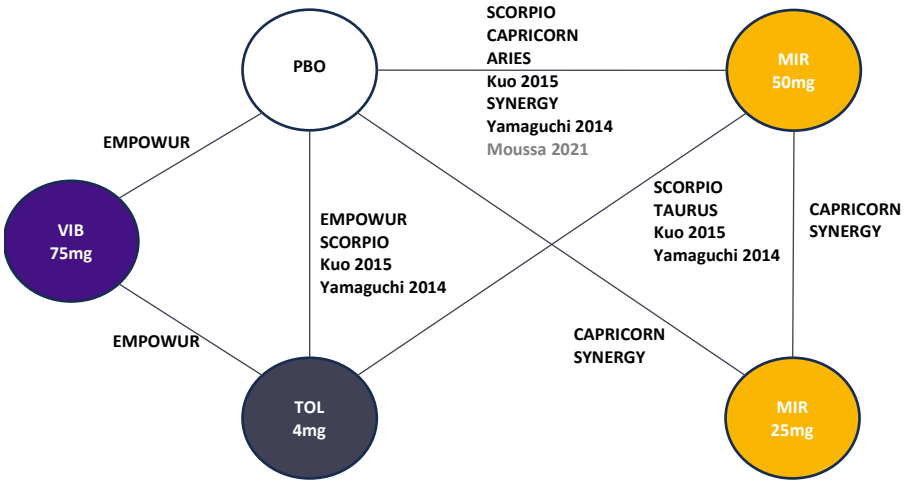
††Corrected by EAG to ER from IR based on dosage stated in the primary publication (one 4 mg capsule taken one daily)[43]

NB: Where sample sizes used to assess outcomes differed from the sample size for the whole treatment arm, this has been indicated below the data point

4.4.2 NMA methods

Fixed-effect and random effects Bayesian NMAs were implemented using Markov Chain Monte Carlo simulation using JAGS via the R package '*gemtc*'.[44] All analyses were performed in R 4.2.1. NMAs were run with 25,000 adaptation iterations and either 25,000 (fixed-effect models) or 50,000 (random effects models) simulation iterations. Vague priors were used for the relative effects — normal(0,100), and for the between study heterogeneity for random effects models — uniform(0, 5). Using code provided by the company at clarification, the EAG was able to successfully reproduce the NMA results. Example networks for the Week 12 and Week 52 NMAs are presented in Figure 6 and Figure 7.

Figure 6. Typical network used in the NMAs at Week 12. Reproduced from CS Figure 20.



Abbreviations: MIR, mirabegron; NMA, network meta-analysis; PBO, placebo TOL, tolterodine; VIB, Vibegron.
This specific network is the comparison of daily micturitions at 12 weeks.

Figure 7. Typical network used in the NMAs at Week 52. Reproduced from CS Figure 21.

Abbreviations: MIR, mirabegron; NMA, network meta-analysis; TOL, tolterodine; VIB, Vibegron.

4.4.3 Efficacy NMA results

Full results of the company efficacy NMAs at Week 4, Week 8, Week 12 and Week 52 are presented in CS Section B.3.9.2 and the ITC report. Here, the EAG presents the comparisons between vibegron 75 mg and comparators at Week 12 and Week 52. For each NMA at Week 12, the company preferred the random effects model if heterogeneity was detected and if the deviance information criterion (DIC) was lower for the random effects model, or within 5 of the fixed effect model. The EAG notes such criteria is likely to prefer the random effects model in most scenarios, and notes that at Week 12:

- the deviance information criterion (DIC) was lower for the random effects model than the fixed effect model for the micturitions NMA, fixed effect model DIC: 43.1, random effects model DIC: 38.3
- The DIC was numerically higher for the random effects model for the UUI NMA (fixed effect model DIC: 21.7, random effects model DIC: 23.5) and incontinence NMA (fixed effect DIC: 27.5, random effects DIC: 29.1), but was within the 5 difference specified by the company in order to prefer the random effects model.

In-line with the company's preference, the EAG presents the results of the random effects models but provides the results of the fixed effect models in Appendix 1.1. The EAG notes the results of the random effects models are directly in-line with fixed effect models, and the choice to prefer the random effects models does not appear to have systematically favoured vibegron over mirabegron.

4.4.3.1 Week 12

At Week 12 in the random effects NMAs, vibegron 75 mg was associated with (Table 15):

- A similar change from baseline in the daily number of micturitions as mirabegron 25 mg (mean difference: –0.03, 95% credible interval [CrI]: –0.65 to 0.61) and mirabegron 50 mg (mean difference: 0.01, 95% CrI: –0.53 to 0.58), and the 95% CrIs crossed 0;
- A numerically greater reduction in daily number of UUI episodes compared to mirabegron 25 mg (mean difference: –0.27, 95% credible interval [CrI]: –0.66 to 0.13) and mirabegron 50 mg (mean difference: –0.22, 95% CrI: –0.59 to 0.14), although the 95% CrIs crossed 0; and
- A numerically greater reduction in daily number of incontinence episodes compared to mirabegron 25 mg (mean difference: –0.27, 95% credible interval [CrI]: –0.73 to 0.17) and

mirabegron 50 mg (mean difference: –0.24, 95% CrI: –0.66 to 0.16), although the 95% CrIs crossed 0.

Table 15. Company random effects NMA results comparing vibegron 75 mg and comparators at Week 12 for daily number of micturitions, daily number of UUI episodes and daily number of incontinence episodes. Reproduced from CS Table 17, Figure 25 and response to clarification Figure 2.

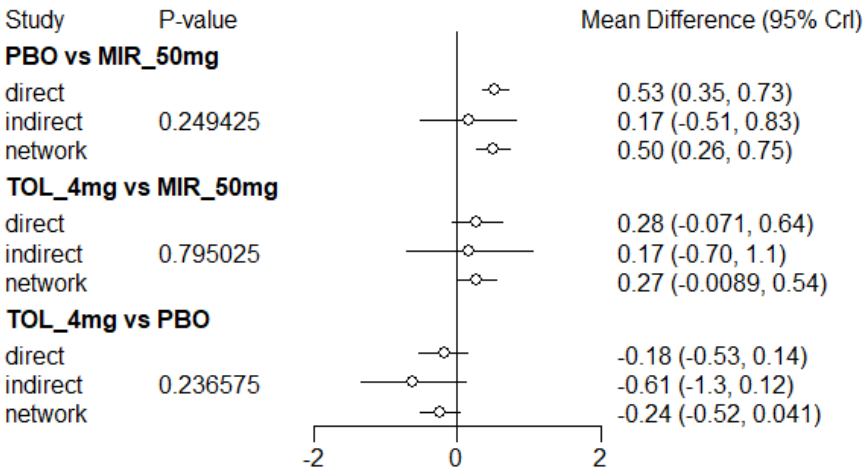
Week 12	vibegron 75 mg (95% Credible Interval)		
Comparator	Change from baseline in daily number of micturitions	Change from baseline in daily number of UUI episodes	Change from baseline in daily number of incontinence episodes
mirabegron 25 mg	–0.03 (–0.65 to 0.61)	–0.27 (–0.66 to 0.13)	–0.27 (–0.73 to 0.17)
mirabegron 50 mg	0.01 (–0.53 to 0.58)	–0.22 (–0.59 to 0.14)	–0.24 (–0.66 to 0.16)
placebo	–0.49 (–1.02 to 0.04)	–0.58 (–0.93 to –0.22)	–0.63 (–1.03 to –0.24)
tolterodine 4 mg	–0.20 (–0.74 to 0.32)	–0.23 (–0.59 to 0.13)	–0.37 (–0.78 to 0.02)

