Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for mirabegron

Proprietary Product Name: Betmiga

Sponsor: Astellas Pharma Australia Pty Ltd

Date of first round CER: 7 February 2013
Date of second round CER: 9 April 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
AR	Adrenoceptor
AUR	Acute urinary retention
BCS	Biopharmaceutical Classification System
BMI	Body mass index
BOO	Bladder outlet obstruction
bpm	Beats per minute
cAMP	Cyclic adenosine 3', 5'-monophosphate
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council of International Organizations of Medical Sciences
CL	Total body clearance
CLcr	Creatinine clearance
CLR	Renal clearance

Abbreviation	Meaning
CNS	Central nervous system
CSR	Clinical study report
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
ddQTcI	Difference in baseline-adjusted QTcI from placebo
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
Emax	Maximum effect
ER	Extended release
EU/NA	Europe, North America and Australia
FAS	Full analysis set
FAS-I	Full analysis set-incontinence
GCP	Good Clinical Practice
HRQL	Health-related quality of life
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IOP	Intraocular pressure
IR	Immediate release
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
ITT-I	Intent-to-treat-incontinence
LOCF	Last observation carried forward
LUTS	Lower urinary tract symptoms
MAA	Marketing Authorization Application

Abbreviation	Meaning
MDRD	Modification of diet in renal disease
MRHD	Maximum recommended human dose (50mg mirabegron daily)
NDA	New Drug Application
NSA	National Scientific Advice
OAB	Overactive bladder
OCAS	Oral controlled absorption system
OCAS-M	Oral controlled absorption system with an intermediate dissolution rate
OCT	Organic cation transporters
PCS	Potential clinically significant
PD	Pharmacodynamic
PDCO	Paediatric Committee
P-gp	P-glycoprotein
PIP	Pediatric Investigation Plan
PK	Pharmacokinetic
PPBC	Patient perception of bladder condition
PPIUS	Patient perception of intensity of urgency scale
PPS	Per protocol set
PPS-I	Per protocol set-incontinence
PT	Preferred term
PVR	Postvoid residual
PYE	Patient-years of exposure
QTc	Corrected QT interval
QTcF	Corrected QT interval by Fridericia's formula
QTcI	Individually corrected QT interval
SAE	Serious adverse event

Abbreviation	Meaning
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SPA	Special protocol assessment
TEAE	Treatment-emergent adverse event
TEN	Toxic epidermal necrolysis
TQT	Thorough QT
TS-VAS	Treatment satisfaction – visual analog scale
UGT	Uridine diphospho-glucuronosyltransferase
US	United States
UTI	Urinary tract infection

1. Introduction

Mirabegron is a selective agonist for human beta 3-adrenoceptor (beta-3 adrenergic receptors, beta 3-AR) that is indicated for the treatment of Overactive Bladder (OAB).

Mirabegron is a new chemical entity, a first-in-class compound with a different mechanism of action than the current agents used to treat OAB.

The proposed indication is:

"Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in patients with overactive bladder (OAB) syndrome."

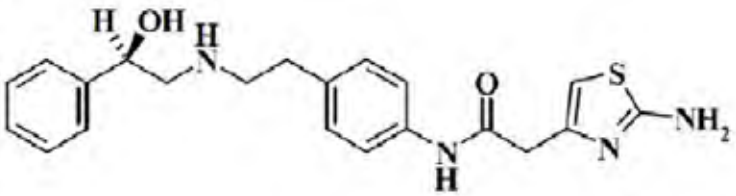
The *standard* recommended dose for mirabegron is one 50mg tablet once daily, with or without food.

In patients with severe renal or moderate hepatic impairment, the recommended dose is one 25mg tablet once daily.

Figure 1. Structure of mirabegron

Active ingredient: mirabegron

Chemical structure:



Chemical name: 2-(2-amino-1,3-thiazol-4-yl)-*N*-[4-(2-{[(2*R*)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide

2. Clinical rationale

The urinary bladder has two main roles: the storage of urine produced by the kidneys, and the release of that stored urine during voluntary voiding at a convenient time. The neurophysiological control of these two opposing functions is complex. At the simplest level, voiding is triggered by a stretch reflex initiated in the bladder wall, leading to relaxation of the urinary sphincter and contraction of the main bladder muscle, the detrusor. In a normal toilet-trained subject, this reflex is inhibited by higher centres, so that the subject experiences a desire to void but can post-pone the void, often for prolonged periods. In a variety of conditions, including cerebral and spinal cord disease, bladder damage, or more subtle idiopathic disturbances, the balance between storage and voiding, and the central inhibition of the stretch reflex, can be disturbed. A common syndrome of bladder dysfunction is over-active bladder (OAB), in which subjects have the urge to void at relatively low bladder volumes, have difficulty postponing voiding, may be excessively aware of the need to void, or may lose urine involuntarily because of active detrusor contraction. A hallmark of this syndrome is *urgency*, in which patients experience a rapid escalation from initial awareness of bladder fullness to a strong desire to void, have difficulty postponing voiding, and may be incontinent if they do not get to a toilet in time.

The main two arms of the autonomic nervous system, the parasympathetic and sympathetic systems, exert opposing influences on bladder function. Contractions of the detrusor are enhanced by parasympathetic activity, mediated by muscarinic acetylcholine receptors, and traditional approaches to OAB have involved the use of antimuscarinic (anticholinergic) agents. Problems with such agents include lack of efficacy, constipation, dry eyes, dry mouth, and sedation. Many patients abandon antimuscarinic therapy because of these side effects, or because efficacy is inadequate. Others continue antimuscarinic agents but suffer continued symptoms of OAB. These symptoms may include urinary frequency, urgency, incontinence, social isolation and low self esteem. Many patients can only avoid incontinence by planning each trip around the location of toilets, or by frequent pre-emptive voiding.

Mirabegron is a new agent that works by stimulating a subclass of sympathetic receptors in the bladder, the beta-3 adrenergic receptors (beta-3 AR). Whereas stimulation of muscarinic receptors facilitates detrusor contraction, activation of beta-ARs in the bladder's triangular base (the trigone) facilitates urine storage by flattening and lengthening the bladder base (Yamanishi et al, 2003). The dominant beta-AR subtype in the human detrusor muscle is beta 3-AR, and activation of beta 3-ARs has been shown to promote urine storage in the bladder (Kumar et al, 2003; Yamaguchi, 2002).

A range of animal studies have supported the idea that a beta-3 AR agonist might be useful in promoting urine storage. Using the beta 3-AR agonists FK175 and CL-316243, it has been shown that activation of beta 3-ARs promoted urine storage in rats by increasing bladder capacity (Fujimura et al, 1999; Takeda et al, 2000). Also, CL-316243 increased urinary bladder capacity in OAB models in rats (Woods et al, 2001; Takeda, Yamazaki, Igawa et al, 2002; Leon et al, 2008), leading some authors to propose use of beta 3-AR agonists as bladder relaxant drugs for treatment of OAB (Yamaguchi, 2002).

The sponsor reports that preclinical work with mirabegron showed it to be a selective beta 3-AR agonist, although the evidence for this is beyond the scope of this clinical evaluation report. Mirabegron reportedly showed selective agonistic activity and high affinity for human beta 3- as compared with beta 1- and beta 2-ARs, and it had little affinity for a wide panel of other receptors, ion channels, and transporters. It did not have any inhibitory effects on the activity of a panel of enzymes. Mirabegron increased cyclic adenosine 3', 5'-monophosphate (cAMP) concentrations in bladder tissues isolated from rats and it showed a potent relaxant effect in isolated rat and human bladder strips precontracted with carbachol. It also decreased the resting intravesical (intra-bladder) pressure in rats. It decreased the frequency of rhythmic bladder contractions in anaesthetised rats, without affecting the force of the contractions. In water-loaded conscious cynomolgus monkeys, it increased the volume voided per micturition and decreased the voiding frequency. In a cerebral infarction (stroke) model of OAB in rats, mirabegron increased the mean voided volume per micturition. In rats with partial urethral obstruction, it decreased the frequency of non-voiding contractions without affecting the voided volume per micturition, voiding pressure, or residual urine volume. Overall, this evidence suggests that mirabegron enhances urine storage function by stimulating beta 3-ARs in the bladder, without affecting voiding contractions.

OAB is a common and distressing condition, so the prospect of a new agent for relieving OAB symptoms is welcome. The main question raised by the proposed mechanism of action is whether the beta-3 receptors play a sufficiently potent role in modifying urine storage to allow a meaningful improvement of OAB symptoms with this approach, and whether stimulation of adrenergic receptors can be achieved without causing systemic adrenergic side effects, such as hypertension.

2.1. Guidance

The European Medicines Agency (EMA) for the evaluation of medicinal products has produced guidelines for the clinical investigation of products intended to treat urinary incontinence, which the Australian Therapeutic Goods Administration (TGA) has adopted[*]. Those guidelines suggest that the primary aim of incontinence treatment is to provide a subjective improvement, so subjective response should be a major clinical outcome measure. The guidelines argue that quantification of symptoms in terms of frequency of incontinence or micturition is worthwhile but cannot be used as a surrogate for subjective improvement. The sponsor's pivotal studies partially conform to these general principles; the co-primary endpoints of all three pivotal studies were the same, and consisted of a quantification of urinary frequency and incontinence. Subjective endpoints were included, but were secondary or tertiary in importance. Because these subjective endpoints were positive in most cases, with mirabegron achieving statistically significant superiority over placebo, the sponsor's initial ranking of these endpoints ranking is not critical.

In other respects, the sponsor's submission conforms to suggestions in the EMA guidelines, such as the use of a parallel, placebo-controlled design, and pivotal study durations of at least 3 months.

[*] *"Note for Guidance on the Clinical Investigation of Medicinal Products for the Treatment of Urinary Incontinence."* CPMP, December 2002.

According to the sponsor, *"Regulatory interactions with the Competent Authorities in Europe have been held at regular intervals during the mirabegron development program. National Scientific Advice (NSA) meetings have been conducted with the Competent Authorities in The Netherlands (March 2010), Sweden (March 2010), and Spain (March 2010) for the OAB development program. The phase 3 protocols were shared with the Competent Authorities at NSA meetings with The Netherlands (Oct 2007) and Spain (Dec 2007) prior to conduct and the protocols were adapted accordingly."*

The protocols for primary phase 3 studies 178-CL-046 and 178-CL-047 were also submitted to the FDA, and the recommendations of the FDA were followed in producing the statistical analysis plans (SAPs). The sponsor also agreed to perform a pivotal phase 3 assessment of the 25mg dose in response to a suggestion from the FDA Division of Reproductive and Urologic Products. According to the sponsor *"Agreement on the SAPs for Studies 178-CL-046 and 178-CL-047 was received from the FDA in May 2009."*

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical studies included in this submission are summarised below. They include 29 clinical pharmacology studies, 3 phase 2 OAB studies and 6 phase 3 OAB studies, three of which are considered pivotal. Three phase 2 studies for other indications (diabetes and bladder outlet obstruction) contributed safety data.

Table 3. Overview of the Clinical Development Program for Mirabegron*

Phase	IR Formulation		OCAS Formulation	
	Single Dose	Multiple Dose	Single Dose	Multiple Dose
Phase 1	178-CL-001 SAD 178-CL-007 MB†	178-CL-002 MAD 178-CL-005 DDI § 178-CL-006 DDI	178-CL-033BA¶ 178-CL-036 DDI 178-CL-038 Renal 178-CL-039 Hepatic 178-CL-041 FE 178-CL-053 CI 178-CL-064 FE‡ 178-CL-066 DP‡ 178-CL-070 DDI 178-CL-076§ PK¶ 178-CL-078 FE‡	178-CL-030 PK† 178-CL-031 PK 178-CL-034 PK‡§ 178-CL-037 TQT 178-CL-040 DDI 178-CL-058 DDI 178-CL-059 DDI 178-CL-068 DDI 178-CL-069 DDI§ 178-CL-072 A/G 178-CL-077 TQT 178-CL-080 DDI 178-CL-081 IOP
Phase 2 (Other)		178-CL-003 POC DM 12-weeks 178-CL-004 POC DM 12-weeks		178-CL-060 Urodynamics LUTS/BOO
Phase 2 (OAB)		178-CL-008 POC 4-weeks		178-CL-044 DF 12-weeks 178-CL-045‡ DF 12-weeks
Phase 3 (OAB)				178-CL-046 E/S, 12-weeks 178-CL-047 E/S, 12-weeks 178-CL-074 E/S, 12-weeks 178-CL-048 ‡ E/S, 12-weeks 178-CL-049 E/S, 52-weeks 178-CL-051‡ E/S, 52-weeks

A/G: age and gender; BA: bioavailability; CI: cardiac impedance; DDI: drug-drug interaction; DF: dose finding; DM: type 2 diabetes mellitus; DP: dose proportionality; E/S: efficacy and safety; FE: food effect; IOP: intraocular pressure; IR: immediate release; LUTS/BOO: lower urinary tract symptoms/bladder outlet obstruction; MB: mass balance; MAD: multiple ascending dose; OAB: overactive bladder; OCAS: oral controlled absorption system; PK: pharmacokinetics; POC: proof of concept; SAD: single ascending dose; TQT: thorough QT.

† Study 178-CL-030 also included the IR formulation and Study 178-CL-007 used an oral solution of radiolabeled mirabegron.

‡ Studies conducted in Japan.

§ Studies 178-CL-005, 178-CL-034 and 178-CL-069 also included single doses.

¶ Used an intravenous formulation.

The contents of the submission are as follows:

Module 5

- 41 clinical studies, as above.
- Literature references
- *Integrated Summary of Efficacy, Integrated Summary of Safety*

Module 1

- Application letter, application form, draft Australian PI and CMI

Module 2

- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety.

* All figures and tables contained in this evaluation report have been copied from the sponsor's submission. Note: Tables 1 and 2 of the CER are not included in this Extract.

3.2. Paediatric data

The submission did not include paediatric data. According to the sponsor, *"a Pediatric Investigation Plan (PIP) for mirabegron has been submitted to the EMA Pediatric Committee (PDCO), with a positive opinion communicated in August 2010; the measures of the agreed PIP were deferred until after submission of the MAA for the adult indication."*

3.3. Good clinical practice

All submitted studies included an assurance that they were conducted in keeping with current guidelines on Good Clinical Practice.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The table below shows the studies relating to each pharmacokinetic topic.

Table 4. Overview of Mirabegron Phase 1 Studies.

Study No./ Region	Type of Study	Dose (mg)	No. E/C	Subject Type/ Diagnosis	Design
MIRABEGRON BIOPHARMACEUTIC STUDIES					
178-CL-030 (EU)	OCAS Selection	200 qd OCAS-F, OCAS-S and OCAS-M 100 bid IR tablet	36/34	HV	OL, XO
178-CL-033 (EU)	Absolute BA	50, 150 sd OCAS; 15, 50 sd iv over 2 hrs	12/12	HV	OL, XO
178-CL-076 (US)	IVIVC, Absolute BA	25, 50, 100 sd OCAS-H, OCAS-L, OCAS-M, OCAS-M other batch; 7.5 15, 30 sd iv over 2 hrs	91/75	HV	OL, XO
178-CL-041 (US)	Effect of Food; Pivotal	50, 100 sd OCAS	76/64	HV	OL, XO
178-CL-064 (JP)	Effect of Food	50 sd OCAS	24/23	Male HV	OL, XO
178-CL-078 (JP)	Effect of Food; Pivotal	50, 100 sd OCAS	72/70	HV	OL, XO
MIRABEGRON HEALTHY SUBJECT PK AND INITIAL TOLERABILITY STUDIES					
Studies using Oral Solution and IR (Immediate-Release) Capsule					
178-CL-001 (EU)	Single-dose PK and Food Effect	0.1, 0.3, 1, 3, 10, 30, 100, 160, 240, 340 sd capsule	85/85	Male HV	DB, PC
		160 sd capsule	12/12		OL, XO
178-CL-002 (EU)	Multiple-dose PK and Food Effect	40, 80, 160, 240 qd for 7 days capsule	40/38	Male HV	DB, PC
178-CL-007 (EU)	Mass Balance	^{14}C-mirabegron 160 sd drinking solution	4/4	Male HV	OL
Studies using OCAS Formulation					
178-CL-031 (EU)	Single- and Multiple-dose PK in Young and Elderly	50, 100, 200, 300 sd followed by 50, 100, 200, 300 qd for 10 days	96/96	HV (18-55 yrs and 65-80 yrs)	DB, PC
178-CL-066 (JP)	Dose Proportionality	25, 50, 100 sd	12/12	Male HV	OL
178-CL-034 (JP)	Single- and Multiple-dose PK in Japanese Subjects	0, 50, 100, 200, 300, 400 sd 0, 100, 200 qd	40/40 24/24	Male HV	SB, PC
MIRABEGRON STUDIES IN SPECIAL POPULATIONS (INTRINSIC FACTORS)					
Studies using OCAS Formulation					
178-CL-072 (EU)	Age and Sex	25, 50, 100 qd	75/67	HV (18-45 yrs and ≥ 55 yrs)	OL, XO
178-CL-038 (US)	Renal Impairment	100 sd	33/32	Normal, mild, moderate, severe renal impairment (eGFR-MDRD)	OL
178-CL-039 (EU)	Hepatic Impairment	100 sd	32/32	Normal, mild, moderate hepatic impairment (Child-Pugh A, B)	OL

Table 4 continued. Overview of Mirabegron Phase 1 Studies.