Results are presented as posterior median estimates (95% credible interval)

Abbreviations: CS, company submission; mg, milligram; NMA, network-meta-analysis; UUI, urge urinary incontinence

The company noted that for the daily number of micturitions NMA at 12 weeks, statistically significant inconsistency was identified between direct and indirect evidence (Q_B = 13.09, p = 0.01), suggesting the presence of imbalanced treatment effect modifiers across the network. In response to clarification question A11, the company considered the TAURUS study to be the source of the inconsistency, stating that, "the relative effect of mirabegron 50mg vs tolterodine 4mg in TAURUS study differed substantially compared with other studies". However, this was not formally tested. The EAG notes that the results of the EAG's requested sensitivity analysis, which excluded the TAURUS study (Section 4.4.1), is in-line with the company's primary NMA. Using the code provided by the company, the EAG also conducted a local, node-splitting, assessment of inconsistency within the company's primary network. In contrast to the global assessment performed by the company, no significant inconsistency was detected between the indirect and direct evidence within each loop (Figure 8).

Figure 8. Results of an EAG node-splitting analysis of the company's primary NMA for micturitions at Week 12.



Abbreviations: EAG, external assessment group; MIR, mirabegron; NMA, network meta-analysis; PBO, placebo; TOL, tolterodine

Analysis conducted using the '*gemtc'* package in R 4.4.0. Small differences in the network estimate for PBO vs MIR 50 mg from the EAG and company analyses are due to the EAG digitising the absolute effects from Kuo 2015 for use in the analysis, rather than the relative effects used in the company NMA.

4.4.3.1.1 Sensitivity analysis

In clarification question A21, the EAG requested a sensitivity analysis of the efficacy NMAs at Week 12 that:

- Excluded the TAURUS study, in which approximately 80% of participants had previously received treatment in other mirabegron Phase 3 trials, and as such provides non-independent data in the NMA as individual participants may have contributed data two studies; and
- Included two Phase 2 RCTs of mirabegron, namely DRAGON and Yamaguchi 2015, that were originally excluded from the company's NMA based on a pre-specified inclusion criteria of Phase 3 or above.

The company provided the results of random-effects NMAs for the change from baseline in daily micturitions, number of UUI episodes and total incontinence episodes. These data are presented in Table 16. The EAG notes that:

- The results of the sensitivity analysis are similar to the company's primary analysis, with all point estimates in the same direction aside from vibegron 75 gm compared to mirabegron 25 mg for the micturitions NMA; and
- For all comparisons between vibegron 75 mg and mirabegron 50 mg or 25 mg, the point estimates are close to 0 and 95% CrIs cross 0.

Table 16. Random effects NMA sensitivity analysis results comparing vibegron 75 mg and comparators at Week 12 for daily number of micturitions, daily number of UUI episodes and daily number of incontinence episodes. Reproduced from company response to clarification Tables 8, 10 and 12.

Week 12	vibegron 75 mg (95% Credible Interval)		
Comparator	Change from baseline in daily number of micturitions	Change from baseline in daily number of UUI episodes	Change from baseline in daily number of incontinence episodes
mirabegron 25 mg	0.01 (–0.44 to 0.46)	–0.16 (–0.54 to 0.23)	–0.15 (–0.58 to 0.27)
mirabegron 50 mg	0.11 (–0.31 to 0.53)	–0.17 (–0.53 to 0.2)	–0.18 (–0.59 to 0.22)
placebo	–0.49 (–0.89 to –0.08)	–0.56 (–0.91 to –0.21)	–0.62 (–1.02 to –0.23)
tolterodine 4 mg	–0.22 (–0.62 to 0.2)	–0.25 (–0.6 to 0.12)	–0.39 (–0.8 to –0.01)

Results are presented as posterior median estimates (95% credible interval)

Abbreviations: CS, company submission; mg, milligram; NMA, network-meta-analysis; UUI, urge urinary incontinence

4.4.3.2 Week 52

At Week 52 in the fixed effect NMAs, which approximate a Bucher comparison between EMPOWUR (extension) and TAURUS, vibegron 75 mg was associated with (Table 17):

- A numerically greater reduction from baseline in the daily number of micturitions compared to mirabegron 50 mg (mean difference: –0.60, 95% CrI: –1.31 to 0.12), although the 95% CrIs crossed 0;
- A greater reduction in daily number of UUI episodes compared to mirabegron 50 mg (mean difference: –0.62, 95% CrI: –1.13 to –0.10); and
- A greater reduction in daily number of incontinence episodes compared to mirabegron 50 mg (mean difference: –0.82, 95% CrI: –1.38 to –0.26).

Table 17. Company fixed effects NMA results comparing vibegron 75 mg and comparators at Week 52 for daily number of micturitions, daily number of UUI episodes and daily number of incontinence episodes. Reproduced from CS Figure 23, Figure 24 and CS Section B.3.9.2.3.

Week 52	vibegron 75 mg (95% Credible Interval)		
Comparator	Change from baseline in daily number of micturitions	Change from baseline in daily number of UUI episodes	Change from baseline in daily number of incontinence episodes
mirabegron 50 mg	–0.60 (–1.31 to 0.12)	–0.62 (–1.13 to –0.10)	–0.82 (–1.38 to –0.26)
tolterodine 4 mg	–0.40 (–1.07 to 0.27)	–0.50 (–0.96 to –0.04)	–0.60 (–1.10 to –0.10)

Results are presented as posterior median estimates (95% credible interval)

Abbreviations: CS, company submission; mg, milligram; NMA, network-meta-analysis; UUI, urge urinary incontinence

4.4.4 EAG comment

The company's efficacy NMAs provide evidence of clinically similar outcomes following treatment with vibegron 75 mg, mirabegron 50 mg and mirabegron 25 mg at Week 12 and at Week 52. For each comparison of micturitions, UUI episodes and incontinence episodes, the point estimates were either close to 0 or in favour of vibegron 75 mg. The EAG's clinical experts considered Week 12 to be an appropriate time to assess effectiveness of treatments for OAB. At Week 12, the 95% credible intervals crossed 0 for all comparisons between vibegron 75 mg and both mirabegron doses. At Week 52, only comparisons with mirabegron 50 mg were possible. The point estimates favoured vibegron for each comparison, and the 95% credible interval excluded 0 for the correlated UUI and incontinence episode outcomes.