Study No./ Region	Type of Study	Dose (mg)	No. E/C	Subject Type/ Diagnosis	Design
MIRABEGRON STUDIES OF DRUG-DRUG INTERACTION (EXTRINSIC FACTORS)					
Studies using IR Capsule or Tablet					
178-CL-005 (EU)	CYP2D6 Genotype, Metoprolol PK Interaction	160 sd capsule	16/16	Male HV; CYP2D6 PM and EM	OL
		160 qd capsule; metoprolol 100 sd	12/12	Male HV; CYP2D6 EM	
178-CL-006 (EU)	Metformin PK Interaction	160 qd tablet; metformin 500 bid	32/31	Male HV	OL
Studies using OCAS Formulation					
178-CL-036 (US)	Ketoconazole PK Interaction	100 sd; ketoconazole 400 qd	24/23	HV	OL, XO
178-CL-040 (EU)	Warfarin PK and PD Interaction	100 qd; warfarin 25 sd	24/24	HV	OL
178-CL-058 (EU)	Desipramine PK Interaction	100 qd; desipramine 50 sd	28/27	HV	OL
178-CL-068 (EU)	COC PK Interaction	100 or placebo qd; COC (EE 30 mcg + LNG 150 mcg) qd	30/23	Female HV	DB, PC
178-CL-059 (EU)	Digoxin PK Interaction	100 qd; digoxin 0.250 sd	25/23	HV	OL
178-CL-069 (EU)	Solifenacin PK Interaction	100 sd; solifenacin 10 qd 100 qd; solifenacin 10 sd	41/40	HV	OL
178-CL-070 (US)	Rifampin PK Interaction	100 sd; rifampin 600 qd	24/24	HV	OL
178-CL-080 (EU)	Tamsulosin Cardiovascular PD Interaction	100 qd; tamsulosin 0.4 sd (prolonged release) 100 sd; tamsulosin 0.4 qd (prolonged release)	48/46	Male HV	OL, XO
MIRABEGRON PD STUDIES					
Studies using OCAS Formulation					
178-CL-053 (EU)	Mechanism of Cardiovascular Responses	200 sd; bisoprolol 10 sd; propranolol 160 sd (prolonged release)	12/12	Male HV	SB, XO
178-CL-037 (US)	Thorough QT	100, 200 qd for 7 days; moxifloxacin 400 sd	49/43	HV	DB, XO PC/AC
178-CL-077 (US)	Thorough QT	50, 100, 200 qd for 10 days; moxifloxacin 400 qd for 10 days	352/319	HV	DB, XO, PC/AC
178-CL-081 (US)	Intraocular Pressure	100 qd	321/305	HV or adults with OAB	DB, PG, PC

EU: Europe; JP: Japan; US: United States; E/C: enrolled/completed; sd: single dose; DB: double-blind; SB: single-blind; OL: open-label; PC: placebo-controlled; PG: parallel group; AC: active-controlled; XO: crossover; HV: healthy volunteers (male and female unless indicated otherwise); qd: once a day; bid: twice a day; OCAS: oral-controlled absorption system (-F [fast], -M [medium], -S [slow], -H [high], -L [low]); IR: immediate release; iv: intravenous; PK: pharmacokinetic(s); PD: pharmacodynamic(s); BA: bioavailability; IVIVC: in-vitro-in-vivo correlation; eGFR-MDRD: estimated glomerular filtration rate using abbreviated modification of diet in renal disease formula; PM: poor metabolizer; EM: extensive metabolizer; COC: combined oral contraceptive (containing ethinyl estradiol and levonorgestrel); EE: ethinyl estradiol; LNG: levonorgestrel; OAB: overactive bladder.

Table 5. Location of Clinical Pharmacology Synopses

[Table 5 is not included in this Extract from the Clinical Evaluation Report]

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies.

4.2.1. Pharmacokinetics in healthy subjects

4.2.1.1. Absorption

4.2.1.1.1. Sites and mechanisms of absorption

No clinical studies were submitted that established the precise sites and mechanisms of absorption of mirabegron, but the speed and extent of absorption depends on the formulation, dose and presence of food in the stomach.

After administration of 160mg mirabegron as a drinking solution, peak concentrations were attained at ~ 1.0 hour (Study 178-CL-007). The immediate-release (IR) solid formulation of mirabegron was associated with a t_{max} of ~2.5 – 3.5 hours (Studies 178-CL-001 and 178-CL-002). After oral administration of the proposed OCAS-M formulation in healthy volunteers, mean peak plasma concentrations were reached between 3 and 4.3 hours (Studies 178-CL-031 and 178-CL-034).

Absorption also depends on the dose. Pre-clinical *in vitro* studies suggest that mirabegron is a substrate for the efflux transporter P-gp and for the influx organic cation transporters (OCT) OCT1, OCT2, and OCT3 (Studies 178-ME-031, 178-ME-132, 178-ME-092, not evaluated in this report). Clinical PK studies showed that higher doses are associated with a more-than-dose proportional exposure, which is likely to be due to saturation of efflux transporters in the intestine.

Mirabegron is also susceptible to a substantial food effect, as discussed below.

4.2.1.2. Bioavailability

4.2.1.2.1. Absolute bioavailability

Bioavailability depends on the dose administered, but at the proposed dose of 50mg, bioavailability of the OCAS-M formulation was estimated to be 35% in Study 178-CL-076, compared to 29% at 25mg and 45% at 100mg . Similar trends were seen in Studies 178-CL-066 and 178-CL-034, which also showed greater-than-dose-proportional exposure at increasing oral doses. The sponsor proposes that the increase in absolute bioavailability with increasing dose is probably due to saturation of efflux transport proteins (particularly P-glycoprotein, P-gp).

Bioavailability appeared to be higher in females compared with males (Study 178-CL-072). Across the doses tested, mean C_{max} and AUC_{tau} were approximately 44% and 38% higher, respectively, in females relative to males. Normalisation for weight reduced the gender difference but did not eliminate it: weight-normalized values for C_{max} and AUC_{tau} were approximately 23% and 18% higher, respectively, in females.

4.2.1.2.2. Bioavailability relative to an oral solution or micronised suspension

Direct comparisons of an oral solution of mirabegron and the proposed formulation at the same dose have not been performed. The mirabegron solution (160mg) used in the mass balance study (178-CL-007) had a bioavailability of at least 55% (based on the percentage of administered radioactivity recovered in urine, though an additional 11% of administered radioactivity was unaccounted for). This is higher than the bioavailability of OCAS_M formulation discussed above. The lower bioavailability for the OCAS-M formulation compared with the solution is possibly due to more efficient efflux (less saturation of transporters) and reduced absorption from more distal gut regions, which play a greater role with the OCAS-M formulation as a result of slower release of mirabegron.

4.2.1.2.3. Bioequivalence of clinical trial and market formulations

The OCAS-M tablets used for the pivotal phase 3 clinical studies were used also used for the majority of the phase 2 and clinical pharmacology studies. The proposed commercial formulations of mirabegron 25mg and 50mg are identical to the tablets used in phase 3, except that the commercial product will be debossed.

Some clinical pharmacology studies used an immediate release (IR) formulation instead of OCAS-M: 178-CL-005 (CYP2D6 genotype and metoprolol drug-interaction study), 178-CL-006 (a metformin interaction study), and multi-dose PK and food-effect studies, 178-CL-001 and 178-CL-002. As noted above, the mass-balance study (178-CL-007) used an oral solution of mirabegron, and is not directly comparable to the IR or OCAS-M formulations.

For the few clinical pharmacology studies that did not employ the OCAS-M formulation, it is reasonable to draw qualitative conclusions, but exposure with the IR formulation was not quantitatively equivalent to that expected with OCAS-M. The mean relative bioavailability for the OCAS-M tablet (200mg qd) compared to the IR tablet (100mg bid) was estimated to be 80% in Study 178-CL-030.

A complete listing of the Phase 1 clinical studies and the formulation used is contained in Table 4, above.

4.2.1.2.4. Bioequivalence of different dosage forms and strengths

The proposed commercial 25mg and 50mg tablets have identical compositions, and would not be expected to differ significantly in their bioavailability.

4.2.1.2.5. Bioequivalence to relevant registered products

Not applicable.

4.2.1.2.6. Influence of food

Mirabegron exhibits a decrease in plasma exposure with food. Co-administration of a mirabegron 50mg tablet with a high-fat meal reduced mirabegron C_{max} and AUC_{inf} by 45% and 17%, respectively. A low-fat meal had a more marked effect, decreasing mirabegron C_{max} and AUC_{inf} by 75% and 51%, respectively. Similar results were obtained with mirabegron 100mg. (See studies 178-CL-041, 178-CL-064, 178-CL-078, 178-CL-001, 178-CL-002).

The sponsor proposes that the mechanism behind the food effect is likely to be a combination of adsorption to meal constituents and competition for drug uptake and efflux from meal constituents.

Although the food effect is substantial, the safety and efficacy of the proposed 50mg dose was assessed in the pivotal studies without food restrictions; subjects took mirabegron variably with and without food. This suggests that problems related to variability in exposure from the food effect have already been accounted for in considering the efficacy and safety of mirabegron in those studies.

Population PK analysis of the phase 3 data suggests that mirabegron plasma exposure was similar in subjects who took within 30 minutes before or after food compared to those who did not. This suggests that the food effect might have been obscured by interpatient variability.

On the basis of pre-clinical studies (not evaluated in this report), it appears that alcohol is unlikely to accelerate the dissolution and release of mirabegron from the OCAS-M formulation. Adding 4% ethanol to the dissolution medium did not significantly modify the dissolution profiles for mirabegron OCAS-M tablets, but adding 40% ethanol delayed dissolution profiles.

4.2.1.2.7. Dose proportionality

Deviations from dose proportionality have been noted for oral preparations, as discussed above. When given orally, mirabegron exposure increases more than dose-proportionally with increasing dose, which is likely to reflect saturation of efflux mechanisms. The mechanism is not likely to be due to saturable first-pass metabolism, because mirabegron metabolites also demonstrated a more-than-dose-proportional increase in C_{max} and AUC_{tau} after multiple mirabegron doses (25 to 200mg qd), which was similar to the increases observed with the parent compound.

By contrast, no deviations from dose proportionality in mirabegron PK parameters were observed after single-dose intravenous administration of mirabegron.

4.2.1.2.8. Bioavailability during multiple-dosing

Multi-dose studies (178-CL-031, 178-CL-034, 178-CL-002) suggest that steady state plasma concentrations of mirabegron are achieved within 7 days of once daily dosing. Comparison between AUC_{tau} values following a single dose and at steady state indicated a 2-fold accumulation of mirabegron with once daily dosing.

At the proposed therapeutic dose of 50mg, no time-dependency in PK handling of mirabegron was observed. At higher doses (100mg and 200mg), a small increase (<20%) was observed in AUC_{tau} at steady state compared with single-dose AUC_{inf}, suggesting that mirabegron may exhibit time-dependent PK at supratherapeutic doses. This effect appears small compared to the food effect and intersubject variability, and is not likely to be clinically relevant.

4.2.1.2.9. Effect of administration timing

No studies specifically assessed the influence of timing of dose, apart from the noted food effect. There are no *a priori* reasons to suspect a major timing effect.

4.2.1.3. Distribution

4.2.1.3.1. Volume of distribution

Mirabegron has a large apparent volume of distribution at steady state (~1670 L), well in excess of body water, indicating extensive distribution and binding to tissue constituents. (Study 178-CL-033).

4.2.1.3.2. Plasma protein binding

Mirabegron is moderately bound (approximately 71%) to human plasma proteins, including albumin and alpha-1 acid glycoprotein. (178-CL-038).

4.2.1.3.3. Erythrocyte distribution

In vitro assessments showed that erythrocyte concentrations of 14C-mirabegron were approximately 2-fold higher than in plasma, indicating that mirabegron distributes to erythrocytes.

4.2.1.3.4. Tissue distribution

The large apparent volume of distribution (~1670 L) suggests that mirabegron is distributed to multiple tissues and binds extensively to tissue constituents, but no clinical studies explored the details of the tissue distribution.

4.2.1.4. Metabolism

4.2.1.4.1. Interconversion between enantiomers

Mirabegron has a chiral center, and it has been developed as the R-configured enantiomer.

The sponsor reports that, after oral administration of radiolabeled mirabegron in healthy subjects, there was no evidence of chiral inversion (Study 178-ME-041).

4.2.1.4.2. Sites of metabolism and mechanisms / enzyme systems involved

Mirabegron is cleared by multiple mechanisms: renal and possibly biliary excretion of unchanged drug, and hepatic metabolism of the drug by multiple drug-metabolizing enzymes, with no single predominating clearance pathway.

Following an initial more rapid distribution phase, the $t_{½}$ of mirabegron is approximately 50 hours. Total body clearance (CL) of mirabegron from plasma is ~57 L/h. Blood clearance is estimated to be ~ 41 L/hr, which is about half the liver blood flow. The $t_{½}$ is independent of

dose, route of administration and formulation. The effective half-life including distribution effects is estimated to be ~ 19 hours (based on population PK analysis).

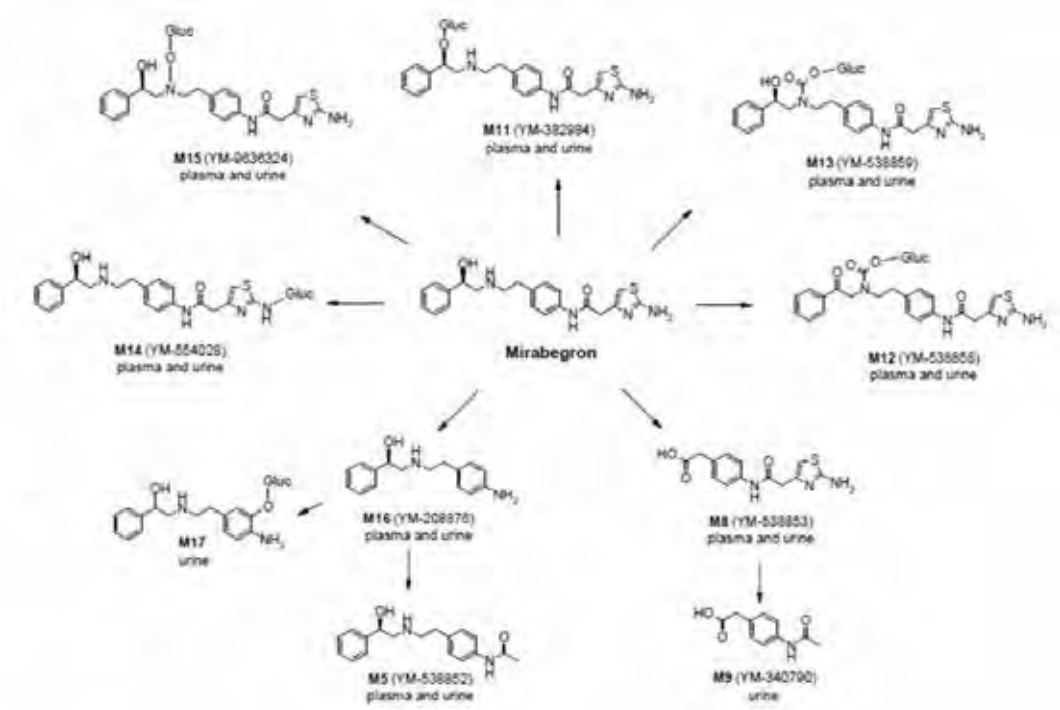
4.2.1.4.3. Non-renal clearance

Renal clearance (CLR) is independent of dose and averages approximately 13 L/h, which corresponds to nearly 25% of CL, implying that non-renal clearance accounts for ~75% of clearance. Following the administration of 160mg radiolabelled mirabegron to healthy volunteers (Study 178-CL-007), ~ 55% of the radioactivity was recovered in the urine and 34% in the faeces. Unchanged mirabegron accounted for 45% of the urinary radioactivity and the majority of the faecal radioactivity; the remainder had undergone hepatic metabolism to a variety of metabolites as shown below.

4.2.1.4.4. Metabolites identified in humans

The sponsor proposes the following metabolic pathways in humans.

Figure 2. Postulated Metabolic Pathways of Mirabegron in Humans



As shown in the figure above, mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, glucuronidation, and amide hydrolysis. Metabolites recovered from urine suggest that butyrylcholinesterase is the most important matabolising enzyme, in addition to uridine diphosphate-glucuronosyltransferase (UGT), CYP3A4 and CYP2D6 enzymes and possibly alcohol dehydrogenase. *In vitro* studies suggested that CYP3A4 is the primary isoenzyme involved in hepatic oxidative metabolism of mirabegron, with a minor role of CYP2D6.

The metabolites designated M11 and M12 (see figure above) were considered to be the major metabolites. Both are phase 2 glucuronides representing 16% and 11% of total exposure in plasma.

None of the metabolites found in plasma appeared to be pharmacologically active. Agonist activities of metabolites on beta 3-AR were less than 1/400 of mirabegron activity, and activities on other beta ARs were negligible. No other affinities for a panel of biological targets were observed.

4.2.1.4.5. Pharmacokinetics of metabolites

Metabolite plasma concentration profiles were delayed by ~0.5 to 1.5 hours compared to mirabegron, with mean t_{max} values from ~ 3.6 and 6.3 hours. Metabolite-to-parent AUC ratios were essentially constant across multiple oral doses of 25 to 200mg qd, suggesting that the metabolism of mirabegron is not saturable over clinically relevant doses. For details, see Study 178-CL-007.

4.2.1.4.6. Consequences of genetic polymorphism

The sponsor assessed the PK of mirabegron in poor and extensive CYP2D6 metablizers in Study 178-CL-005. Genetic polymorphism for the CYP2D6 isozyme appeared to have no clinically relevant impact on mirabegron exposure. Following mirabegron 160mg administered as a single oral dose (IR formulation), the mean C_{max} and AUC_{inf} were 14% and 19% higher, respectively, in CYP2D6 poor metabolizers compared to extensive metabolizers.