In the CS, the company noted how the upper boundary of the 95% credible intervals of micturitions NMA and UUI episodes NMA excluded the pre-specified effect size used in the power calculation of the EMPOWUR trial (change in micturitions: 0.6, change in UUI episodes: 0.51). The EAG notes this equally applies to the sensitivity NMAs, and also when using the EAG's clinical experts' approximate minimum clinically important differences rather than the EMPOWUR trial power calculation values (Table 18). Based on this, the company considers the NMAs to be consistent with the non-inferiority of vibegron 75 mg compared with mirabegron 50 mg, and the EAG agrees with this interpretation.

Table 18. Summary of the results of the Week 12 NMAs comparing vibegron 75 mg with mirabegron 50 mg and mirabegron 25 mg for daily number of micturitions and UUI episodes and the MCIDs identified by the company and EAG.

Week 12 vibegron 75 mg	Primary NMA	Sensitivity NMA	Company inferred MCID	EAG clinical experts' approximate MCID
Mirabegron 50 mg				

Micturitions	0.01 (–0.53 to 0.58)	0.11 (–0.31 to 0.53)	0.6	1.2
UUI episodes	–0.22 (–0.59 to 0.14)	–0.17 (–0.53 to 0.2)	0.51	0.5
Mirabegron 25 mg				
Micturitions	–0.03 (–0.65 to 0.61)	0.01 (–0.44 to 0.46)	0.6	1.2
UUI episodes	–0.27 (–0.66 to 0.13)	–0.16 (–0.54 to 0.23)	0.51	0.5

Abbreviations: CS, company submission; EAG, external assessment group; MCID, minimum clinically important difference; mg, milligram; NMA, network-meta-analysis; UUI, urge urinary incontinence

4.4.5 Safety NMAs results

4.4.5.1 Week 12

Due to inconsistent reporting across studies, the number of studies contributing to the primary safety NMAs ranged from four studies (headache) to seven studies (dry mouth and any AE leading to study treatment discontinuation) out of a total possible eight studies in the primary network. Aside from any AEs, the overall event rate for serious AEs, AEs leading to treatment discontinuation and specific AEs (headache, hypertension, urinary tract infection, dry mouth and constipation) were low across all included studies.

The results of the primary safety NMAs at Week 12 are presented in Table 19, alongside the results of the EAG's requested sensitivity analysis (excluding TAURUS but including the Phase 2 trials of mirabegron). The EAG notes for the primary NMAs that:

- The point estimates of the any AE NMA favoured mirabegron 25 mg (odds ratio [OR] 1.44, 95% CrI: 0.85 to 2.49) and mirabegron 50 mg (OR 1.43, 95% CrI: 0.90 to 2.32) compared to vibegron 75 mg, although the 95% CrIs crossed 1; and
- For all other outcomes, the event rates were low across all studies, leading to point estimates close to 1 but with very wide credible intervals. At such low event rates, the position of the point estimate is heavily sensitive to sampling variance and individual events, especially in the EMPOWUR trial. Nevertheless, there was no evidence of a large difference between vibegron 75 mg, mirabegron 50 mg and mirabegron 25 mg in the frequency of these events.

The EAG considers that the results of the sensitivity NMAs are similar to the results of the primary NMAs. The EAG notes the company presented the results of the random effects NMAs in the CS, and the EAG has provided a comparison of the random effects results with those of the fixed-effect models in Appendix 9.3.

Table 19. Summary of the results of the company safety NMAs at Week 12 comparing vibegron 75 mg and mirabegron 25 mg and mirabegron 50 mg. Reproduced from CS Figures 26 and 27 and response to clarification question A22.

			NMA comparator OR, (95% Credible Interval)			
Week 12 AE outcome	AE incidence in EMPOWUR (12+4 weeks)		Primary NMA		NMA sensitivity analysis (excluding TAURUS, including Phase 2 trials)	
	placebo	vibegron 75 mg	mirabegron 25 mg	mirabegron 50 mg	mirabegron 25 mg	mirabegron 50 mg
Any AE	33.3%	38.7%	1.44 (0.85 to 2.48)	1.43 (0.90 to 2.32)	1.36 (0.81 to 2.23)	1.35 (0.85 to 2.13)
Any serious AE*	1.1%	1.5%	1.10 (0.20 to 5.69)	1.05 (0.24 to 4.53)	1.09 (0.21 to 5.64)	1.03 (0.25 to 4.56)
Any AE leading to study treatment discontinuation	1.1%	1.7%	0.81 (0.26 to 2.57)	0.74 (0.27 to 2.00)	0.91 (0.31 to 2.68)	0.72 (0.26 to 1.91)
Headache	2.4%	4.0%	3.01 (0.27 to 34.92)	1.68 (0.24 to 12.02)	1.94 (0.40 to 7.29)	1.51 (0.40 to 5.19)
Hypertension	1.7%	1.7%	0.79 (0.16 to 4.59)	0.93 (0.23 to 4.12)	0.77 (0.18 to 3.25)	0.94 (0.26 to 3.35)
Urinary tract infection	6.1%	5.0%	0.74 (0.21 to 2.75)	0.73 (0.23 to 2.46)	0.74 (0.20 to 2.72)	0.73 (0.23 to 2.43)
Dry mouth	0.9%	1.7%	0.84 (0.19 to 3.96)	1.10 (0.32 to 4.05)	0.74 (0.20 to 2.72)	1.02 (0.31 to 3.35)
Constipation	1.3%	1.7%	1.82 (0.40 to 8.92)	1.11 (0.34 to 3.42)	2.08 (0.58 to 7.50)	1.03 (0.34 to 2.86)

*Updated analysis provided in response to clarification question A22

NMA estimates are median posterior estimates and 95% CrIs.