In Study 178-CL-058, following multiple 50mg and 100mg doses of mirabegron OCAS, mean AUC_{tau} was 8% and 12% higher, respectively, in CYP2D6 poor metabolizers compared to extensive metabolizers, and mean C_{max} values were similar. The relatively minor effect of polymorphism is consistent with the multiple elimination pathways for mirabegron.

4.2.1.5. Excretion

4.2.1.5.1. Routes and mechanisms of excretion

Excretion of unchanged mirabegron and inactive mirabegron metabolites is predominantly renal. Following the administration of 160mg radiolabelled mirabegron to healthy volunteers (Study 178-CL-007), ~ 55% of the radioactivity was recovered in the urine and 34% in the faeces, which thus accounts for 89% of the administered dose. Of the radioactivity that was not recovered from stool, renal excretion accounts for at least 83% (55/(100-34)). It is unclear if some biliary excretion also occurs.

4.2.1.5.2. Mass balance studies

See Study 178-CL-007.

4.2.1.5.3. Renal clearance

Renal clearance (CLR) is independent of dose and averages approximately 13 L/h, which corresponds to nearly 25% of CL. The sponsor proposes that renal elimination of mirabegron is primarily through active tubular secretion along with glomerular filtration. The urinary excretion of unchanged mirabegron is dose-dependent and rages from ~6% after a daily dose of 25mg to ~9% after a daily dose of 50mg (Studies 178-CL-039, 178-CL-001, 178-CL-033 and other basic PK studies). In the mass balance study, following 160mg, unchanged mirabegron accounted for 45% of the radioactivity in urine, or 25% of the total radioactivity.

4.2.1.6. Intra- and inter-individual variability of pharmacokinetics

Mirabegron PK after oral administration shows substantial variability, with *inter*subject variability estimates (%CVs) for C_{max} and AUC_{inf} of ~40% to 52% and ~39% to 45%, respectively. The corresponding estimates for the *intra*subject variability ranged from approximately 33% to 45% for C_{max} and 19% to 31% for AUC_{inf}.. Most of the variability appears to be related to absorption, as suggested by relatively low intersubject variability after intravenous administration: for IV mirabegron %CVs for C_{max} and AUC_{inf} were ~20% (Study 178-CL-076). Part of the variability in mirabegron exposure is related to body weight, and gender also plays a role even after normalising for weight (178-CL-072). A major source of intraindividual variability in clinical settings would be expected to come from the marked food effect.

4.2.2. Pharmacokinetics in the target population

The sponsor assessed the PK of mirabegron in subjects with OAB (in phase 1 Study 178-CL-081, and also the major phase 2 and 3 clinical efficacy studies), and found that mean AUC_{tau} estimates in patients with OAB were approximately 20% to 50% lower compared with fasted AUC_{tau} values in healthy volunteers.

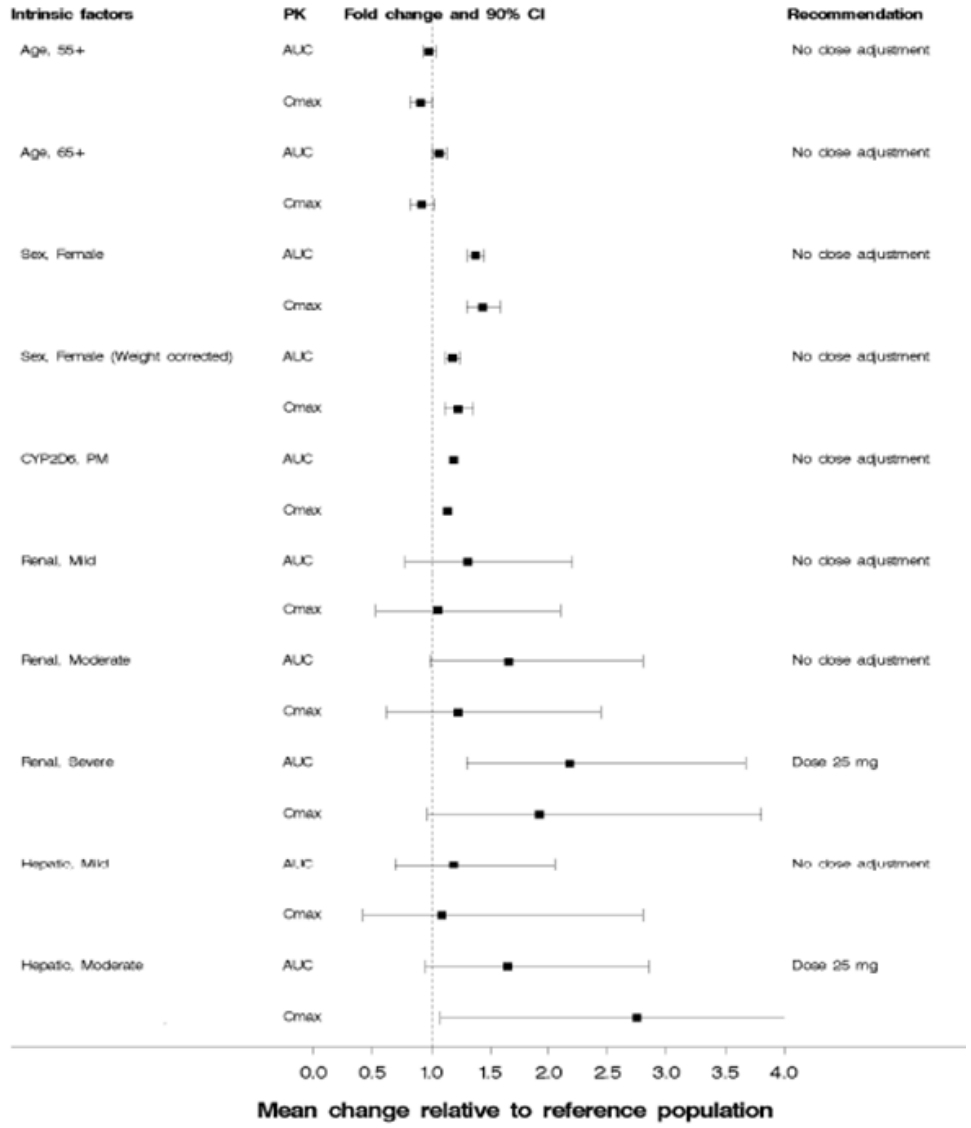
This could reflect a food effect, because patients in the efficacy studies were not required to take mirabegron under fasting conditions. Also, PK estimates during efficacy studies were based on a relatively sparse sampling scheme, which could have missed the peak concentrations and thus underestimated the true exposure.

In general, patients with OAB are generally healthy, but are likely to be older than the healthy volunteers of the phase 1 program. As discussed below, age does not appear to have a major effect on the PK of mirabegron, so the PK characteristics of mirabegron are not expected to be significantly different in the target population. Even if exposure was lower in the target population, this would not pose clinically relevant concerns: safety would be greater at lower exposure, and any compromise in efficacy at lower exposure has already been accounted for in the pivotal study results.

4.2.3. Pharmacokinetics in other special populations

The sponsor performed a number of studies assessing the effects of a range of intrinsic factors on the PK of mirabegron, including age, gender, CYP2D6 genotype, renal and hepatic function. The results are displayed graphically below. For details, see the sections. Overall, the PK in these different populations was similar to that in healthy volunteers, but exposure was slightly higher in women, and moderately higher in the setting of hepatic or renal impairment. Dose adjustment is recommended in the presence of moderate hepatic impairment or severe renal impairment.

Figure 3. Effect of Intrinsic Factors on the Pharmacokinetics of Mirabegron



4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

The PK of mirabegron in volunteers with hepatic impairment were compared to those in healthy control volunteers matched for sex, age and body mass index (BMI) in Study 178-CL-034. Following mirabegron 100mg in volunteers with *mild* hepatic impairment (Child-Pugh Class A), mean C_{max} and AUC_{inf} were 9% and 19% higher, respectively, relative to healthy volunteers. In volunteers with *moderate* hepatic impairment (Child-Pugh Class B), mean C_{max} and AUC_{inf} values were 175% and 65% higher, respectively. A reduction of the dose to 25mg once daily in patients with moderate hepatic impairment is therefore recommended.

The magnitude of the increases in exposure with mild hepatic impairment are unlikely to be clinically relevant, and are small compared to intersubject variability with healthy volunteers, so no dose adjustment is recommended.

Mirabegron has not been studied at all in patients with severe hepatic impairment (Child-Pugh Class C) and should not be used in this patient population, even at a reduced dose. The Proposed Product Information sheet (PI) contains appropriate warnings against use in this population.

4.2.3.2. Pharmacokinetics in subjects with impaired renal function

In Study 178-CL-038, the PK of mirabegron in volunteers with renal impairment were compared to the PK in healthy volunteers matched for sex, age and weight.

Following mirabegron 100mg, in volunteers with mild renal impairment (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m^2), mean mirabegron C_{max} and AUC_{inf} were 6% and 31% higher, respectively, relative to volunteers with normal renal function. In volunteers with moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m^2), C_{max} and AUC_{inf} were 23% and 66% higher, respectively. In volunteers with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m2), mean C_{max} and AUC_{inf} values were 92% and 118% higher, respectively.

On the basis of these results, the sponsor's proposed Product Information sheet recommends a halving of the dose to 25mg once daily in patients with severe renal impairment, but no adjustment in patients with mild to moderate renal impairment. This appears reasonable, given that doses up to 100mg were assessed in pivotal phase 3 studies and had an acceptable safety profile.

Mirabegron has not been studied in patients with End Stage Renal Disease (eGFR < 15 mL/min/1.73 m^2 or patients requiring hemodialysis) and should not be used in this patient population. The PI warns against such use.

4.2.3.3. Pharmacokinetics according to age

The effects of age and gender on the PK of mirabegron were assessed in Study 178-CL-072. No statistically significant differences in C_{max} and AUC_{tau} were found in mirabegron between older volunteers (≥55 years) and younger volunteers (18-45 years). Similar results were obtained for the subpopulation aged ≥ 65 years.

Given that mirabegron clearance is affected by renal function, and that renal function declines with advancing age, it would be surprising if there were no PK differences between elderly subjects and younger subjects. A population PK analysis of phase 2 and 3 data confirmed that age increased mirabegron exposure, but the effect was minimal. AUC was estimated as 11% higher in a subject aged 90 years compared to a subject aged 60 years.

Overall, given that the changes in PK with age are minor, no dosage adjustment is recommended on the basis of age.

4.2.3.4. Pharmacokinetics related to genetic factors

There are no known genetic factors significant affecting the PK of mirabegron. Polymorphism for the CYP2D6 isozyme, as discussed previously (above), has a minimal effect on mirabegron exposure, which is not likely to be clinically significant.

4.2.3.5. Pharmacokinetics according to gender

In multiple PK studies, mirabegron C_{max} and AUC_{tau} were ~40% to 50% higher in females compared to males. The magnitude of the differences was lessened but not eliminated by weight-normalisation: weight-normalized values for C_{max} and AUC_{tau} were ~ 20% to 30% higher in females (See Study 178-CL-072).

The sponsor does not propose dose adjustment based on sex, and this seems reasonable. All the major studies contributing to the efficacy and safety evidence for mirabegron recruited both men and women with OAB, so the clinical effects of this variation in exposure have already been factored in to the efficacy and safety analysis. The increased exposure in women does not appear to compromise the safety of mirabegron, and the relatively reduced exposure in men does not appear to significantly compromise efficacy.

4.2.3.6. Pharmacokinetics according to race

Race did not influence any PK parameters in a population PK analysis of phase 2 and 3 data. Plasma exposure in healthy Japanese subjects was higher than in Western subjects, but the differences are largely accounted for by differences in body weight. Dose adjustment based on race is not necessary.

4.2.4. Pharmacokinetic interactions

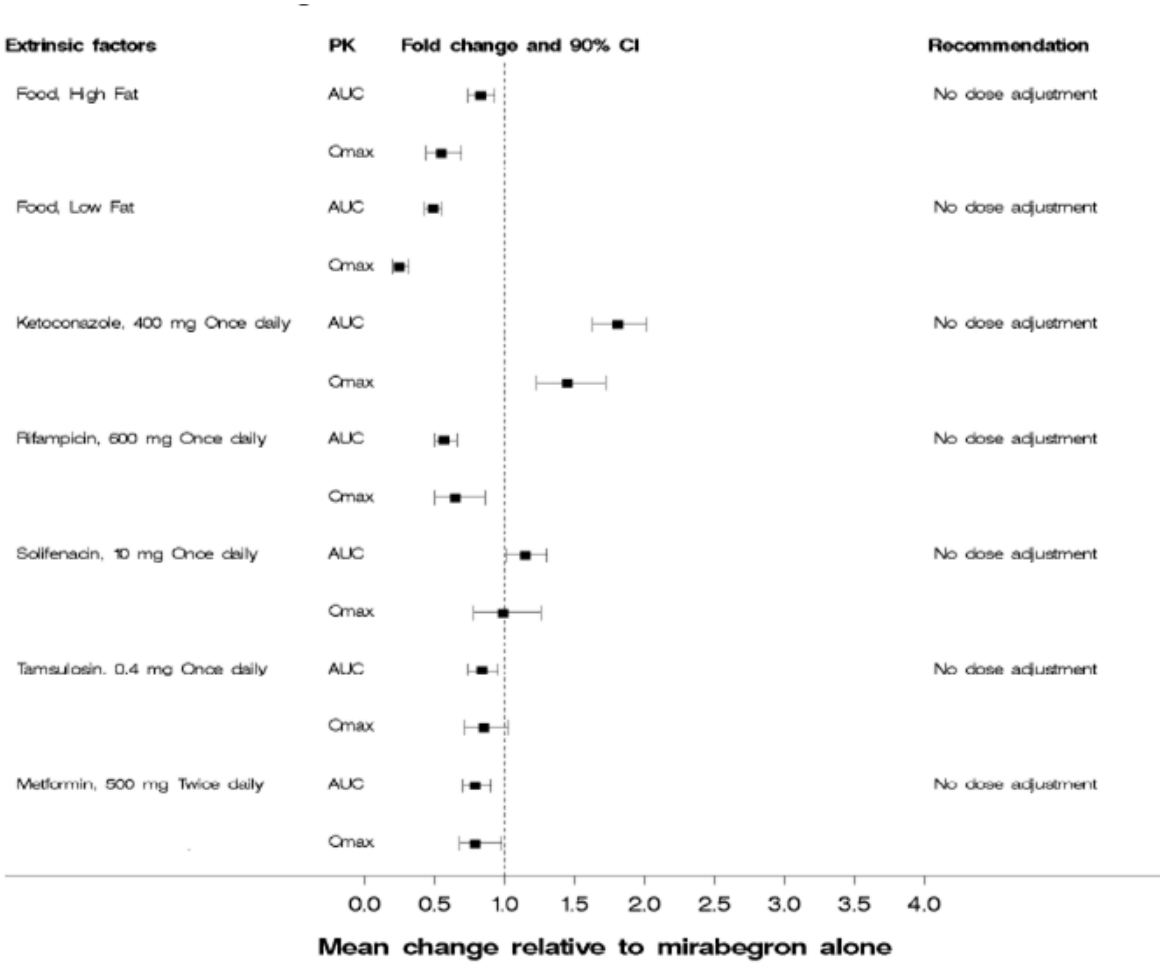
4.2.4.1. Pharmacokinetic interactions demonstrated in human studies

The clinical pharmacology program suggested that mirabegron is susceptible to a variety of pharmacokinetic interactions, but each interaction has a relatively minor effect, which is not surprising considering the drug is cleared by multiple mechanisms (both hepatic and renal), with no single predominating clearance pathway.

4.2.4.1.1. Effect of co-administered drugs on mirabegron.

The interactions identified in the study program are displayed graphically below. The most substantial interaction was observed with ketoconazole (400mg qd), which is a potent CYP3A and P-gp inhibitor. Ketoconazole caused a 45% increase in the C_{max} and an 81% increase in the AUC_{inf} of mirabegron (100mg single dose). This is less than the increase in exposure that would be achieved if the dose were doubled (estimated to produce a 190% and 160% increase in C_{max} and AUC, respectively). Given that mirabegron was assessed in pivotal studies at 100mg daily (twice the proposed therapeutic dose), the increase in exposure with ketoconazole does not raise substantial clinical concerns.

Figure 4. Effect of Co-administered Drugs or Food on the Pharmacokinetics of Mirabegron



Other drug interactions were less substantial. Co-administration with rifampin (600mg qd), a potent CYP3A and P-gp inducer, resulted in a 35% decrease in C_{max} and a 44% decrease in AUC_{inf} of a single dose of mirabegron (Study 178-CL-070).

An interaction of mirabegron with an inhibitor of CYP2D6 was not expected, so the effect of a potent CYP2D6 inhibitor on mirabegron PK was not directly studied in human subjects. Subjects who were poor metabolizers of CYP2D6 substrates exhibited only slightly higher mirabegron plasma exposure compared with extensive metabolizers. Therefore, no dose adjustment of mirabegron is recommended for mirabegron when co-administered with CYP2D6 inhibitors or in patients who are CYP2D6 poor metabolisers. (The reverse interaction, of mirabegron on other CYP2D6 substrates, could be more significant as discussed below).