Abbreviations: AE, adverse event; CS, company submission; CrI, credible interval; NMA, network meta-analysis; OR, odds ratio

4.4.5.2 Week 52

The results of the safety NMAs at Week 12 are presented in Table 20. The EAG notes that:

- There was a greater incidence of any AEs for vibegron 75 mg compared to mirabegron 50 mg (OR 1.59, 95% CrI: 1.06 to 2.39) and the 95% CrIs did not cross 1; and
- For the other comparisons of serious AEs, AEs leading to treatment discontinuation and specific AE rates, the overall event rates were low in both EMPOWUR and TAURUS across the 52 Week follow up period. For each outcome, the point estimate of the odds ratios were close to 1, with the possible exception of AEs leading to study treatment discontinuation, where the OR numerically favoured vibegron 75 mg (OR 0.38, 95% CrI: 0.09 to 1.33).

Table 20. Summary of the results of the company safety NMAs at Week 52 comparing vibegron 75 mg and mirabegron 50 mg. Reproduced from CS Figures 26 and 28

Week 52 AE outcome	Incidence in EMPOWUR-extension (52+4 weeks)		NMA comparator OR (95% Credible Interval)	
	vibegron 75 mg	tolterodine 4 mg	mirabegron 25 mg	mirabegron 50 mg
Any AE	171 (62.6)	126 (54.3)	-	1.59 (1.06 to 2.39)
Any serious AE	9 (3.3)	10 (4.3)	-	0.79 (0.28 to 2.23)
Any AE leading to study treatment discontinuation	4 (1.5)	8 (3.4)	-	0.38 (0.09 to 1.33)
Headache	15 (5.5)	9 (3.9)	-	0.87 (0.31 to 2.46)
Hypertension	24 (8.8)	20 (8.6)	-	1.07 (0.53 to 2.21)
Urinary tract infection	18 (6.6)	17 (7.3)	-	0.98 (0.45 to 1.79)
Dry mouth	5 (1.8)	12 (5.2)	-	1.07 (0.30 to 3.34)
Constipation	10 (3.7)	6 (2.6)	-	1.40 (0.42 to 4.96)

Abbreviations: AE, adverse event; CS, company submission; CrI, credible interval; NMA, network meta-analysis; OR, odds ratio

NMA estimates are median posterior estimates of the odds ratio and 95% CrIs

4.4.6 EAG comment

At both Week 12 and Week 52, the adverse event profile of vibegron 75 mg, mirabegron 50 mg and mirabegron 25 mg (data available for Week 12 only) are similar. In particular:

- The frequency of dry mouth and constipation, the adverse events included in the cost-effectiveness model of mirabegron (TA290),[2] were low and similar between vibegron 75 mg, mirabegron 50 mg and mirabegron 25 mg (OR point estimates and 95% CrIs ranged from 0.74 [0.20 to 2.72] to 2.08 [0.58 to 7.50], with wide 95% CrIs that cross 1);

- The frequency of serious AEs, i.e., those most likely to incur meaningful costs, were low and similar between vibegron 75 mg, mirabegron 50 mg and mirabegron 25 mg (OR point estimates ranged from 1.03 [0.25 to 4.56] to 1.10 [0.20 to 5.69], with wide CrIs);

The rates of any AEs were numerically higher for vibegron 75 mg than mirabegron 25 mg (primary NMA Week 12 OR 1.44, 95% CrI: 0.85 to 2.49; sensitivity NMA Week 12 OR 1.36, 95% CrI: 0.81 to 2.23) and mirabegron 50 mg (primary NMA Week 12 OR 1.43, 95% CrI: 0.90 to 2.32; sensitivity NMA Week 12 OR 1.35, 95% CrI: 0.85 to 2.13; Week 52 NMA OR: CrI: 1.06 to 2.39) and the 95% CrIs did not cross 1 for the comparison with mirabegron 50 mg at Week 52. However, the EAG notes that:

- In the absence of specific increases in serious AEs or AEs included in the cost-effectiveness model of TA290, it is unclear if there would be any meaningful costs associated with an increase in any AEs of any severity on vibegron; and
- The EAG's clinical experts noted that some of the individual AEs that were elevated for vibegron 75 mg relative to tolterodine 4 mg or placebo in EMPOWUR may be unlikely to be related to vibegron treatment, raising the possibility that sampling variance is a contributing factor to the larger ORs for vibegron compared to mirabegron in the any AE safety NMAs.

4.4.7 Treatment discontinuation

4.4.7.1 Week 12

The company presented the disposition of participants across RCTs including a vibegron arm in Appendix D1.2, and also presented data from the active arms (mirabegron and tolterodine arms) of RCTs included in the company's NMAs in response to clarification question A4. To this, the EAG has also extracted the relevant data from the placebo arm of each trial. Table 21 presented the percentage of participants who had discontinued by arm for each trial included in the NMA at Week 12. At Week 12 in EMPOWUR, all-cause discontinuation was 8.2% for vibegron 75 mg, 10.0% for placebo and 10.7% for tolterodine 4 mg.

Table 21. The percentage of participants who had discontinued treatment by arm for each trial included in the company's NMAs at Week 12

Arm	Percentage all-cause discontinuation, Week 12								
	Staskin 2020	Nitti 2013	Herschorn 2013	Kuo 2015	Khullar 2013	Yamaguchi 2014	Herschorn 2017	Chapple 2013 (Phase 2	Yamaguchi 2015 (Phase 2)
Vibegron 75 mg	8.2	-	-	-	-	-	-	-	-

Placebo	10.0	15.2	15.2	20.4	8.9	8.1	9.6	7.1	7.5
Mirabegron 50 mg	-	13.3	12.3	16.4	11.5	8.2	11.4	9.5	5.2
Mirabegron 25 mg	-	-	10.6	-	-	-	10.0	9.5	6.3
Tolterodine ER 4 mg	10.7	-	-	17.8	10.1	6.1	-	3.5	-

Data from TAURUS not reported, as TAURUS did not report discontinuation at Week 12

Abbreviations: ER, extended release; mg, milligram; NMA, network meta-analysis

In response to clarification question A20, the company performed an NMA of all-cause discontinuation at Week 12, using both the company's primary network and a sensitivity analysis network which included the two Phase 2 trials of mirabegron. In each of these networks, vibegron 75 mg was associated with a numerically lower odds of discontinuation by Week 12 than mirabegron 25 mg (OR primary analysis: 0.92 [0.51 to 1.63]; OR sensitivity analysis: 0.86 [0.50 to 1.44]) and mirabegron 50 mg (OR primary analysis: 0.78 [0.46 to 1.29]; OR sensitivity analysis: 0.77 [0.47 to 1.22]; Table 22).

Table 22. Results of the primary and sensitivity NMAs of all-cause discontinuation at Week 12 for vibegron 75 mg compared to mirabegron 25 mg and mirabegron 50 mg. Reproduced from company response to clarification A20 Table 3 and Table 5.

All-cause discontinuation NMAs, Week 12 OR (95% CrI)	Primary NMA	NMA sensitivity analysis
mirabegron 25 mg	0.92 (0.51 to 1.63)	0.86 (0.50 to 1.44)
mirabegron 50 mg	0.78 (0.46 to 1.29)	0.77 (0.47 to 1.22)

Abbreviations: ER, extended release; mg, milligram; NMA, network meta-analysis; OR, odds ratio

4.4.7.2 Week 52

At Week 52, the EAG notes comparing the rate of all-cause discontinuation between EMPOWUR extension and TAURUS is difficult to interpret because of differences in the study designs:

- The EMPOWUR extension study recruited participants who had completed 12 weeks of the EMPOWUR study, and therefore discontinuations with EMPOWUR extension exclude the first 12 weeks of treatment; and

- TAURUS was a 52-week study, but participants who had already completed Phase 3 trials of mirabegron were eligible to participate. Thus, it is potentially unlikely that participants who discontinued treatment within the original Phase 3 trials would be likely to enrol in TAURUS.

Nevertheless, the EAG presents the rates of discontinuation by Week 52 for EMPOWUR extension and TAURUS in Table 23.

Table 23. The percentage of participants who had discontinued treatment by arm in EMPOWUR extension and TAURUS at Week 52

	Percentage all-cause discontinuation		
Arm	**EMPOWUR extension (vibegron and tolterodine continuers after Week 12)**	**EMPOWUR extension (placebo participants re-randomised at Week 12)**	**TAURUS**
Time period	**Week 12 to Week 52**		**Baseline to Week 52**
Vibegron 75 mg	14.3% (N at Week 12 = 182)	14.1% (N at Week 12 = 92)	-
Mirabegron 50 mg	-	-	22.8% (N randomised = 815)
Tolterodine ER 4 mg	12.8% (N at Week 12 = 141)	20.9% (N at Week 12 = 91)	23.6% (N randomised = 813)

Abbreviations: ER, extended release; mg, milligram

4.4.8 EAG comment

The EAG considers the Week 12 all-cause discontinuation NMAs to provide evidence of a similar rate of discontinuation between vibegron 75 mg and mirabegron 25 mg or mirabegron 50 mg. The EAG notes the point estimates favour vibegron 75 mg, but that the 95% CrIs are wide and cross 1. The EAG considers a similar rate of discontinuation to be consistent with vibegron 75 mg being non-inferior to mirabegron 25 mg and mirabegron 50 mg in terms of clinical effectiveness, and there being a similar AE profile of vibegron 75 mg and mirabegron 25 mg and 50 mg.

The EAG notes, however, that there are no robust long-term comparative data concerning the discontinuation rate of vibegron 75 mg and mirabegron 25 mg and mirabegron 50 mg. Differences in the study design and participant recruitment of the EMPOWUR extension study and TAURUS precluded a formal indirect comparison between vibegron 75 mg and mirabegron 50 mg at 52 weeks, and TAURUS did not have a mirabegron 25 mg arm. As such, the EAG considers there to be

remaining uncertainty concerning the long-term rate of continuation between vibegron 75 mg, mirabegron 50 mg and mirabegron 25 mg.

4.5 Summary and conclusions of clinical effectiveness

The company has submitted evidence in support of the clinical similarity of vibegron 75 mg, mirabegron 50 mg and mirabegron 25 mg for treating symptoms of OAB. Both vibegron and mirabegron are selective β3-AR agonists that increase bladder capacity by relaxing the detrusor smooth muscle during bladder filling, and the EAG agrees that mirabegron 25 mg and mirabegron 50 mg are appropriate comparators for a CCA with vibegron 75 mg.

The key clinical evidence of the efficacy of vibegron 75 mg come from the 12-week EMPOWUR RCT and 52-week EMPOWUR extension study. The EAG considered EMPOWUR and EMPOWUR extension to be high-quality double blind RCTs but noted that the proportion of participants with prior anticholinergic drug use (14.6%) was substantially lower than would be expected in in the population vibegron 75 mg is being positioned: people with OAB in whom antimuscarinic drugs are contraindicated, clinically ineffective, or have unacceptable side effects. Mirabegron 50 mg and mirabegron 25 mg were recommended in this population in TA290.

The key outcomes in the economic model of TA290 were:

- Changes in daily micturition frequency;
- Changes in total incontinence episode frequency;
- Incidence of dry mouth;
- Incidence of constipation; and
- Health-related quality of life (EQ-5D) sourced from external sources.

The company presented evidence from EMPOWUR for each of these outcomes, and several supportive outcomes. Of note, the company focused on UUI episode frequency in addition to total incontinence episodes. For people with OAB, UUI episodes comprise a large subset of total incontinence episodes, and the EAG agrees UUI episodes are a more relevant outcome than total incontinence episodes for treatments of OAB.

The EAG consider the EMPOWUR RCT and extension study to provide:

- Over 12 weeks, good evidence of the superiority of vibegron 75 mg over placebo in reducing daily micturitions, total incontinence episodes and UUI episodes; and
- Over 52-weeks, good evidence of a maintained treatment response to vibegron 75 mg, and a similar treatment response to tolterodine ER 4 mg, albeit one that numerically favoured vibegron 75 mg.

Currently, there is no head-to-head trial between vibegron 75 mg and mirabegron 50 mg or mirabegron 25 mg. To address this, the company conducted NMAs. In the company's primary network at Week 12, seven high-quality Phase 3 or Phase 4 RCTs of mirabegron were included alongside EMPOWUR. In an EAG requested sensitivity analysis, one study (TAURUS) was removed from the network and two Phase 2 RCTs were included. At Week 12, both the company's primary NMA and the EAG's requested sensitivity analysis provided evidence for the following outcomes:

- Changes in micturition frequency: Evidence of the similarity and non-inferiority of vibegron 75 mg compared to mirabegron 25 mg and mirabegron 50 mg, with the lower bound of the 95% CrIs excluding both the company's inferred MCIDs and the MCIDs estimated by the EAG's clinical experts;
- Changes in UUI episodes and total incontinence episodes: Evidence of the non-inferiority of vibegron 75 mg compared to mirabegron 25 mg and mirabegron 50 mg, with all point estimates favouring vibegron 75 mg and the lower bound of the 95% CrIs excluding both the company's inferred MCIDs and the MCIDs estimated by the EAG's clinical experts;
- AE profile: Evidence of a similar AE profile between vibegron 75 mg, mirabegron 50 mg and mirabegron 25 mg. The EAG notes that the event rates of specific AEs, such as dry mouth and constipation, and serious AEs, were low across all studies. As such, the point estimates of the calculated odds ratios have with wide 95 CrIs; and
- All-cause discontinuation: Evidence of a similar rate of discontinuation between vibegron 75 mg, mirabegron 50 mg and mirabegron 25 mg, with point estimates favouring vibegron 75 mg.