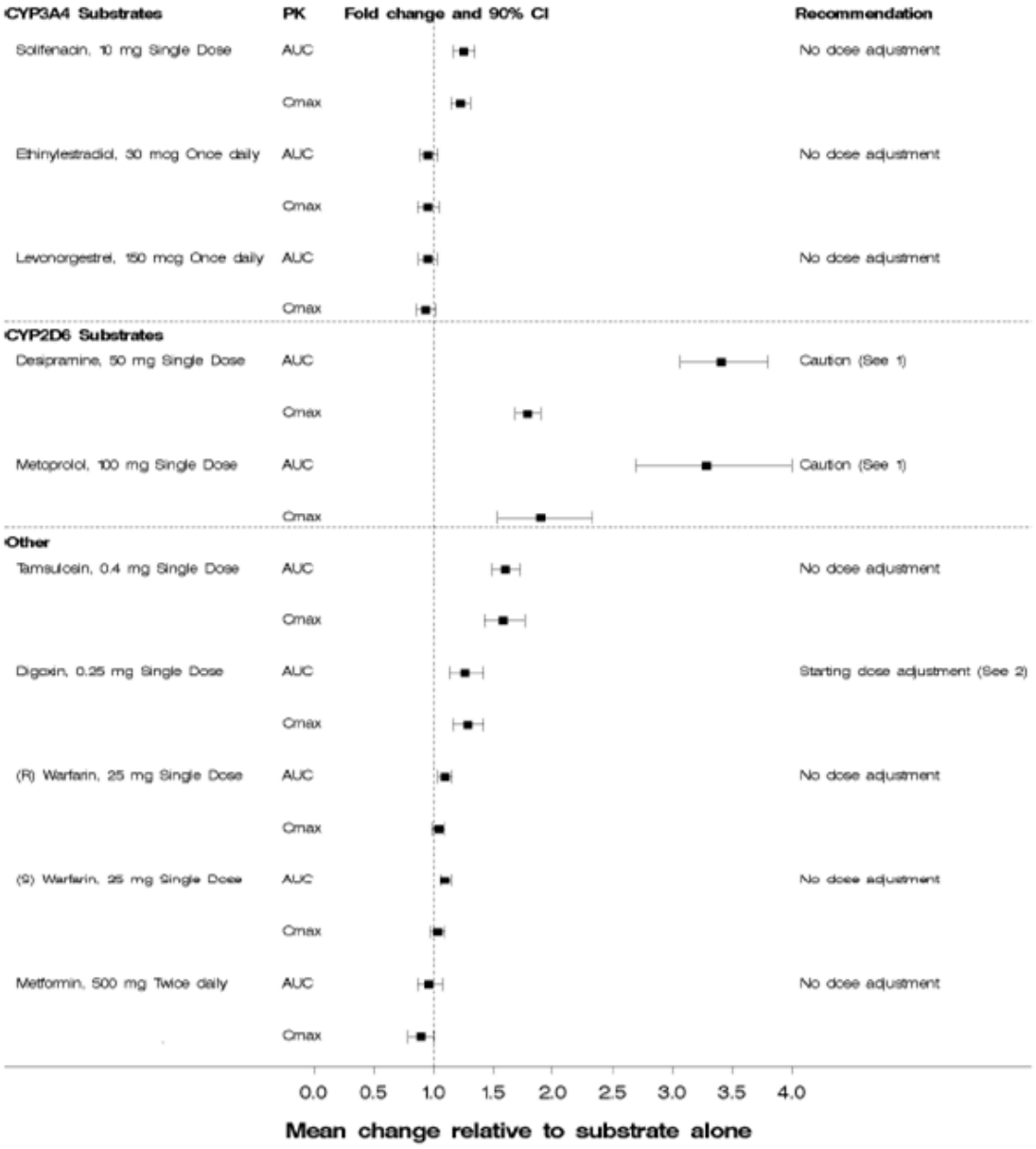
Mirabegron PK was not significantly affected by co-administration with metformin, solifenacin or tamsulosin. There was a minor pharmacodynamic (PD) interaction between tamsulosin and mirabegron, not expected to be clinically relevant.

4.2.4.1.2. Effect of mirabegron on co-administered drugs.

Drug interaction studies were performed with substrates for CYP2D6, CYP3A4 and P-gp, with other urological medications and with the narrow therapeutic index drug warfarin. Studies were also performed with metformin, which, like mirabegron, is a renally secreted organic cation.

The results of these studies are displayed graphically below.

Figure 5. Effect of Mirabegron on the Pharmacokinetics of Co-administered Drugs



The inhibitory effects of mirabegron on CYP2D6 were sufficient to recommend caution when combining mirabegron with other CYP2D6 substrates if these substrates have a narrow therapeutic index. Multiple daily dosing with mirabegron 160mg (IR formulation) resulted in a 90% increase in C_{max} and a 229% increase in AUC_{inf} of a single 100mg dose of the CYP2D6 substrate metoprolol. Similarly, multiple daily dosing with mirabegron 100mg resulted in a 79% increase in C_{max} and a 241% increase in AUC_{inf} of a single 50mg dose of the CYP2D6 substrate desipramine.

By contrast, mirabegron (100mg qd) did not affect the PK of ethinyl estradiol and levonorgestrel (both CYP3A4 substrates) or solifenacin (a CYP3A4 substrate) to a clinically significant extent.

Mirabegron (100mg qd) did increase plasma exposure of the CYP2D6 and CYP3A4 substrate tamsulosin (0.4 mg sd) by approximately 60%, but the cardiovascular results did not suggest a clinically relevant pharmacodynamic interaction between tamsulosin and mirabegron (see Study 178-CL-080). The sponsor recommends no dose adjustment during co-administration of these two drugs, which seems appropriate.

No significant effects of mirabegron on the pharmacokinetics of warfarin (a substrate for CYP2C9) or on prothrombin time were observed when mirabegron (100mg qd) was co-administered with warfarin (25mg sd).

No significant changes in the PK of metformin (500mg bid) were observed when co-administered with a supratherapeutic dose of mirabegron (160mg IR qd).

Although mirabegron inhibits P-gp, the effect was weak. With multiple daily dosing of mirabegron 100mg, the C_{max} of the P-gp substrate digoxin (0.25mg sd) increased 29%, and the AUC_{last} increased 27%. Because digoxin has a narrow therapeutic index, patients commencing combination treatment with mirabegron and digoxin should start with the lowest dose for digoxin, and then titrate the dose according to digoxin levels. (Given the weak efficacy of mirabegron, ceasing it would be another reasonable option.)

4.2.5. Clinical implications of *in vitro* findings

On the basis of *in vitro* tests, mirabegron appears unlikely to inhibit the metabolism of co-administered drugs metabolised by: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2E1. Also, in vitro studies suggest that mirabegron does not affect the metabolism of glibenclamide (a CYP3A4 substrate) or tolbutamide (a CYP2C9 substrate), and mirabegron does not induce CYP1A2 or CYP3A. On the other hand, mirabegron did inhibit P-gp, OCT1- and OCT2-mediated drug transport at high concentrations.

4.3. Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetics of mirabegron have been well characterised. They are adequately described in the sponsor's proposed Product information sheet. Important features are a pronounced food effect, with lower exposure when combined with food, a large volume of distribution, and moderate increases in exposure in the setting of renal or hepatic impairment. Several minor drug interactions were observed with mirabegron, but dose adjustment of mirabegron is generally not required. Drugs that are substrates for CYP2D6 may need dose adjustment when combined with mirabegron, and digoxin should be introduced slowly and titrated with the assistance of drug levels when combined with mirabegron.

5. Pharmacodynamics

5.1. Primary pharmacodynamic studies

No primary pharmacodynamic studies directly assessing bladder physiology in response to mirabegron were submitted.

5.2. Primary pharmacodynamic modelling

The sponsor submitted some PD population modelling, based on the major phase 2 and 3 efficacy studies (178-CL-044, 178-CL-046, 178-CL-047 and 178-CL-074), using a Poisson-Normal mixed effect model. This modelling attempted to create a dose response curve, despite very noisy underlying data. Such modelling does not provide new information beyond a direct assessment of the contributory studies, and inevitably imports a range of assumptions into the model, but the key conclusions of this analysis are shown below. The table below shows the placebo-subtracted changes in micturition frequency and volume voided expected from the oacross the dose range 25mg to 200mg. Similar information is displayed graphically in the subsequent pair of figures, where each curve represents an individual model run that attempts to capture the variability between patients. The underlying idealised model is shown in the final figure.

From 50mg upwards, the dose-response curve is largely flat, suggesting that the proposed dose of 50mg is an appropriate compromise between efficacy and safety – further dose increases could increase the risk of adverse events, but is unlikely to lead to substantially improved efficacy. The model predicts that 25mg produces 52% (29% to 70%) of the maximum effect, 50mg produces 85% (68% to 97%) of the maximum effect, and 100mg produces 98% (86% to 100%).

Table 6. Pharmacodynamic Model of Mirabegron Effect from 25mg to 200mg

Dose (mg)	Micturition frequency	Mean volume voided (mL)
	Estimate (95% prediction interval)	Estimate (95% prediction interval)
25	-0.31 (-0.15 , -0.48)	6.74 (3.41 , 9.83)
30	-0.38 (-0.22 , -0.55)	8.24 (5.03 , 11.30)
35	-0.43 (-0.28 , -0.61)	9.47 (6.41 , 12.50)
40	-0.47 (-0.34 , -0.65)	10.43 (7.53 , 13.40)
50	-0.53 (-0.40 , -0.71)	11.75 (9.04 , 14.64)
60	-0.57 (-0.43 , -0.74)	12.57 (9.79 , 15.45)
70	-0.59 (-0.45 , -0.77)	13.07 (10.18 , 16.01)
75	-0.60 (-0.46 , -0.78)	13.24 (10.33 , 16.20)
80	-0.61 (-0.47 , -0.79)	13.38 (10.40 , 16.40)
100	-0.63 (-0.48 , -0.81)	13.74 (10.67 , 16.90)
125	-0.64 (-0.48 , -0.82)	13.97 (10.78 , 17.29)
150	-0.64 (-0.49 , -0.83)	14.06 (10.82 , 17.53)
200	-0.65 (-0.49 , -0.85)	14.13 (10.86 , 17.78)

Figure 6. First 50 predicted dose-response relationships for micturition frequency (left) and mean volume voided (right)

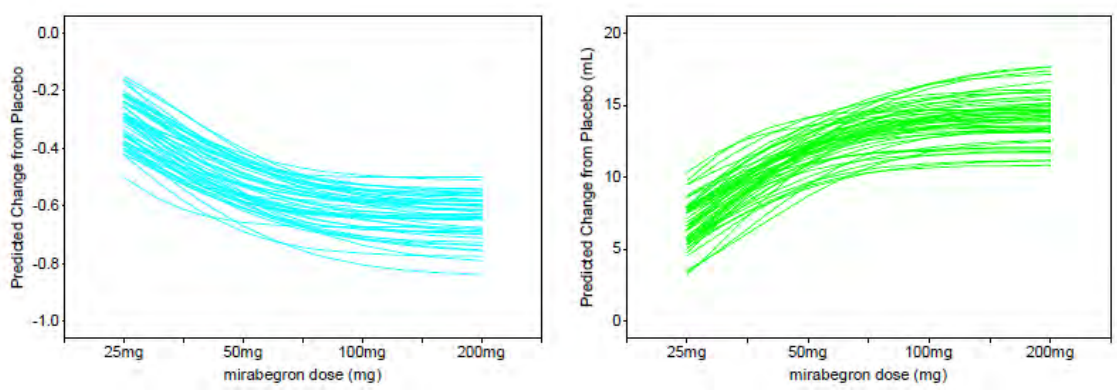
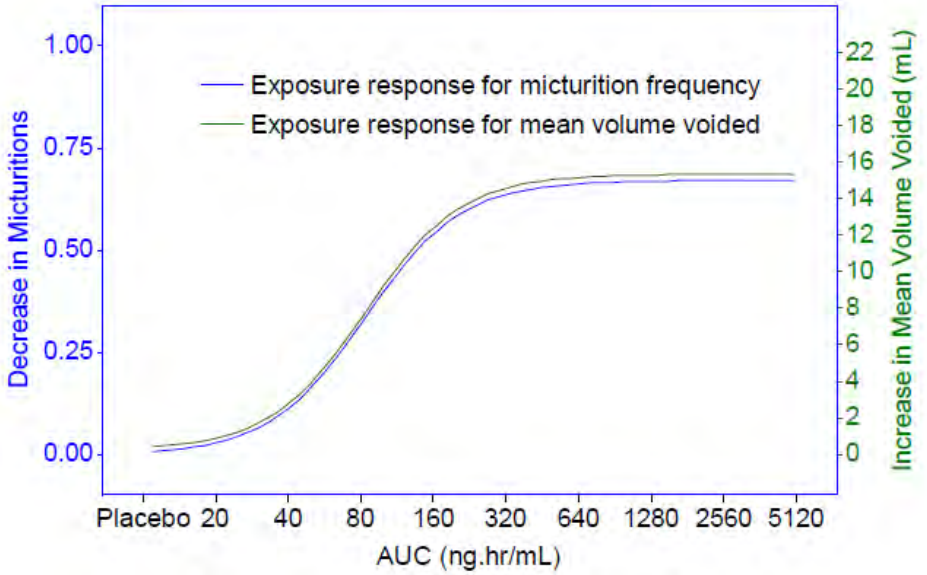


Figure 7. Idealised Dose-response Curve for Mirabegron.



5.3. Secondary pharmacodynamic studies

The sponsor submitted three secondary pharmacodynamic studies related to potential tolerability issues with a systemic beta agonist. One of these assessed the cardiovascular response to mirabegron in the presence or absence of beta blockers, confirming that mirabegron exerts a minor cardiovascular effect that is partially blocked by beta-1-selective and non-selective beta antagonists. This result is consistent with a low degree of beta-1 agonist activity, and shows that selectivity for the beta-3 AR is only relative, but the clinical consequences of the minor beta-1 agonism are minimal. A similar result was obtained in the mirabegron monotherapy arm of the tamsulosin interaction study (178-CL-080).

Another study looked for changes in intraocular pressure with continued use, finding no evidence of this. Two studies assessed the potential QT effects of mirabegron [Thorough QT Studies 178-CL-037 and 178-CL-077], but these are summarised in the Safety section (see Section 8.4.5).

None of these studies had deficiencies that excluded their results from consideration.

6. Dosage selection for the pivotal studies

Dosage selection for the pivotal studies was largely based on the phase 2b study, Study 044, which assessed the following doses:

- mirabegron OCAS 25mg qd
- mirabegron OCAS 50mg qd
- mirabegron OCAS 100mg qd
- mirabegron OCAS 200mg qd

This study is described in detail in Section 7.2.2. Active treatment with mirabegron in this study was associated with a placebo-subtracted improvement in micturition frequency of 0.45, 0.64, 0.68, and 0.80 episodes per 24 hours in the 25mg, 50mg, 100mg and 200mg groups, respectively. There was a dose trend across the range 25mg to 200mg, suggesting that 200mg

might be more effective than lower doses, but mild QT prolongation has been observed at this dose. The results in the 25mg group were not significantly different from placebo, suggesting that 25mg is likely to be an ineffective dose in most OAB patients. The proposed dose of 50mg showed a significant treatment effect, as did 100mg, but the difference between 50mg and 100mg was minor. The sponsor chose 50mg and 100mg for further evaluation, and assessed both of these doses in two pivotal studies (Study 046 and Study 047). The FDA suggested another assessment of the 25mg dose, so the third pivotal study (Study 074) assessed 25mg as well as 50mg (subsequently showing that 25mg achieved some, but nor all efficacy endpoints, and was generally inferior to the 50mg dose).

The population-PD modelling described above in Section 5.2 was performed after the pivotal studies were complete, but provides some retrospective justification of the doses chosen. The proposed 50mg dose appears to offer most of the efficacy available from mirabegron, while avoiding the increased risks expected from higher doses. It also provides a greater safety margin compared to the QT-prolonging dose of 200mg.

7. Clinical efficacy

7.1. Pivotal efficacy studies

The sponsor performed three pivotal efficacy studies, which shared most design features including entry criteria, endpoints and statistical methods. The studies differed in the doses assessed, however, and only one of them employed an active control. They are therefore best considered separately, though a pooled analysis of all three studies resembled the results obtained in each study individually (see Section 7.3).

7.1.1. Pivotal Study 046

7.1.1.1. Study design, objectives, locations and dates

Study 046 was a large (n=1987), randomised, parallel-group, international study comparing mirabegron 50mg (the proposed dose), mirabegron 100mg, tolterodine 4mg and placebo in the treatment of patients with OAB. It had a single-blind placebo run-in period of two weeks, followed by a randomised, double-blind, active and placebo-controlled main study period of 12 weeks.

Patients were randomly assigned to receive placebo, mirabegron 50mg, mirabegron 100mg or tolterodine 4mg once daily in the morning for 12 weeks.

The study was conducted in 27 countries in the EU (Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Netherlands, Poland, Romania, Slovakia, Spain, Sweden, and the United Kingdom) and non-EU countries (Australia, Belarus, Norway, Russian Federation, and Switzerland) and took place from 28 April 2008 to 24 March 2009.

7.1.1.2. Inclusion and exclusion criteria

The inclusion and exclusion criteria, as listed in the study protocol, are summarised below. In most cases, these were straightforward and aimed at recruiting patients with sufficiently symptomatic OAB, while reducing the risk of adverse events and avoiding confounding conditions. The main criterion for inclusion was OAB with 8 micturitions per day and at least one episode of urgency per day (on average) during the 3 day screening diary. Incontinence was not necessary for inclusion in the study. This meant that patients with fairly mild OAB were eligible, and that the study was not well designed for demonstrating improvements in continence. In evaluating the safety of mirabegron, it is also important to note that patients thought to be at high risk of urinary retention, or hypertension, were excluded.

Inclusion criteria at screening

- Patient ≥ 18 years of age, of either gender.
- Had symptoms of OAB (urinary frequency and urgency *with or without* incontinence) for ≥ 3 months.
- Able to give written informed consent.
- Willing and able to complete the micturition diary and questionnaires.

Inclusion criteria at baseline

- Frequency of micturition on average ≥ 8 times per 24-hour period 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.

Exclusion criteria at screening

- Breastfeeding, pregnant, or at significant risk of becoming pregnant.
- Clinically significant bladder outflow obstruction and thought to be at risk of urinary retention.
- Significant stress incontinence or mixed stress/urgency incontinence where stress was the predominant factor as determined by the investigator (confirmed by a cough provocation test).
- Indwelling catheter or practising intermittent self-catheterization.
- Diabetic neuropathy.
- Symptomatic UTI, interstitial cystitis, bladder stones, previous pelvic radiation or history of pelvic malignancy.
- Uncontrolled narrow angle glaucoma, urinary or gastric retention, severe ulcerative colitis, toxic megacolon, myasthenia gravis or any other medical condition that, in the opinion of the investigator, contraindicated the use of anticholinergics.
- Received nondrug bladder treatment including electro-stimulation therapy (bladder training programs or pelvic floor exercises were permitted if started more than 30 days prior to entry).
- Patient using medications intended to treat OAB or other prohibited medications (including anticholinergics, antispasmodics, CYP2D6 substrates with narrow therapeutic indices and other medications recommended not to be used with tolterodine, such as strong CYP3A4 inhibitors, antiarrhythmics).
- Patient had severe hypertension, which was defined as a sitting average systolic blood pressure (SBP) ≥ 180 mm Hg and/or average diastolic blood pressure (DBP) ≥ 110 mm Hg.
- Known or suspected hypersensitivity to tolterodine, other anticholinergics, mirabegron, other beta-AR agonists, or any of the other inactive ingredients.
- Any other clinically significant condition, which in the opinion of the investigator made the patient unsuitable.
- Patient had been treated with any investigational drug or device within 30 days (90 days in the UK) prior to screening.
- Patient professionally associated with the sponsor or study centre.

Exclusion criteria at baseline

- Patient had an average daily urine volume > 3000 mL recorded in the 3-day micturition diary.
- Clinically significant increases in laboratory values in screening blood samples (serum creatinine >150 umol/L, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 times the upper limit of normal range (ULN), or gamma glutamyl transferase (GGT) >3 times the ULN).
- Severe hypertension, defined as a sitting average SBP ≥ 180 mmHg or average DBP ≥ 110 mmHg.
- An abnormal ECG (at the investigator's discretion).

7.1.1.3. Study treatments

Patients were randomised in equal proportions to receive placebo, mirabegron 50mg, mirabegron 100mg or tolterodine slow-release (SR) 4mg once daily in the morning, with or without food, for 12 weeks.

The dose of tolterodine SR selected for this study (4 mg) is the standard daily dose used in the EU, US and Australia for treatment of OAB.

Several concomitant medications were restricted during the study: these included alpha blockers, 5-alpha reductase inhibitors, CYP3A4 inducers and loop diuretics. Restricted medications were permitted provided the patient had not stopped, started or changed treatment within 30 days prior to entering the study.

7.1.1.4. Efficacy variables and outcomes

7.1.1.4.1. Co-primary Endpoints

The main efficacy variables were:

- Mean number of micturitions/24h based on a 3-day micturition diary
- Mean number of incontinence episodes/24h based on a 3-day micturition diary

The co-primary efficacy outcomes were:

- Change from baseline to end of treatment in mean number of micturitions/24h
- Change from baseline to end of treatment in mean number of incontinence episodes/24h

The study seemed poorly designed for assessment of the second co-primary endpoint, incontinence frequency, because it included subjects with *a single episode per 3-day diary period*. The number of incontinence episodes in three days is necessarily an integer, and because subjects with the lowest possible non-zero value were included, any improvement at all in such subjects was necessarily a 100% improvement, without any capacity for more accurate characterisation of their true underlying incontinence frequency.

Such sparse sampling of a discrete event makes accurate characterisation of any potential treatment effect very difficult, and runs the risk that regression-to-the-mean effects will be mistaken for efficacy. If two patients with a baseline incontinence frequency of one episode per week entered this study, but only one happened to have an episode during the three-day baseline diary period, only one would enter the incontinence subgroup. If their situations were reversed at the end of the study with respect to whether the diary caught the weekly episode of incontinence, without any *actual* change in incontinence frequency, the patient who had entered the incontinence subgroup would appear to have a 100% improvement while the other patient would not enter the analysis at all. This produces a potential bias towards an appearance of improvement even when the actual incontinence frequency across the population has not

changed. Although such effects could also occur on the placebo group, it is not necessarily simple to disentangle this methodological bias from any potential treatment. (In fact, a responder analysis across the pivotal population showed a high proportion of 100% responders in the placebo group, as discussed in Section 7.3.

7.1.1.4.2. Secondary efficacy outcomes

Change from baseline in volume voided per micturition was considered a key secondary outcome. Note that, for any specified volume of urine production, the volume per micturition is inversely related to the number of micturition episodes, so this endpoint would not be expected to capture substantial new clinical information. The two co-primary efficacy variables were also assessed at Week 4, and results at this time point were considered key secondary efficacy outcomes.

Non-key secondary endpoints are listed below. (Subjective endpoints have been italicised.)

- Change from baseline in mean number of urgency incontinence episodes per 24h.
- Change from baseline in mean number of severe urgency episodes (grade 3 or 4) per 24h.
- *Change from baseline in mean level of urgency.*
- *Change from baseline in symptom bother and health related quality of life scores as assessed by OAB-q questionnaire.*
- Change from baseline in mean number of pads used per 24h.
- *Change from baseline in scores as assessed by Work Productivity and Activity Impairment: Specific Health Problem (WPAI:SHP) questionnaire.*
- *Change from baseline in scores as assessed by European Quality of Life-5 Dimensions (EQ-5D) questionnaire.*
- *Change from baseline in Patient Perception of Bladder Condition (PPBC).*
- *Change from baseline in the Treatment Satisfaction Visual Analog Scale (TS-VAS).*
- Change from baseline in the number of physician visits for the subject's bladder condition (excluding study related visits).
- Change from baseline in mean number of nocturia episodes per 24h.

The first of these secondary endpoints is the change in frequency of urgency incontinence – which differs from the primary endpoint of all-cause incontinence because it excludes incontinence attributed by the patient to other causes, such as stress incontinence. Although mirabegron is proposed for treatment of urgency, and urgency incontinence is thus a major clinical target of treatment, it is appropriate to consider this a mere secondary endpoint. The attribution of the cause of incontinence is not necessarily reliable, and a treatment would not be useful if it merely shifted the attribution of the cause of incontinence without actually reducing the number of episodes.

The 'mean level of urgency' was calculated from subjective urgency assessments entered into the 3-day micturition diary. For each episode of voluntary or involuntary voiding, the patient rated the degree of associated urgency according to the following 5-point categorical scale (Patient Perception of Intensity of Urgency Scale, or PPIUS):

- 0. No urgency, I felt no need to empty my bladder, but did so for other reasons.
- 1. Mild urgency, I could postpone voiding as long as necessary, without fear of wetting myself.
- 2. Moderate urgency, I could postpone voiding for a short while, without fear of wetting myself.

- 3. Severe urgency, I could not postpone voiding, but had to rush to the toilet in order not to wet myself.
- 4. Urge incontinence, I leaked before arriving to the toilet.

Many of the secondary endpoints were subjective, and were based on patients completing questionnaires (OAB-q, WPAI:SHP, EQ-5D), selecting a value from a Likert scale (PPBC) or marking a line on a visual analog scale (TS-VAS). The inclusion of such measures is broadly appropriate. The EU Note for Guidance on studies of incontinence specifically recommends that at least one subjective endpoint be included to assess the overall impact of treatment. On the other hand, the large number of such endpoints in this study meant that no clear hypothesis was being assessed, and the multiplicity of endpoints leaves room to emphasize one subjective finding over another, leaving no clear way to interpret the clinical significance of the various results.

Specific OAB symptoms and QoL in relation to OAB were assessed by the OAB-q, as described by Coyne et al (2005); this questionnaire, also known as International Consultation on Incontinence Questionnaire for OAB (ICIQ-OAB) has been recommended by the International Consultation on Incontinence (Coyne and Matza, 2002, Coyne et al 2003, 2005). The questionnaire is reported to have good psychometric properties, and has shown to be valid and responsive in treatment trials (Sussman & Garely, 2002, Garely et al, 2007). It is a self-report questionnaire described by Coyne et al (2005) as follows:

> "The OAB-q consists of an 8-item symptom bother scale and 25 HRQL items that form 4 subscales (coping, concern, sleep, and social interaction) and a total HRQL score. Patients rate each item on a 6-point Likert scale ranging from 'none of the time' to 'all of the time' for the HRQL items and 'not at all' to 'a very great deal' for the symptom bother items. Subscales are summed and transformed into scores ranging from 0 to 100; higher symptom bother scores indicate increasing symptom bother, higher HRQL scores indicate better HRQL."

The 'symptom bother' subscale was treated as one secondary endpoint, and the HRQL component of the OAB-q as another. The OAB-q was administered at baseline and weeks 4, 8, and 12 (or the end of treatment).

The Patient Perception of Bladder Condition (PPBC) is a global assessment tool. Subjects are asked to rate their subjective impression of their current bladder condition using a 6-point Likert scale in which a score of 1 indicates "no problems at all" and a score of 6 indicates "many severe problems." Negative changes therefore indicate improvements. The PPBC was assessed at baseline and at week 12 (or the end of treatment).

The Treatment Satisfaction-Visual Analog Scale (TS-VAS) is a simple visual analog scale (VAS) in which higher values indicate higher satisfaction. Subjects are asked to rate their satisfaction with the treatment of interest by placing a mark on a line that runs from 0 ("No, not at all") to 10 ("Yes, completely").

Validation of the PPBC and TS-VAS was not discussed in the clinical study report, but these are very simple assessment tools with a fairly straightforward interpretation. As with any subjective tool, they would be expected to be quite susceptible to a placebo effect, and so only placebo-subtracted differences have any meaning. The magnitude of a small shift on such scales is also difficult to put into clinical context; no means of calibrating the results was provided or discussed.

The WPAI:SHP and EQ-5D are more general quality of life assessment tools, intended to detect changes in the broader context of the patient's life and the impact of their symptoms on their social, psychological and employment conditions. The EQ-5D has been used in many similar studies and is widely regarded as a valid and responsive tool (Walters et al, 2009); it is an international, standardised instrument, not specific to any disease, used for describing and

evaluating health status in five dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression. Each dimension has 3 response levels (e.g, no problems, some problems, unable to perform the activity). It also includes a visual analog scale (VAS) that elicits a self-rating of the subject's overall health status.

The WPAI:SHP has been described and validated by Reilly et al (1993) as a tool for assessing the interference of health problems with work and productivity. It is a self-administered questionnaire with 6 questions referring to the patient's experiences in the previous week. The 6 questions cover: employment status; hours absent from work due to a specific health problem; hours absent from work due to other reasons; hours actually worked; impact of the health problem on productivity while working; impact of the health problem on productivity while doing regular daily activities other than work. Overall, it was an appropriate tool for assessing the impact of OAB on productivity, but because it was one of many subjective measures used in the pivotal studies, it added little to the overall assessment.

Finally, the frequency of nocturia was also assessed. This endpoint is not suitable as a primary endpoint because psychological factors and patient expectations may affect the decision to void pre-emptively before bed or to defer voiding until after getting up. Nonetheless, it is an endpoint that can reflect important intrusions on quality of life, with nocturia causing sleep interruptions, and it was appropriate to include it.

7.1.1.5. Randomisation and blinding methods

Subjects were randomised if they were still eligible after a placebo run-in period. Randomisation to each treatment group was equal, with stratification by country, and was performed using a computer-generated randomization scheme prepared by *Pierrel Research Europe*.

Blinding was maintained by using a centralised randomisation procedure and placebo tablets that matched the appearance of active treatments, with the randomisation code only broken after the study was complete. The drug did not produce characteristic side effects that are likely to have led to unblinding, and the treatment effect was modest enough that subjects are unlikely to have guessed their treatment group.

7.1.1.6. Analysis populations

The sponsor defined four analysis populations: the Safety Analysis Set (SAF), the Full Analysis Set (FAS, almost equivalent to an intent-to-treat population), the Per Protocol Set (PPS) and the Pharmacokinetics Analysis Set (PKAS).

The primary efficacy analysis was based on the FAS, which included subjects who took at least one dose of double-blind study medication after randomisation and also provided data on micturitions at baseline and on at least one post baseline visit (without at least one post-baseline micturition frequency, these subjects could not be assessed).

Note that the sponsor assessed incontinence in a subgroup of the FAS, defined as those with at least one episode of incontinence in the baseline 3-day screening diary. This population is referred to in the tables as the FAS-incontinence or FAS-I population.

The SAF included all subjects who received at least one dose. The PPS excluded FAS subjects with major protocol violations. The PKAS included subjects with at least one quantifiable level of mirabegron.

7.1.1.7. Statistical methods

The sponsor described the statistical analysis of the primary efficacy variables in detail, and provided appropriate corrections for multiplicity of the mirabegron dose groups for the separate analyses of the two variables of micturition and incontinence, as described below. The sponsor also controlled the overall analysis for multiplicity between the variables at a type I error rate at the alpha = 0.05 level, using a stepwise parallel gate-keeping procedure. That is,

analysis of lower-ranking variables only proceeded if significance was demonstrated for higher-ranking variables. Also, since 2 mirabegron groups were being compared with placebo, the Hochberg procedure was performed in this stepwise approach: if only 1 dose group proceeded to the next stage, then the comparison between mirabegron and placebo was assessed at the alpha = 0.025 level.

These corrections and the overall statistical approach were appropriate, but the incontinence analysis was flawed by the recruitment of subjects with minimal incontinence.

Primary endpoint: change in mean number of micturitions per 24h

Changes from baseline to end of treatment in the mean number of micturitions per 24h were analysed using ANCOVA including treatment and country as fixed factors and baseline frequency as a covariate. The sponsor stated the hypothesis for the comparison as follows:

> H0: Mean number of micturitions per 24h at end of treatment is the same for placebo and mirabegron 50mg and the same for placebo and mirabegron 100mg.
>
> H1: Mean number of micturitions per 24h at end of treatment is not the same for placebo and mirabegron 50mg or not the same for placebo and mirabegron 100mg.

Because two mirabegron dose groups were used, increasing the probability that one of them could do better than placebo, the sponsor used Dunnett's procedure within the ANCOVA analysis to adjust for multiplicity, keeping the significance level at 5%.

Co-primary endpoint: change in mean number of incontinence episodes per 24h

Changes from baseline in the mean number of incontinence episodes per 24h were analysed by a stratified Wilcoxon rank-sum test with study centre as the stratification factor. Mirabegron 50mg and mirabegron 100mg were separately compared with placebo, and the Bonferroni-Holm procedure was applied to keep the overall two-sided significance level at the 5% level. The protocol specified that Hodges-Lehman estimates and CI's would be provided for each of the comparisons vs placebo.

Note that only subjects with at least one incontinence episode recorded in the baseline diary were included in the analysis of mean number of incontinence episode per 24h.

7.1.1.8. Sample size

For analysis of micturition frequency, the sponsor estimated that a sample size of 362 evaluable patients per treatment group would provide about 90% power to detect a reduction of 0.7 in the mean number of micturitions per 24 hours over placebo in at least one dose group at a 2-sided significance level of 0.05. For this estimation, the standard deviation of the primary efficacy variable was assumed to be up to 2.7, based on Study 178-CL-044, where a SD of 2.5 was found with an upper 97.5% CI limit of 2.65. Both mirabegron doses were compared with placebo by means of the Dunnett's test, which takes into account multiplicity.