At Week 52, only a comparison between vibegron 75 mg (EMPOWUR extension) and mirabegron 50 mg (TAURUS) was possible, i.e., there were no comparisons between vibegron 75 mg and mirabegron 25 mg. At Week 52 the indirect comparison provided:

- Changes in micturition frequency: Evidence of the similarity and non-inferiority of vibegron 75 mg compared to mirabegron 50 mg, with the lower bound of the 95% CrIs excluding both the company's inferred MCID and the MCID estimated by the EAG's clinical experts;
- Changes in UUI episodes and total incontinence episodes: Evidence of the superiority of vibegron 75 mg compared to mirabegron 50 mg, with all point estimates favouring vibegron 75 mg and the lower bound of the 95% CrIs excluding 0;
- AE profile: Evidence of a higher overall AE rate for vibegron 75 mg than mirabegron 50 mg, but a similar AE profile for dry mouth, constipation and serious AEs, i.e., the AEs included in the economic model of TA290 or those likely to incur substantial cost;
- All-cause discontinuation: No formal comparisons were feasible due to differences in the study design of the EMPOWUR extension study and TAURUS.

A summary of the NMA results between vibegron 75 mg, mirabegron 50 mg and mirabegron 25 mg is presented in Table 24. Table 24 includes the outcomes included in the TA290 economic model, as well as additional outcomes highlighted by the EAG in the Assessment Report.

Table 24. Summary of the NMA results between vibegron 75 mg, mirabegron 50 mg and mirabegron 25 mg for the outcomes included in the TA290 economic model and additional outcomes highlighted by the EAG.

Outcome	Primary NMA		NMA sensitivity analysis (excluding TAURUS, including Phase 2 trials)	
	mirabegron 25 mg	**mirabegron 50 mg**	**mirabegron 25 mg**	**mirabegron 50 mg**
Week 12 NMA				
Outcomes informing economic model of TA290				
Change from baseline in daily number of micturitions	–0.03 (–0.65 to 0.61)	0.01 (–0.53 to 0.58)	0.01 (–0.44 to 0.46)	0.11 (–0.31 to 0.53)
Change from baseline in daily number of incontinence episodes	–0.27 (–0.73 to 0.17)	–0.24 (–0.66 to 0.16)	–0.15 (–0.58 to 0.27)	–0.18 (–0.59 to 0.22)
Dry mouth, OR	0.84 (0.19 to 3.96)	1.10 (0.32 to 4.05)	0.74 (0.20 to 2.72)	1.02 (0.31 to 3.35)
Constipation, OR	1.82 (0.40 to 8.92)	1.11 (0.34 to 3.42)	2.08 (0.58 to 7.50)	1.03 (0.34 to 2.86)
All-cause discontinuation, OR	0.92 (0.51 to 1.63)	0.78 (0.46 to 1.29)	0.86 (0.50 to 1.44)	0.77 (0.47 to 1.22)
Other outcomes highlighted by EAG				
Change from baseline in daily number of UUI episodes	–0.27 (–0.66 to 0.13)	–0.22 (–0.59 to 0.14)	–0.16 (–0.54 to 0.23)	–0.17 (–0.53 to 0.2)
Any AE, OR	1.44 (0.85 to 2.48)	1.43 (0.90 to 2.32)	1.36 (0.81 to 2.23)	1.35 (0.85 to 2.13)
Any serious AE, OR	1.10 (0.20 to 5.69)	1.05 (0.24 to 4.53)	1.09 (0.21 to 5.64)	1.03 (0.25 to 4.56)
Week 52 NMA				
Outcomes informing TA290 economic model				
Change from baseline in daily number of micturitions	-	–0.60 (–1.31 to 0.12)	-	-

Change from baseline in daily number of incontinence episodes	-	–0.82 (–1.38 to –0.26)	-	-
Dry mouth, OR	-	1.07 (0.30 to 3.34)	-	-
Constipation, OR	-	1.40 (0.42 to 4.96)	-	-
All-cause discontinuation	-	NA	-	-
Other outcomes highlighted by EAG				
Change from baseline in daily number of UUI episodes	-	–0.62 (–1.13 to –0.10)	-	-
Any AE, OR	-	1.59 (1.06 to 2.39)	-	-
Any serious AE, OR	-	0.79 (0.28 to 2.23)	-	-

NMA estimates are median posterior estimates and 95% CrIs

Abbreviations: AE, adverse event; CS, company submission; CrI, credible interval; NMA, network meta-analysis; OR, odds ratio

Limited data were available in EMPOWUR to detect subgroup effects of either sex or prior treatment experience, however the EAG notes that:

- The EAG's clinical experts did not expect the treatment effects of mirabegron or vibegron to differ between prior treatment experience subgroups, or between men and women providing other causes of urinary incontinence were adequately treated in men.

Men and women

In EMPOWUR, 14.8% of participants were male**:**

- The point estimate for the placebo-adjusted difference was similar between males (–0.6, 95% CI: –1.4 to 0.1) and females (–0.5, 95% CI –0.8 to –0.2). For the change in daily episodes of UUI, the placebo-adjusted point estimate for males (–0.1, 95% CI: –0.9 to 0.8) was numerically smaller than for females (–0.7, 95% CI: –1.0 to –0.4);
- In a large sample Phase 3 RCT of vibegron 75 mg versus placebo in men with OAB symptoms who were receiving therapy for benign prostatic hyperplasia, a vibegron 75 mg treatment effect was reported that was consistent with the EMPOWUR FAS and FAS-I analyses, independent of sex.

Prior treatment exposure

In EMPOWUR, 14.6% of participants reported prior anticholinergic use:

- The placebo adjusted point estimates for the change from baseline in daily micturition and UUI episodes in the prior anticholinergic subgroup (micturitions: –0.7, UUI episodes: –0.7) were similar but numerically greater than the no prior anticholinergic subgroup (micturitions: –0.4, UUI episodes: –0.5);
- As EMPOWUR participants had the lowest rate of treatment experience in the network, where this was reported, any bias in the efficacy NMAs resulting from imbalances in prior treatment experience is likely to be small in magnitude and conservative.

Hence, the EAG considers it uncertain whether there are clinically meaningful subgroup effects for vibegron or mirabegron for treating OAB, but does not consider there to be: i) evidence of large subgroup effects; or ii) evidence that any subgroup effects have introduced substantial bias into the NMAs.