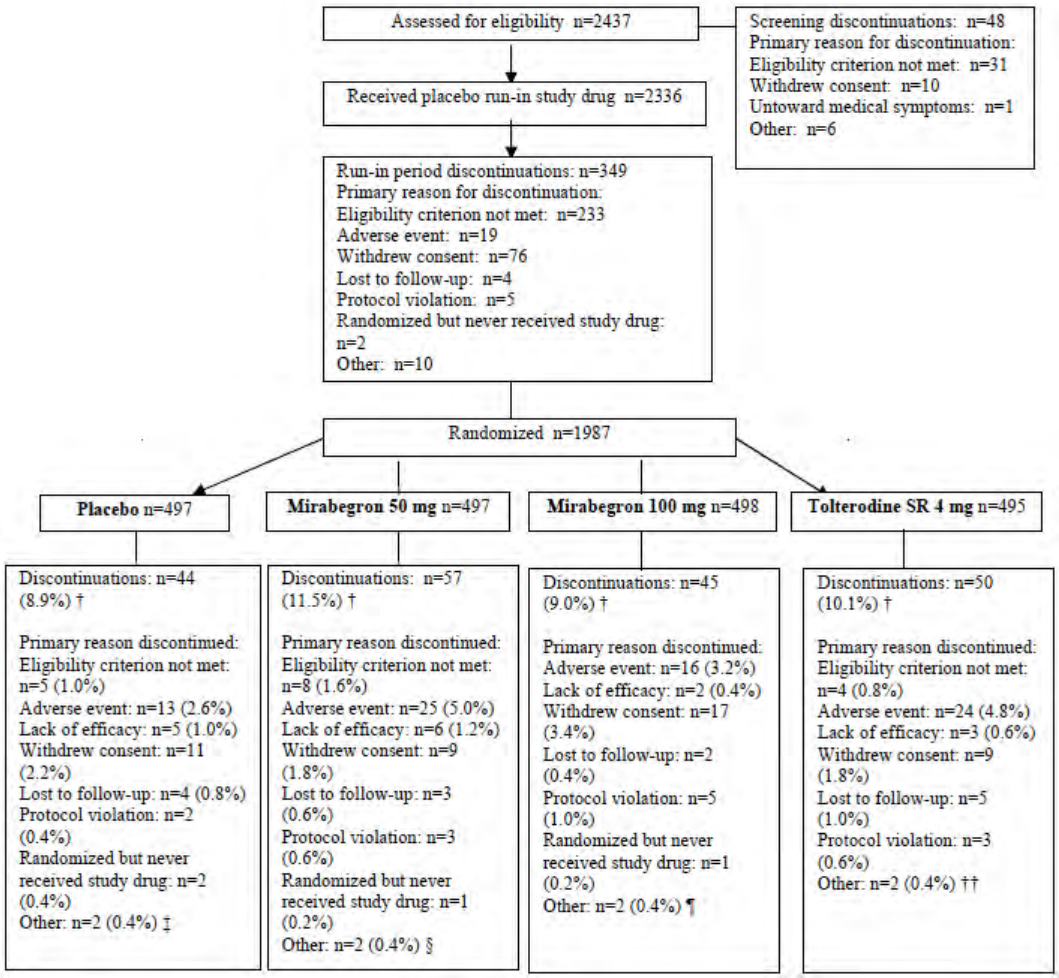
For the analysis of incontinence, power calculations were based on the expected size of the subset of patents with incontinence in their baseline diary. From Study 178-CL-044, it was estimated that this would be ~65% of the study population (234 patients per group, if the target of 362 subjects was met for the other co-primary endpoint). The sponsor performed a power analysis with nQuery 6.0 for a Wilcoxon rank-sum test based on ordered categories of incontinence, and this revealed a power of 97% for a 2-sided significance level of 2.5%.

Allowing for 20% dropouts in the placebo run-in phase and for 15% of randomised subjects being non-evaluable, the target recruitment was 430 patients per treatment group. The study achieved its recruitment targets and also demonstrated statistical significance for its primary endpoints, indicating that it was adequately powered.

7.1.1.9. Participant flow

Patient disposition is summarised in the figure below. Discontinuations occurred in 8.9% to 11.5% of randomised subjects across the different treatment groups, which is acceptable for a study of this nature. The differences in withdrawal rates across the treatment groups were small and therefore it is unlikely that withdrawal bias contributed to the positive findings of this study.

Figure 8. Patient Disposition in Study 046



7.1.1.10. Major protocol violations/deviations

Protocol deviations are summarised in the table below. A range of deviations occurred, with the most common being failure to complete the micturition diary for the full study period. Overall, these deviations were similar across treatment groups and do not appear likely to have introduced any major biases into the study.

Table 7. Reasons for Exclusion from the Per Protocol Analysis Set, FAS, Study 046

Parameter, n (%)	Placebo (n=480)	Mirabegron 50 mg (n=473)	Mirabegron 100 mg (n=478)	Tolterodine SR 4 mg (n=475)
Total number of patients excluded, n (%)	55 (11.5%)	56 (11.8%)	52 (10.9%)	49 (10.3%)
Reasons				
Eligibility Violations Based on 3-Day Micturition Diary				
During 3-day baseline diary period:				
Average of < 8 micturitions per 24 hours	11 (2.3%)	11 (2.3%)	6 (1.3%)	9 (1.9%)
< 3 episodes of urgency (grade 3 or 4)	5 (1.0%)	2 (0.4%)	3 (0.6%)	2 (0.4%)
Average daily volume voided > 3000 mL	5 (1.0%)	4 (0.8%)	3 (0.6%)	4 (0.8%)
Eligibility Violations Not Based on 3-Day Micturition Diary				
Symptomatic UTI, chronic inflammation or malignant disease of the pelvic organs	6 (1.3%)	5 (1.1%)	4 (0.8%)	7 (1.5%)
Nondrug treatment for OAB prior to screening	1 (0.2%)	0	0	1 (0.2%)
Error in Study Drug Administration Compared to Assigned Treatment				
Accidental intake of incorrect study drug during double-blind treatment period†	2 (0.4%)	2 (0.4%)	1 (0.2%)	1 (0.2%)
Poor Study Drug Compliance				
Poor study drug compliance (< 70%) during the double-blind treatment period	2 (0.4%)	3 (0.6%)	6 (1.3%)	5 (1.1%)
Inadequate Duration of Treatment				
Duration of placebo treatment in placebo run-in period was too short	1 (0.2%)	6 (1.3%)	1 (0.2%)	3 (0.6%)
Last diary day of the Final Visit was < 53 days	18 (3.8%)	29 (6.1%)	20 (4.2%)	18 (3.8%)
Unblinding of Treatment				
Unblinding of treatment for double-blind study drug	7 (1.5%)	9 (1.9%)	6 (1.3%)	9 (1.9%)
Prohibited Concomitant Medication				
Treatment during placebo run-in or double-blind period with prohibited concomitant medication of anticholinergics/antispasmodics indicated for treatment of OAB	2 (0.4%)	4 (0.8%)	4 (0.8%)	1 (0.2%)

7.1.1.11. Baseline data

Baseline data in the full analysis set (FAS) is summarised in the tables below. In terms of demographics (Table 8), the groups were well-matched at baseline. They were moderately well-matched in terms of previous OAB history (Table 10), but the proportion of patients with prior OAB surgery was slightly higher in the mirabegron 50mg group than in other groups. This could indicate a slightly more refractory population in this group, and might be expected to make it more difficult to demonstrate the efficacy of mirabegron. The baseline micturition frequencies (Table 11) were well-matched. Overall, the minor differences at baseline are not likely to have compromised interpretation of the results.

Table 8. Summary of Patient Demographics and Baseline Characteristics, FAS, Study 046

Parameter	Placebo (n=480)	Mirabegron 50 mg (n=473)	Mirabegron 100 mg (n=478)	Tolterodine SR 4 mg (n=475)	Total (n=1906)
Sex (n, %)					
Male	134 (27.9%)	133 (28.1%)	138 (28.9%)	129 (27.2%)	534 (28.0%)
Female	346 (72.1%)	340 (71.9%)	340 (71.1%)	346 (72.8%)	1372 (72.0%)
Age (years)					
Mean (SD)	59.3 (12.15)	59.2 (12.15)	58.9 (12.69)	59.1 (12.75)	59.1 (12.43)
Age group (years) (n, %)					
< 65	302 (62.9%)	302 (63.8%)	306 (64.0%)	291 (61.3%)	1201 (63.0%)
≥ 65	178 (37.1%)	171 (36.2%)	172 (36.0%)	184 (38.7%)	705 (37.0%)
< 75	437 (91.0%)	430 (90.9%)	435 (91.0%)	442 (93.1%)	1744 (91.5%)
≥ 75	43 (9.0%)	43 (9.1%)	43 (9.0%)	33 (6.9%)	162 (8.5%)
Race (n, %)					
White	477 (99.4%)	468 (98.9%)	474 (99.2%)	472 (99.4%)	1891 (99.2%)
Black or African American	2 (0.4%)	1 (0.2%)	1 (0.2%)	2 (0.4%)	6 (0.3%)
Asian	0	2 (0.4%)	2 (0.4%)	1 (0.2%)	5 (0.3%)
Other †	1 (0.2%)	2 (0.4%)	1 (0.2%)	0	4 (0.2%)
BMI (kg/m^2)					
n	480	473	477	475	1905
Mean (SD)	27.8 (4.97)	27.5 (4.90)	28.0 (4.87)	27.9 (4.97)	27.8 (4.93)
Geographical region (n, %)					
Eastern Europe	221 (46.0%)	210 (44.4%)	221 (46.3%)	221 (46.5%)	873 (45.8%)
Western Europe‡	259 (54.0%)	263 (55.6%)	257 (53.8%)	254 (53.5%)	1033 (54.2%)

Table 9. Overactive Bladder History, FAS, Study 046

Parameter	Placebo (n=480)	Mirabegron 50 mg (n=473)	Mirabegron 100 mg (n=478)	Tolterodine SR 4 mg (n=475)
Type of OAB (n, %) †				
Urgency incontinence	201 (41.9%)	192 (40.6%)	179 (37.4%)	184 (38.7%)
Frequency	177 (36.9%)	173 (36.6%)	183 (38.3%)	186 (39.2%)
Mixed	102 (21.3%)	108 (22.8%)	116 (24.3%)	105 (22.1%)
Prior OAB Surgery (n, %)				
Yes	22 (4.6%)	33 (7.0%)	28 (5.9%)	17 (3.6%)
Previous OAB drug (n, %)				
Yes	238 (49.6%)	240 (50.7%)	237 (49.6%)	231 (48.6%)
Reason for previous OAB drug discontinuation (n, %) ‡				
Insufficient effect				
Yes	159 (66.8%)	160 (66.7%)	159 (67.1%)	155 (67.1%)
Poor tolerability				
Yes	68 (28.6%)	65 (27.1%)	64 (27.0%)	56 (24.2%)
Duration of OAB symptoms (months)				
Mean (SD)	76.9 (92.15)	78.7 (85.68)	85.3 (95.24)	76.3 (93.40)
Median	50.5	49.9	53.4	47.2
Range	3 – 688	3 – 637	3 – 567	3 – 711

Table 10. Overactive Bladder-related Baseline Characteristics, FAS, Study 046

Parameter	Placebo (n=480)	Mirabegron 50 mg (n=473)	Mirabegron 100 mg (n=478)	Tolterodine SR 4 mg (n=475)
Mean number of micturitions per 24 hours Mean (SD) Range	11.71 (3.138) 5.3 – 25.0	11.65 (2.972) 6.7 – 25.7	11.51 (2.703) 6.7 – 23.3	11.55 (2.779) 6.0 – 22.7
Mean number of incontinence episodes per 24 hours Mean (SD) Range	NA	NA	NA	NA
Mean number of urgency incontinence episodes per 24 hours Mean (SD) Range	NA	NA	NA	NA
Mean volume voided per micturition (mL) n Mean (SD) Range	(n=480) 156.7 (52.51) 51 – 336	(n=472) 161.1 (58.40) 30 – 397	(n=478) 158.2 (53.14) 37 – 367	(n=475) 158.6 (54.13) 19 – 402
Mean number of urgency episodes (grade 3 or 4) per 24 hours n Mean (SD) Range	(n=480) 5.76 (3.994) 0 – 24.3	(n=473) 5.69 (3.653) 0 – 20.7	(n=477) 5.94 (3.705) 0 – 22.3	(n=474) 5.77 (3.446) 0 – 22.7
Mean level of urgency n Mean (SD) Range	(n=480) 2.37 (0.562) 0 – 4.0	(n=473) 2.40 (0.543) 0.5 – 4.0	(n=477) 2.45 (0.520) 0.6 – 4.0	(n=474) 2.41 (0.556) 0.5 – 4.0
Mean number of nocturia episodes per 24 hours Mean (SD) Range	1.98 (1.412) 0 – 9.7	1.87 (1.293) 0 – 6.3	1.90 (1.356) 0 – 8.0	1.95 (1.412) 0 – 8.3

7.1.1.12. Results for the primary efficacy outcome

Results for the two co-primary endpoints and three key secondary endpoints are summarised in the table below. This study was positive for both of its co-primary endpoints, but the magnitude of the treatment effect was small.

A beneficial change from baseline (BL) to final visit (FV) in the mean number of micturitions was observed in all treatment groups, including the placebo group. In placebo recipients, the mean improvement in micturition frequency was 1.34 episodes per 24 hrs (95%CI for change was -1.55 to -1.12) from a baseline of 11.7 episodes per 24 hrs. This is likely to be due to a combination of the placebo effect and regression to the mean. A pronounced placebo response in urinary urgency studies has been noted by many investigators and is explicitly mentioned in the EU guide for analysis of such studies. Given that voluntary voiding can often be postponed, and that urgency is subjective, many patients may have deferred voiding in the expectation of a response to treatment, lowering their micturition frequency. Also, subjects with variable urgency are likely to have been recruited during periods of greater urgency and then regressed to their average level of urgency during the course of the study.

Compared to the placebo effect, the actual treatment effect was even smaller: the lower dose group (mirabegron 50mg) experienced a reduction of 0.6 micturition episodes per 24 hrs (based on the adjusted mean change) compared to placebo, and the higher dose group (mirabegron 100mg) experienced a reduction in micturition frequency of 0.44 episodes per 24hrs. Across both mirabegron groups, the treatment effect was about half an episode of micturition. That is, over the course of two days, when ~23 episodes of voiding would be expected, about one episode of *voluntary* voiding would be prevented by active treatment. This

hardly seems clinically worthwhile, though it was statistically significant. (For p-values in all pivotal studies and for all major endpoints, see Section 7.3).

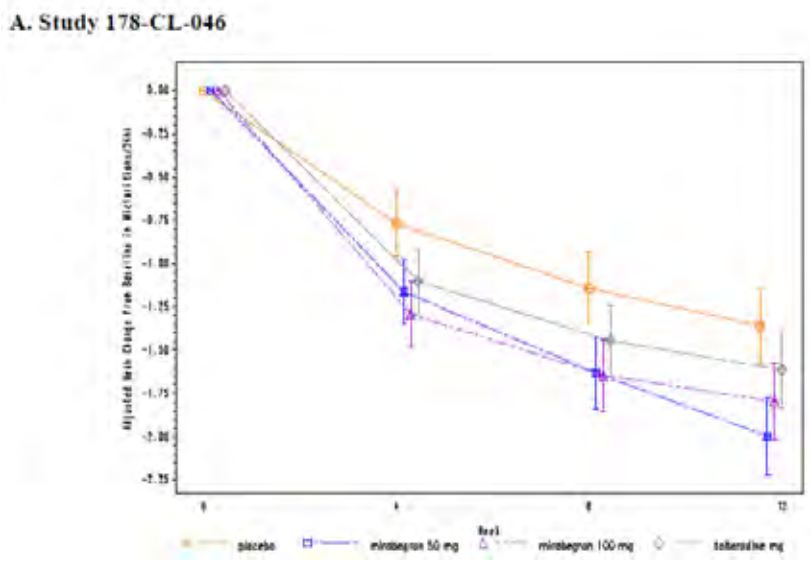
The change in micturition frequency with tolterodine was even more disappointing: the adjusted mean difference from placebo was 0.25 episodes per 24 hrs, or one episode of micturition prevented every four days, with a 95% CI including the possibility of zero difference from placebo.

Table 11. Results for Coprimary and Key Secondary Endpoints, Study 046

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Statistic	Coprimary Efficacy Endpoints+		Key Secondary Efficacy Endpoints+		
			Change from BL to FV in Mean Number of Incontinence Episodes per 24 Hours (FAS-I)	Change from BL to FV in Mean Number of Micturitions per 24 Hours (FAS)	Change from BL to FV in Mean Volume Voided (mL) per Micturition (FAS)	Change from BL to Week 4 in Mean Number of Incontinence Episodes per 24 Hours (FAS-I)	Change from BL to Week 4 in Mean Number of Micturitions per 24 Hours (FAS)
178-CL-046 (SCORPIO)	Placebo 497/453	n	291	480	480	291	479
		Baseline	2.67 (0.140)	11.71 (0.143)	156.7 (2.40)	2.67 (0.140)	11.72 (0.143)
		Change from Baseline	-1.17 (0.113) (-1.39, -0.95)	-1.34 (0.110) (-1.55, -1.12)	12.3 (1.99) (8.4, 16.3)	-0.65 (0.118) (-0.88, -0.42)	-0.77 (0.096) (-0.96, -0.58)
	Mirabegron OCAS 50 mg 497/440	n	293	473	472	293	471
		Baseline	2.83 (0.165)	11.65 (0.137)	161.1 (2.69)	2.83 (0.165)	11.64 (0.137)
		Change from Baseline	-1.57 (0.113) (-1.79, -1.35)	-1.93 (0.111) (-2.15, -1.72)	24.2 (2.01) (20.3, 28.2)	-1.04 (0.118) (-1.27, -0.81)	-1.16 (0.097) (-1.35, -0.97)
		Difference from Placebo	-0.41 (0.160)# (-0.72, -0.09)	-0.60 (0.156)# (-0.90, -0.29)	11.9 (2.83)# (6.3, 17.4)	-0.39 (0.167)# (-0.71, -0.06)	-0.40 (0.136)# (-0.66, -0.13)
	Mirabegron OCAS 100 mg 498/453	n	281	478	478	281	477
		Baseline	2.89 (0.147)	11.51 (0.124)	158.2 (2.43)	2.89 (0.147)	11.51 (0.124)
		Change from Baseline	-1.46 (0.115) (-1.68, -1.23)	-1.77 (0.110) (-1.99, -1.56)	25.6 (2.00) (21.6, 29.5)	-1.03 (0.120) (-1.27, -0.79)	-1.29 (0.096) (-1.48, -1.10)
		Difference from Placebo	-0.29 (0.162)# (-0.61, 0.03)	-0.44 (0.156)# (-0.74, -0.13)	13.2 (2.82)# (7.7, 18.7)	-0.38 (0.169)# (-0.71, -0.05)	-0.52 (0.136)# (-0.79, -0.26)
	Tolterodine ER 4 mg 495/445	n	300	475	475	299	474
		Baseline	2.63 (0.148)	11.55 (0.128)	158.6 (2.48)	2.64 (0.148)	11.55 (0.128)
		Change from Baseline	-1.27 (0.112) (-1.49, -1.05)	-1.59 (0.111) (-1.80, -1.37)	25.0 (2.00) (21.1, 28.9)	-1.00 (0.117) (-1.23, -0.77)	-1.10 (0.096) (-1.29, -0.91)
		Difference from Placebo	-0.10 (0.159) (-0.42, 0.21)	-0.25 (0.156) (-0.55, 0.06)	12.6 (2.83)* (7.1, 18.2)	-0.35 (0.166)* (-0.68, -0.03)	-0.33 (0.136)* (-0.60, -0.06)

These results are displayed graphically below. Note that the sponsor's method of displaying the results provides no reference to the baseline values, and the vertical axis has been scaled so that the modest improvements discussed above take up most of the vertical space. If the vertical axis showed actual micturition frequency (rather than change in frequency) and ranged from zero up to the baseline values of 11-12, the fall in frequency with treatment would have a shallow gradient rather than the steep fall displayed. As a percentage of baseline urinary frequency, the treatment effect was only 5% (0.60/11.65) and 4% (0.44/11.51) respectively.

Figure 9. Adjusted Mean Change in Micturition Frequency, Study 046



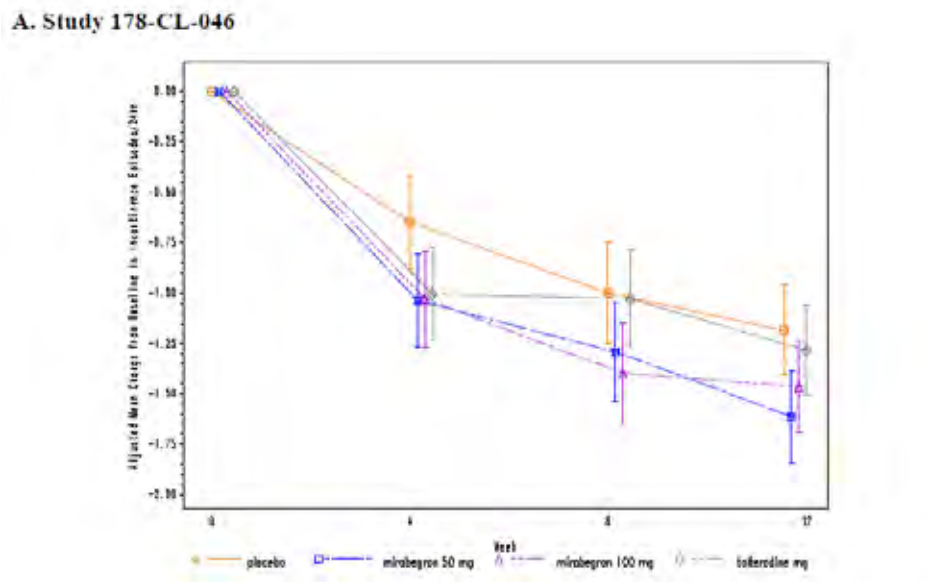
The other co-primary endpoint, incontinence frequency, was only assessed in the FAS-I subgroup, which included about 60% of subjects. The placebo effect for this endpoint was quite

pronounced: from a baseline incontinence frequency of 2.67 episodes per 24 hrs, the placebo group experienced a mean reduction of 1.17 episodes (95%CI -1.39 to -0.95). This degree of improvement would be clinically worthwhile if sustained – it represents an approximate halving of baseline incontinence – but it has been achieved without active treatment and is likely to reflect psychological placebo effects and regression to the mean.

Compared to the placebo effect, the additional improvement in incontinence attributable to active treatment was modest. In the mirabegron 50mg dose group, the mean reduction in incontinence compared to placebo was 0.41 episodes. In the mirabegron 100mg dose group, the reduction was 0.29 episodes per 24 hours (about one episode prevented every three to four days). This is of marginal clinical value. For the mirabegron 50mg group, the treatment-effect of 0.41 episodes represents 14% of the baseline incontinence (0.41/2.83) and 26% of the observed improvement (0.41/1.57). For the mirabegron 100mg group, the treatment-effect of 0.29 episodes represents 10% of baseline incontinence (0.29/2.89) and 20% of the observed improvement (0.29/1.46).

These results are displayed in the table above, and represented graphically below. The y-axis has again been scaled so that the change takes up most of the vertical space.

Figure 10. Adjusted Mean Change in Incontinence Frequency, Study 046

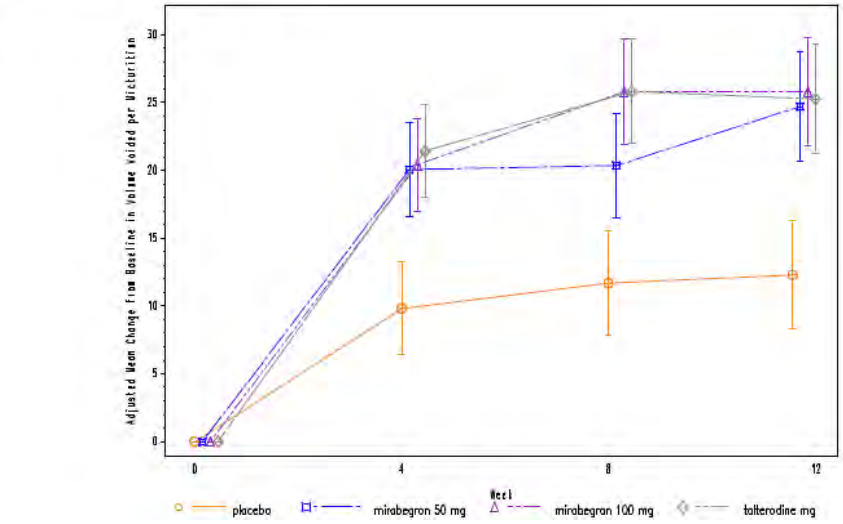


7.1.1.13. Results for other efficacy outcomes

Results for key secondary endpoints are included in the last three columns of the table above, reproduced below. The volume voided per micturition was ~160mL in all groups at baseline, and increased by a mean of 12.3 mL in the placebo group, 24.2 mL with mirabegron 50mg, 25.6 mL with mirabegron 100mg, and 25 mL with tolterodine. The mean differences from placebo were 12-13 mL across all active groups, with 95%CIs showing that these differences were significantly separated from the placebo results. The tolterodine results were similar to the mirabegron results. Despite achieving statistical significance, the clinical value of storing another 12 mL of urine between voids is marginal. The results are depicted graphically below; again the y-axis has been scaled according to the maximum change in volume, not the baseline volume.

Figure 11. Adjusted Mean Change in Volume Voided, Study 046

A. Study 178-CL-046



Changes for the key efficacy variables of incontinence and micturition frequency were also assessed at the non-primary endpoint of 4 weeks. Differences from placebo were broadly similar to the 12-week results, as is best appreciated from the figures above. The frequency of micturition and the frequency of incontinence both continued to improve across the 12 week study, a pattern that was also seen with the placebo group. There was no consistent pattern in the difference between active and placebo treatment in this regard. For micturition frequency, the difference from placebo was 0.40 episodes and 0.52 episodes at 4 weeks, compared to 0.6 and 0.44 at 12 weeks for the 50mg and 100mg dose groups, respectively.

Table 12. Results for Key Secondary Endpoints, Study 046

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Statistic	Key Secondary Efficacy Endpoints†		
			Change from BL to FV in Mean Volume Voided (mL) per Micturition (FAS)	Change from BL to Week 4 in Mean Number of Incontinence Episodes per 24 Hours (FAS-I)	Change from BL to Week 4 in Mean Number of Micturitions per 24 Hours (FAS)
178-CL-046 (SCORPIO)	Placebo 497/453	n	480	291	479
		Baseline	156.7 (2.40)	2.67 (0.140)	11.72 (0.143)
		Change from Baseline	12.3 (1.99) (8.4, 16.3)	-0.65 (0.118) (-0.88, -0.42)	-0.77 (0.096) (-0.96, -0.58)
	Mirabegron OCAS 50 mg 497/440	n	472	293	471
		Baseline	161.1 (2.69)	2.83 (0.165)	11.64 (0.137)
		Change from Baseline	24.2 (2.01) (20.3, 28.2)	-1.04 (0.118) (-1.27, -0.81)	-1.16 (0.097) (-1.35, -0.97)
		Difference from Placebo	11.9 (2.83)# (6.3, 17.4)	-0.39 (0.167)# (-0.71, -0.06)	-0.40 (0.136)# (-0.66, -0.13)
	Mirabegron OCAS 100 mg 498/453	n	478	281	477
		Baseline	158.2 (2.43)	2.89 (0.147)	11.51 (0.124)
		Change from Baseline	25.6 (2.00) (21.6, 29.5)	-1.03 (0.120) (-1.27, -0.79)	-1.29 (0.096) (-1.48, -1.10)
		Difference from Placebo	13.2 (2.82)# (7.7, 18.7)	-0.38 (0.169)# (-0.71, -0.05)	-0.52 (0.136)# (-0.79, -0.26)
	Tolterodine ER 4 mg 495/445	n	475	299	474
		Baseline	158.6 (2.48)	2.64 (0.148)	11.55 (0.128)
		Change from Baseline	25.0 (2.00) (21.1, 28.9)	-1.00 (0.117) (-1.23, -0.77)	-1.10 (0.096) (-1.29, -0.91)
		Difference from Placebo	12.6 (2.83)* (7.1, 18.2)	-0.35 (0.166)* (-0.68, -0.03)	-0.33 (0.136)* (-0.60, -0.06)

Results for non-key secondary endpoints are listed below. The mean 'level of urgency' (PPIUS) was ~2.4 at baseline across all groups (based on a 5-point rating scale). This is intermediate

between the scale points designated *"2. Moderate urgency, I could postpone voiding for a short while, without fear of wetting myself"* and *"3. Severe urgency, I could not postpone voiding, but had to rush to the toilet in order not to wet myself."* During the course of the 12-week study, placebo recipients improved by 0.22 of a grade, on average. Mirabegron recipients showed a slightly greater improvement: 0.31 in the 50mg group and 0.30 in the 100mg group, representing a placebo-subtracted difference of 0.09 and 0.08, respectively. The clinical value of a change this small is unclear. Tolterodine showed a similar mild treatment effect (mean 0.07 points better than placebo). The 95% CIs were consistent with a *marginally* significant treatment effect in all active groups, approaching zero (no effect) within 0.01 or 0.02 points.

The second column of results below shows the incidence of *urgency* incontinence at Final Visit (FV), which is a subset of the primary efficacy variable, total (all-cause) incontinence. For this endpoint, the improvements observed during the study and the differences relative to placebo were broadly similar to those observed for all-cause incontinence, but of lower magnitude: the placebo-subtracted treatment effect was 0.35 episodes for the mirabegron 50mg group and 0.22 for the 100mg group (compared to 0.41 and 0.29 for all-cause incontinence). For the 50mg group, the difference from placebo was statistically significant as reflected in the 95%CIs (-0.65 to -0.05 episodes); for the 100mg group, the 95% CI included zero effect (-0.53 to +0.09). Tolterodine showed a difference from placebo of only 0.07 episodes, which was not significant (95%CI -0.38 to 0.23).

The table also shows the incidence of episodes with higher grade urgency (Grade 3 or 4), which improved from baseline in all groups, including placebo. The 95%CIs for the difference from placebo showed a significant treatment effect for mirabegron 50mg, but not for mirabegron 100mg or tolterodine (see table below).

The number of episodes of nocturia was also assessed. At baseline, most subjects were voiding about twice per night. The number of episodes of nocturia improved in all groups, with greater increases seen with active treatment. The differences compared to placebo were clinically modest: 0.15 episodes for the mirabegron 50mg group and 0.09 for the 100mg group. The 95%CIs show that these differences narrowly achieved statistical significance. For tolterodine, the improvement in nocturia was similar to that seen with placebo and not statistically significant (see table below).

Table 13. Results for Non-key Secondary Endpoints, Study 046

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Statistic	Change from BL to FV in Mean Level of Urgency (FAS) †	Change from BL to FV in Mean Number of Urgency Incontinence Episodes per 24 Hours (FAS-I) †	Change from BL to FV in Mean Number of Urgency Episodes (Grade 3 or 4) per 24 Hours (FAS) †	Change from BL to FV in Mean Number of Nocturia Episodes per 24 Hours (FAS) †
178-CL-046 (SCORPIO)	Placebo 497/453	n	480	283	479	428
		Baseline	2.37 (0.026)	2.43 (0.129)	5.78 (0.182)	2.22 (0.063)
		Change from Baseline	-0.22 (0.028) (-0.28, -0.17)	-1.11 (0.110) (-1.32, -0.89)	-1.65 (0.151) (-1.94, -1.35)	-0.41 (0.047) (-0.50, -0.32)
	Mirabegron OCAS 50 mg 497/440	n	472	286	470	423
		Baseline	2.40 (0.025)	2.52 (0.154)	5.72 (0.168)	2.09 (0.058)
		Change from Baseline	-0.31 (0.028) (-0.37, -0.26)	-1.46 (0.109) (-1.67, -1.24)	-2.25 (0.152) (-2.55, -1.95)	-0.56 (0.047) (-0.66, -0.47)
		Difference from Placebo	-0.09 (0.040)* (-0.17, -0.02)	-0.35 (0.155)* (-0.65, -0.05)	-0.60 (0.214)* (-1.02, -0.18)	-0.15 (0.067)* (-0.28, -0.02)
	Mirabegron OCAS 100 mg 498/453	n	475	276	474	422
		Baseline	2.45 (0.024)	2.65 (0.138)	5.97 (0.170)	2.15 (0.060)
		Change from Baseline	-0.30 (0.028) (-0.36, -0.25)	-1.33 (0.111) (-1.55, -1.11)	-1.96 (0.151) (-2.26, -1.67)	-0.50 (0.047) (-0.59, -0.40)
		Difference from Placebo	-0.08 (0.040)* (-0.16, -0.01)	-0.22 (0.156)* (-0.53, 0.09)	-0.31 (0.214) (-0.73, 0.11)	-0.09 (0.067) (-0.22, 0.04)
	Tolterodine ER 4 mg 495/445	n	473	289	472	435
		Baseline	2.41 (0.026)	2.37 (0.134)	5.79 (0.158)	2.14 (0.064)
		Change from Baseline	-0.29 (0.028) (-0.34, -0.23)	-1.18 (0.109) (-1.40, -0.97)	-2.07 (0.152) (-2.37, -1.77)	-0.45 (0.047) (-0.54, -0.36)
		Difference from Placebo	-0.07 (0.040) (-0.15, 0.01)	-0.07 (0.154) (-0.38, 0.23)	-0.42 (0.214)* (-0.84, -0.00)	-0.04 (0.066) (-0.17, 0.09)

The mean number of incontinence pads used per 24 hours improved in all groups, including placebo. The changes in the active groups were slightly better than in the placebo group, but the placebo-subtracted differences were not significant at Week 12 or the Final Visit, and the 95%CIs included zero, as shown in the tables below.

Table 14. Change from Baseline in Mean Number of Pads Used Per 24 Hours, Study 046

Change from Baseline to Each Visit in Mean Number of Pads Used Per 24 Hours
Full Analysis Set

Visit	Statistics	placebo (N=480)	mirabegron 50mg (N=473)	mirabegron 100mg (N=478)	tolterodine 4mg (N=475)
Week 12	Baseline				
	n	200	172	181	165
	Mean (SE)	2.67 (0.138)	2.84 (0.167)	2.91 (0.144)	2.69 (0.146)
	Median	2.33	2.33	2.67	2.33
	Min to Max	0.3 to 9.3	0.3 to 13.3	0.3 to 12.3	0.3 to 11.7
	Mean (SE)	1.73 (0.148)	1.54 (0.154)	1.75 (0.144)	1.78 (0.150)
	Median	1.33	1.00	1.33	1.33
	Min to Max	0.0 to 12.0	0.0 to 17.3	0.0 to 12.7	0.0 to 9.3
	Change From Baseline				
	Mean (SE)	-0.94 (0.134)	-1.30 (0.139)	-1.17 (0.149)	-0.91 (0.129)
	Median	-0.67	-1.00	-1.00	-1.00
	Min to Max	-8.7 to 8.3	-9.7 to 8.7	-11.3 to 7.7	-5.3 to 7.7
	Adjusted Change From Baseline				
	Adjusted Mean (SE)	-0.99 (0.117)	-1.26 (0.126)	-1.11 (0.123)	-0.95 (0.128)
	95% Two-Sided CI	(-1.21,-0.76)	(-1.51,-1.01)	(-1.35,-0.87)	(-1.20,-0.70)
	Difference vs. Placebo				
	Adjusted Mean (SE)		-0.28 (0.172)	-0.12 (0.169)	0.03 (0.173)
	95% Two-Sided CI		(-0.61,0.06)	(-0.46,0.21)	(-0.31,0.37)
	p-value		0.11	0.46	0.85
Final Visit	Baseline				
	n	209	183	195	181
	Mean (SE)	2.63 (0.134)	2.87 (0.164)	2.88 (0.138)	2.74 (0.140)
	Median	2.00	2.33	2.67	2.33
	Min to Max	0.3 to 9.3	0.3 to 13.3	0.3 to 12.3	0.3 to 11.7
	Mean (SE)	1.74 (0.143)	1.66 (0.159)	1.73 (0.140)	1.81 (0.144)
	Median	1.33	1.00	1.33	1.33
	Min to Max	0.0 to 12.0	0.0 to 17.3	0.0 to 12.7	0.0 to 9.3
	Change From Baseline				
	Mean (SE)	-0.89 (0.129)	-1.21 (0.136)	-1.16 (0.142)	-0.93 (0.126)
	Median	-0.67	-1.00	-1.00	-1.00
	Min to Max	-8.7 to 8.3	-9.7 to 8.7	-11.3 to 7.7	-6.0 to 7.7
	Adjusted Change From Baseline				
	Adjusted Mean (SE)	-0.95 (0.115)	-1.17 (0.123)	-1.12 (0.119)	-0.95 (0.123)
	95% Two-Sided CI	(-1.18,-0.73)	(-1.41,-0.93)	(-1.35,-0.89)	(-1.19,-0.70)
	Difference vs. Placebo				
	Adjusted Mean (SE)		-0.22 (0.168)	-0.17 (0.165)	0.01 (0.168)
	95% Two-Sided CI		(-0.55,0.11)	(-0.49,0.16)	(-0.32,0.34)
	p-value		0.20	0.31	0.97

Results for subjective endpoints are listed below. On a visual analog scale (VAS), all treatment groups including placebo reported a favourable change in 'Treatment Satisfaction' and the differences were greater in the active groups, with the 95%CIs showing that these differences were significant (see the table below). The magnitude of the between-group differences was small, however: 0.66 for the mirabegron 50mg group, and 0.77 for the 100mg group, out of a 10-point scale. (Subjects indicated a rating of about 4 at baseline, so complete satisfaction with treatment would potentially produce a 6-point improvement.) Results in the tolterodine group were similar, with a placebo-subtracted improvement of 0.55.