Overall, the EAG consider that:

- Vibegron and mirabegron have similar mechanisms of action for treating symptoms of OAB;
- The clinical evidence provided by the company is consistent with vibegron 75 mg being similarly effective or more effective as mirabegron 50 mg and mirabegron 25 mg at:
    - Reducing micturition frequency;
    - Reducing total incontinence episodes; and
    - Reducing UUI episodes.
- The AE profile of vibegron 75 mg appears similar to mirabegron 50 mg and mirabegron 25 mg in terms of serious AEs, and the AEs included in TA290 – dry mouth and constipation. However, there is some evidence that the overall AE rate may be higher for vibegron 75 mg than mirabegron 50 mg based on the indirect comparison at Week 52; and
- At Week 12, the observed rate of discontinuation is similar between vibegron 75 mg, mirabegron 50 mg and mirabegron 25 mg, with point estimates favouring vibegron 75 mg.

The EAG notes the following outstanding uncertainties, but considers these to be minor and not to preclude a conclusion of clinical similarity between vibegron 75 mg, mirabegron 50 mg and mirabegron 25 mg:

- The low rate of prior anticholinergic use (14.6%) in EMPOWUR limits the representativeness of the trial population to the population vibegron is being positioned for: people with OAB in whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects;
- There are limited subgroup data available for those who are treatment experienced or who are male;
- No formal comparison of discontinuation at Week 52 was possible between vibegron 75 mg and mirabegron 50 mg;
- No comparisons were possible at Week 52 between vibegron 75 mg and mirabegron 25 mg due to a lack of data for mirabegron 25 mg;
- In the indirect comparison at Week 52, vibegron 75 mg had a higher rate of any AEs compared to mirabegron 50 mg, with the 95% CrI of the OR not crossing 1. However, the rates of serious AEs, i.e., those most likely to incur cost, and the AEs included in TA290, dry mouth and constipation, were similar between vibegron 75 mg and mirabegron 50 mg.

5 Summary of the EAG's critique of cost comparison evidence submitted

For the purposes of the cost-comparison analysis, the company has only considered one-year drug acquisition costs for vibegron and mirabegron. In addition to the primary assumption of clinical similarity between vibegron and mirabegron, the other key assumptions that underpin the company's approach are as follows:

- Vibegron and mirabegron are oral drugs and thus do not incur administration costs.
- There are no treatment stopping rules for either vibegron or mirabegron.
- Treatment discontinuation is likely to be similar for both drugs based on the indirect treatment comparison (ITC) of treatment discontinuation data from key trials, discussed in Section 4.4.7.
- Adherence to treatment is likely to be similar for both drugs based on the assumption of similar effectiveness.
- The safety profile of both drugs is comparable based on the indirect treatment comparisons (ITCs) presented in Section 4.4.5.
- Monitoring of patients is likely to be similar irrespective of whether a patient is on vibegron or mirabegron.
- Once a patient discontinues treatment with either drug, the next line of treatment is the same (as presented in Figure 4 of the company submission).

Based on the assumptions outlined above, the company considered that there will be no other cost differences between vibegron and mirabegron except in the acquisition costs of the two drugs.

The proposed list price of vibegron is [redacted] per pack of 30 x 75 mg tablets. The dose of vibegron is 75 mg taken orally once daily.

The list price of mirabegron is £29.00 per pack of 30 tablets (25 mg or 50 mg).[45] The dose of mirabegron is 50 mg taken orally once daily. The summary of product characteristics (SmPC) for mirabegron states that dose should be adjusted to 25 mg for patients with severe renal impairment, moderate hepatic impairment and patients on CYP3A inhibitors.[9] However, given the price of mirabegron is the same irrespective of dose, this does not impact on total drug acquisition costs. Special populations for mirabegron are discussed in Section 3.3.

The total annual drug acquisition costs for vibegron and mirabegron, which are the company's base results, is presented in Table 25.

Table 25. Drug acquisition costs (company base case)

Treatment	Annual drug acquisition cost	Incremental cost
Mirabegron	£353.08	-
Vibegron	[redacted]	[redacted]

5.1 EAG critique

The External Assessment Group (EAG's) considers that the assumptions underpinning the company's cost-comparison analysis are generally appropriate. The EAG's clinical experts highlighted that mirabegron potentially requires additional blood pressure monitoring, and dose adjustments are required for patients with renal or hepatic impairment. Therefore, patients taking mirabegron might require additional monitoring compared with patients on vibegron.

Conversely, vibegron is currently a black triangle drug and therefore clinicians prescribing the drug may want to monitor patients more closely until the black triangle is removed. However, the EAG notes that in their clarification response, the company explained that vibegron was not classified with a black triangle because of specific identified safety issues, but because vibegron is considered as a medicinal product containing a new active substance. Additionally, there was consensus among the EAG's clinical experts that generally monitoring is likely to be less with vibegron. As such, the EAG considers that the company's assumption of similar monitoring costs is likely to be conservative but overall appropriate.

5.2 Summary statement

The EAG considers that the assumption of clinical similarity between vibegron and mirabegron is appropriate. Therefore, all else being equal, the EAG considers that vibegron is likely to be cost-saving compared with mirabegron.

6 Equalities and innovation

The company has not described any equalities or innovation considerations associated with vibegron in the company submission. Additionally, the External Assessment Group (EAG) is unaware of any equality or innovation considerations.

7 EAG commentary of the robustness of the evidence submitted by the company

The External Assessment Group (EAG) believes none of the issues below would preclude a cost-comparison approach from being appropriate but highlights them as limitations or factors to be aware of.

Clinical

The EAG considers the company has provided evidence of the clinical similarity of vibegron 75 mg, mirabegron 50 mg and mirabegron 25 mg. The results of the indirect comparisons suggests that vibegron is: i) similarly effective and at least non-inferior at reducing the number of daily micturitions compared to mirabegron 50 mg and mirabegron 25 mg; and ii) similarly effective and potentially superior at reducing the number of UUI episodes and total incontinence episodes. However, the following clinical issues remain:

- Whether there are long-term differences, i.e., after Week 12, in treatment discontinuation between vibegron 75 mg and mirabegron 50 mg is uncertain;
- Whether there are long-term differences, i.e., after Week 12, in treatment effectiveness, discontinuation and adverse events between vibegron 75 and mirabegron 25 mg is uncertain;
- Whether the observed higher rate of any AEs for vibegron 75 mg compared to mirabegron 50 mg in the Week 52 NMA is a robust effect is uncertain. The EAG further notes that the rates of serious AEs, i.e., those most likely to incur cost, and the AEs included in TA290, dry mouth and constipation, were similar between vibegron 75 mg and mirabegron 50 mg.

Economic

The EAG considers the company has likely been conservative in their approach to the cost-comparison analysis. Notably, the EAG's clinical experts highlighted that monitoring costs may be lower for vibegron compared with mirabegron. Therefore, under the company's assumptions of all else being equal, the EAG considers that vibegron is likely to be cost-saving compared with mirabegron.

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9 Appendices

9.1 EMPOWUR extension study baseline characteristics

Table 26. EMPOWUR extension study baseline characteristics. Safety Analysis Set. Reproduced from CSR Table 14.1.3.1.1

Variable	40-weeks Vibegron 75mg (N=92) n (%)	52-weeks Vibegron 75mg (N=181) n (%)	Overall Vibegron 75mg (N=273) n (%)	40-weeks Tolterodine ER 4mg (N=91) n (%)	52-weeks Tolterodine ER 4mg (N=141) n (%)	Overall Tolterodine ER 4mg (N=232) n (%)	Overall (N=505) n (%)
Age at study entry (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age category (years), n (%)							
< 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 40 to < 55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 55 to < 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 65 to < 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)							
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Benign prostate hyperplasia (male only), n (%), yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline hypertension, n (%), yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-existing hypertension, n (%), yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OAB type, n (%)							
Wet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Dry	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior anticholinergic use, n (%), yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior beta-3 agonist use, n (%), yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race							
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: CSR, clinical study report; mg, milligrams; OAB, overactive bladder							

Table 27. EMPOWUR extension study baseline OAB severity. Full Analysis Set Extension. Reproduced from CSR Table 14.1.3.2.2

Variable	40-weeks Vibegron 75mg (N=90)	52-weeks Vibegron 75mg (N=176)	Overall Vibegron 75mg (N=266)	40-weeks Tolterodine ER 4mg (N=83)	52-weeks Tolterodine ER 4mg (N=136)	Overall Tolterodine ER 4mg (N=219)
Micturitions						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UUI Episodes						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urgency Episodes						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Incontinence Episodes						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Volume Voided per Micturition (mL)						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CSR, clinical study report; mg, milligrams; mL, millilitre; OAB, overactive bladder; UUI, urge urinary incontinence.

Table 28. EMPOWUR extension study baseline OAB severity. Full Analysis Set Extension for Incontinence. Reproduced from CSR Table 14.1.3.2.3

Variable	40-weeks Vibegron 75mg (N=69)	52-weeks Vibegron 75mg (N=143)	Overall Vibegron 75mg (N=212)	40-weeks Tolterodine ER 4mg (N=64)	52-weeks Tolterodine ER 4mg (N=106)	Overall Tolterodine ER 4mg (N=170)
Micturitions						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UUI Episodes						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urgency Episodes						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Volume Voided per Micturition (mL)						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CSR, clinical study report; mg, milligrams; mL, millilitre; OAB, overactive bladder; UUI, urge urinary incontinence.

9.2 Efficacy NMA fixed effect model results

Table 29. Company fixed effect NMA results comparing vibegron 75 mg and comparators at Week 12 for daily number of micturitions, daily number of UUI episodes and daily number of incontinence episodes. Reproduced from R data files provided by company at clarification.

Week 12: Fixed effect models	vibegron 75 mg		
Comparator	**Daily number of micturitions**	**Daily number of UUI episodes**	**Daily number of incontinence episodes**
mirabegron 25 mg	–0.06 (–0.47 to 0.34)	–0.26 (–0.63 to 0.10)	–0.28 (–0.69 to 0.14)
mirabegron 50 mg	–0.03 (–0.39 to 0.33)	–0.22 (–0.55 to 0.11)	–0.25 (–0.63 to 0.13)
placebo	–0.52 (–0.87 to –0.17)	–0.58 (–0.90 to –0.25)	–0.64 (–1.01 to –0.27)
tolterodine 4 mg	–0.18 (–0.53 to 0.17)	–0.23 (–0.56 to 0.10)	–0.37 (–0.75 to 0.00)

Abbreviations: CSR, clinical study report; mg, milligrams; OAB, overactive bladder; UUI, urge urinary incontinence.

9.3 Safety NMA fixed effect model results

Table 30. Comparison between the company random effects and fixed-effect NMA results comparing vibegron 75 mg and comparators at Week 12 for various safety outcomes. Reproduced from R data files provided by company at clarification.

			NMA comparator OR, (95% Credible Interval)					
Week 12 AE outcome	AE incidence in EMPOWUR (12+4 weeks)		Primary NMA – random effects			Primary NMA – fixed effect		
	placebo	vibegron 75 mg	mirabegron 25 mg	mirabegron 50 mg	DIC	mirabegron 25 mg	mirabegron 50 mg	DIC
Any AE	33.3%	38.7%	1.44 (0.85 to 2.48)	1.43 (0.90 to 2.32)	28.53	1.43 (1.07 to 1.89)	1.42 (1.10 to 1.82)	28.95
Any serious AE*	1.1%	1.5%	1.10 (0.20 to 5.69)	1.05 (0.24 to 4.53)	NA	NA	NA	NA
Any AE leading to study treatment discontinuation	1.1%	1.7%	0.81 (0.26 to 2.57)	0.74 (0.27 to 2.00)	31.02	0.80 (0.29 to 2.01)	0.73 (0.30 to 1.69)	29.38
Headache	2.4%	4.0%	3.01 (0.27 to 34.92)	1.68 (0.24 to 12.02)	23.04	3.07 (1.15 to 8.67)	1.68 (0.81 to 3.50)	19.58
Hypertension	1.7%	1.7%	0.79 (0.16 to 4.59)	0.93 (0.23 to 4.12)	31.08	0.76 (0.29 to 1.82)	0.90 (0.37 to 2.06)	30.08
Urinary tract infection	6.1%	5.0%	0.74 (0.21 to 2.75)	0.73 (0.23 to 2.46)	24.83	0.73 (0.37 to 1.46)	0.72 (0.38 to 1.35)	23.77
Dry mouth	0.9%	1.7%	0.84 (0.19 to 3.96)	1.10 (0.32 to 4.05)	37.24	0.74 (0.28 to 1.86)	0.96 (0.40 to 2.10)	41.62
Constipation	1.3%	1.7%	1.82 (0.40 to 8.92)	1.11 (0.34 to 3.42)	21.33	1.81 (0.49 to 6.99)	1.09 (0.41 to 2.82)	19.23

*Updated analysis provided in response to clarification question A22

NMA estimates are median posterior estimates and 95% CrIs.

Abbreviations: AE, adverse event; CS, company submission; CrI, credible interval; NMA, network meta-analysis; OR, odds ratio