Symptom bother was assessed from the symptom-bother subscale of the OAB-q, which potentially ranges from 0-100; at baseline the mean symptom bother was about 50 in all groups, and improved (decreased) in all groups during the course of the study. The mean placebo improvement was substantial (-14.9 points), and the additional improvement with active treatment was more modest (4.7 points in the mirabegron 50mg group, 5.0 points in the 100mg group). These differences were statistically significant, but it is difficult to know what such a difference means in clinical terms. (Ironically, the more quantitative primary endpoints such as improvement in incontinence frequency, actually give a clearer idea of how much the drug is

likely to have reduced the 'bother' of symptoms, because we can at least imagine what it would be like to have one less episode of incontinence every 2-3 days.)

The other domains of the OAB-q were converted to a mean HRQL score, potentially ranging from 0-100. HQRL was rated as about 60 at baseline, and improved in all groups, with slightly greater improvement in the mirabegron groups compared to placebo. The 95%CIs excluded zero, but only by 0.2 points and 1.2 points in the 50mg and 100mg groups, respectively, a trivial difference in a 100 point scale.

The PPBC showed a similar pattern, with modest improvements in all groups, including the placebo group, and marginally significant superiority demonstrated for mirabegron 100mg. The mirabegron 50mg group was numerically superior to placebo but the 95%CI narrowly included zero.

For the subjective endpoints, tolterodine was significantly superior to placebo for some measures (TS-VAS, symptom-bother) but not others (HRQL, PPBC).

Table 15. Subjective Endpoints, Study 046

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Statistic	Change from BL to FV in Treatment Satisfaction – Visual Analog Scale (FAS) †	Change from BL to FV in Symptom Bother Score (FAS) †	Change from BL to FV in HRQL Total Score (FAS) †	Change from BL to FV in PPBC (FAS) †
178-CL-046 (SCORPIO)	Placebo 497/453	n	428	475	473	433
		Baseline	4.11 (0.172)	49.6 (0.93)	60.9 (1.02)	4.3 (0.05)
		Adjusted Change from Baseline	1.89 (0.146) (1.60, 2.18)	-14.9 (0.84) (-16.5, -13.2)	13.7 (0.76) (12.2, 15.2)	-0.8 (0.05) (-0.9, -0.7)
	Mirabegron OCAS 50 mg 497/440	n	414	465	468	416
		Baseline	3.95 (0.167)	49.6 (0.93)	62.0 (0.96)	4.1 (0.05)
		Adjusted Change from Baseline	2.55 (0.149) (2.26, 2.85)	-19.6 (0.85) (-21.3, -18.0)	16.1 (0.77) (14.6, 17.6)	-1.0 (0.06) (-1.1, -0.9)
		Difference from Placebo	0.66 (0.208)* (0.25, 1.07)	-4.7 (1.19)* (-7.1, -2.4)	2.3 (1.08)* (0.2, 4.5)	-0.2 (0.08)* (-0.3, -0.0)
	Mirabegron OCAS 100 mg 498/453	n	427	473	472	429
		Baseline	4.03 (0.168)	49.7 (0.98)	61.2 (1.00)	4.1 (0.05)
		Adjusted Change from Baseline	2.66 (0.146) (2.37, 2.94)	-19.9 (0.84) (-21.5, -18.2)	17.0 (0.77) (15.5, 18.5)	-1.1 (0.05) (-1.2, -1.0)
		Difference from Placebo	0.77 (0.207)* (0.36, 1.17)	-5.0 (1.19)* (-7.3, -2.6)	3.3 (1.08)* (1.2, 5.4)	-0.2 (0.08)* (-0.4, -0.1)
	Tolterodine ER 4 mg 495/445	n	425	469	470	426
		Baseline	3.87 (0.168)	50.3 (0.93)	61.0 (0.97)	4.3 (0.05)
		Adjusted Change from Baseline	2.44 (0.147) (2.15, 2.73)	-18.4 (0.85) (-20.1, -16.8)	14.8 (0.77) (13.3, 16.3)	-1.0 (0.06) (-1.1, -0.9)
		Difference from Placebo	0.55 (0.207)* (0.14, 0.95)	-3.5 (1.19)* (-5.9, -1.2)	1.1 (1.08) (-1.1, 3.2)	-0.2 (0.08)* (-0.3, -0.0)

The table below summarises the major subjective endpoints (TS-VAS, Symptom Bother, HQRL) across all three pivotal studies, with p-values as well as 95%CIs. The study being discussed (Study 046) was broadly consistent with Study 047, which employed similar doses.

Table 16. Adjusted Mean Difference vs Placebo in Change from Baseline for TS-VAS, Symptom Bother Scale and Health-Related QOL Total Score, Studies 046, 047 and 074

	Study 178-CL-046			Study 178-CL-047		Study 178-CL-074	
	Mirabegron 50 mg (n=473)	Mirabegron 100 mg (n=478)	Tolt ER 4 mg (n=475)	Mirabegron 50 mg (n=425)	Mirabegron 100 mg (n=412)	Mirabegron 25 mg (n=410)	Mirabegron 50 mg (n=426)
TS-VAS - *Adjusted Mean Difference vs Placebo†*							
Mean (SE)	0.66 (0.208)	0.77 (0.207)	0.55 (0.207)	0.85 (0.22)	1.39 (0.22)	0.49 (0.216)	0.83 (0.216)
95% 2-sided CI	(0.25, 1.07)	(0.36, 1.17)	(0.14, 0.95)	(0.4, 1.3)	(1.0, 1.8)	(0.07, 0.91)	(0.41, 1.25)
P value‡	0.001*	< 0.001*	0.008*	< 0.001*	< 0.001*	0.024*	< 0.001*
Symptom Bother Scale - *Adjusted Mean Difference vs Placebo†*							
Mean (SE)							
95% 2-sided	-4.7 (1.19)	-5.0 (1.19)	-3.5 (1.19)	-6.2 (1.38)	-9.3 (1.38)	-1.8 (1.27)	-2.8 (1.26)
CI	(-7.1, -2.4)	(-7.3, -2.6)	(-5.9, -1.2)	(-8.9, -3.5)	(-12.1, -6.6)	(-4.3, 0.7)	(-5.3, -0.3)
P value‡	< 0.001*	< 0.001*	0.003*	< 0.001*	< 0.001*	0.15	0.028*
Health-related Quality of Life Total Score - *Adjusted Mean Difference vs Placebo†*							
Mean (SE)							
95% 2-sided	2.3 (1.08)	3.3 (1.08)	1.1 (1.08)	4.1 (1.26)	6.5 (1.27)	1.3 (1.12)	1.2 (1.12)
CI	(0.2, 4.5)	(1.2, 5.4)	(-1.1, 3.2)	(1.6, 6.6)	(4.1, 9.0)	(-0.9, 3.5)	(-1.0, 3.4)
P value‡	0.031*	0.002*	0.32	0.001*	< 0.001*	0.26	0.28

7.1.1.14. Subgroup analyses

Although the sponsor presented subgroup analyses for the co-primary endpoints, this analysis was relatively underpowered. A more meaningful subgroup analysis was performed on the pooled pivotal data, and this is presented in Section 7.3.

7.1.1.15. Per protocol analyses

The sponsor reassessed all major endpoints in the per protocol population. Overall, the results were very similar to the FAS analysis (data not shown), suggesting that protocol deviations did not distort the overall findings of the study.

7.1.2. Pivotal Study 047

7.1.2.1. Study design, objectives, locations and dates

This was a phase 3, randomised, parallel-group, placebo-controlled, double-blind, multinational study assessing the efficacy of placebo, mirabegron 50mg or mirabegron 100mg in female and male adults with symptoms of OAB (urinary frequency and urgency with or without incontinence) present for at least 3 months.

The study was conducted in 132 sites in the US (115 sites) and Canada (17 sites), from 28 March 2008 to 22 April 2009.

7.1.2.2. Inclusion and exclusion criteria

Inclusion and exclusion criteria for Study 047 were the same as for Study 046. The inclusion criteria are listed below. For exclusion criteria, see the corresponding section for Study 046.

Inclusion criteria at screening

- Patient ≥ 18 years of age, of either gender.
- Had symptoms of OAB (urinary frequency and urgency *with or without* incontinence) for ≥ 3 months.
- Able to give written informed consent.
- Willing and able to complete the micturition diary and questionnaires.

Inclusion criteria at baseline

- Frequency of micturition on average ≥ 8 times per 24-hour period 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.

7.1.2.3. Study treatments

As in Study 046, all subjects completed a single-blind placebo run-in period of 2 weeks. Eligible patients were then randomised to receive placebo, mirabegron 50mg or mirabegron 100mg orally once daily for 12 weeks. Unlike Study 046, there was no active control.

7.1.2.4. Efficacy variables and outcomes

The following bulleted lists of endpoints are repeated essentially verbatim from the main study report. Overall, these endpoints were very similar to Study 046 and were broadly appropriate.

The two co-primary endpoints were identical to Study 046. The number of additional secondary endpoints in Study 047 seemed somewhat excessive, with the same variables being reassessed at multiple time points. The secondary endpoints included several subjective assessments; the conduct and validity of these have already been discussed in the corresponding section for Study 046.

Co-primary Endpoints

- Change from baseline to end of treatment (Final Visit) in mean number of incontinence episodes per 24 hours based on a 3-day micturition diary
- Change from baseline to end of treatment (Final Visit) in mean number of micturitions per 24 hours based on a 3-day micturition diary

Key Secondary Endpoints

- Change from baseline to Final Visit in mean volume voided per micturition
- Change from baseline to week 4 in mean number of incontinence episodes per 24 hours based on a 3-day micturition diary
- Change from baseline to week 4 in mean number of micturitions per 24 hours based on a 3-day micturition diary

Additional Secondary Endpoints

Endpoints derived from the micturition diary:

- Change from baseline to week 8 and week 12 in mean number of incontinence episodes per 24 hours
- Change from baseline to week 8 and week 12 in mean number of micturitions per 24 hours
- Change from baseline to week 4, week 8 and week 12 in mean volume voided per micturition
- Change from baseline to week 4, week 8, week 12 and Final Visit in mean number of urgency incontinence episodes per 24 hours
- Change from baseline to week 4, week 8, week 12 and Final Visit in mean number of urgency episodes (grades 3 or 4) per 24 hours
- Change from baseline to week 4, week 8, week 12 and Final Visit in mean level of urgency
- Change from baseline to week 4, week 8, week 12 and Final Visit in mean number of nocturia episodes per 24 hours
- Change from baseline to week 4, week 8, week 12 and Final Visit in mean number of pads used per 24 hours

Additional secondary efficacy variables not derived from the 3-day diary:

- Change from baseline to week 4, week 8, week 12 and Final Visit in Symptom Bother and HRQL scores as assessed by the OAB-q questionnaire
- Change from baseline to week 12 and Final Visit in scores as assessed by the WPAI:SHP questionnaire
- Change from baseline to week 4, week 8, week 12 and Final Visit in scores as assessed by the EQ-5D questionnaire
- Change from baseline to week 4, week 8, week 12 and Final Visit in scores as assessed by the EQ-5D VAS questionnaire
- Change from baseline to week 12 and Final Visit in PPBC
- Change from baseline to week 12 and Final Visit in TS-VAS
- Change from baseline to week 4, week 8, week 12 and Final Visit in number of physician visits for patient's bladder condition (excluding study-related visits)

7.1.2.5. Randomisation and blinding methods

Randomisation was performed equally to all treatment groups, including placebo, using a computerised randomisation scheme prepared by Pierrel Research Europe. Randomisation was stratified by centre.

The study employed a double-dummy blinding technique. Throughout the study, subjects received 2 study drug tablets (mirabegron 50mg or matching placebo, mirabegron 100mg or matching placebo).

7.1.2.6. Analysis populations

The analysis populations were as defined for Study 046: the Full Analysis Set (FAS), FAS-incontinence set (FAS-I), Per Protocol Set (PPS) and the Safety Analysis Set (SAF).

7.1.2.7. Statistical methods

This study used the same co-primary endpoints as Study 046, and analysed these with the same statistical methods (see Section 7.1.1.7). Overall, the statistical methodology was appropriate.

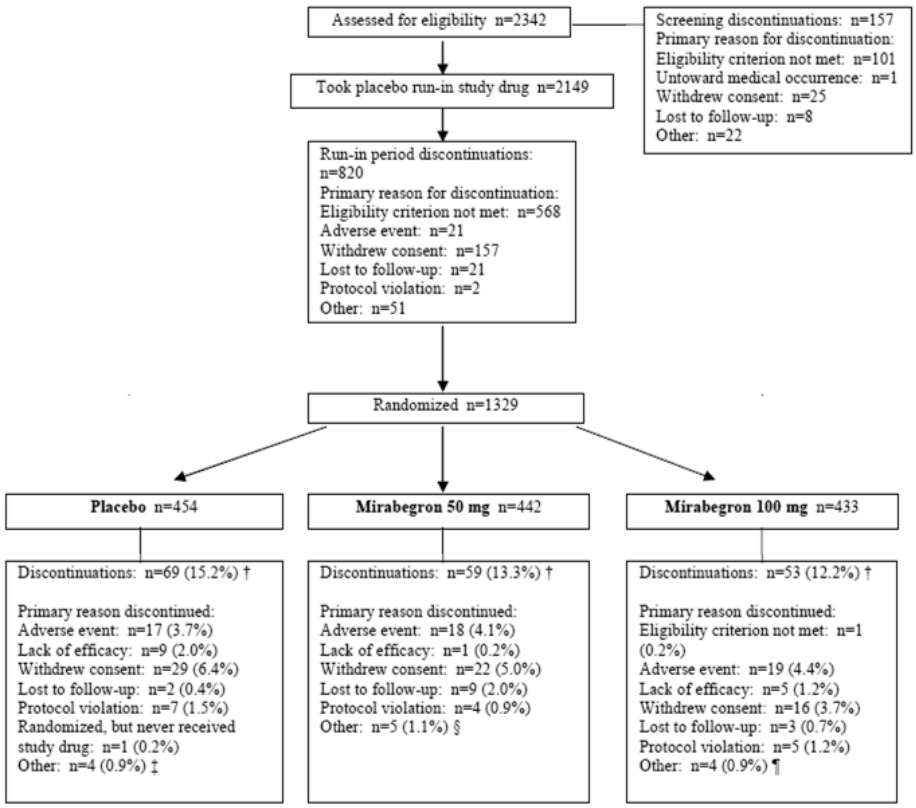
7.1.2.8. Sample size

Sample size considerations for Study 047 were as already described for Study 46. The study achieved its recruitment targets and demonstrated statistical significance for its primary endpoints, indicating an adequate sample size.

7.1.2.9. Participant flow

Patient disposition is summarised in the figure below. The proportion of patients discontinuing after randomisation was 12.2% to 15.2% across the three treatment groups, with about 4% withdrawing because of adverse events. This is reasonable for a study of this nature and duration. Withdrawals were higher in the placebo group, and there is no evidence that significant withdrawal bias contributed to the positive results of this study.

Figure 12. Patient Disposition, Study 047



7.1.2.10. Major protocol violations/deviations

Significant protocol deviations are categorised in the table below. Major protocol violations included 4 patients who were randomised twice and received 2 double-blind treatment assignments from different centres. Sensitivity analyses excluding these 4 patients (8 subject numbers) did not produce different conclusions. Overall, the number of violations was acceptable for a complex study of this nature. The most common protocol violation was a failure to fill in the diary adequately, seen in 3.4 to 6.5% of subjects across the three treatment groups.

Table 17. Reasons for Exclusion from the Per Protocol Set, Study 047

		Mirabegron			Mirabegron	
Parameter, n (%)	**Placebo (n=433)**	**50 mg (n=425)**	**100 mg (n=412)**	**Placebo (n=325)**	**50 mg (n=312)**	**100 mg (n=296)**
Total number of patients excluded, n (%)	53 (12.2%)	53 (12.5%)	40 (9.7%)	39 (12.0%)	41 (13.1%)	26 (8.8%)
Reasons						
Eligibility Violations Based on 3-Day Micturition Diary						
During 3-day baseline diary period: Average of < 8 micturitions per24 hours	6 (1.4%)	9 (2.1%)	4 (1.0%)	6 (1.8%)	8 (2.6%)	2 (0.7%)
< 3 episodes of urgency (grade 3 or 4)	2 (0.5%)	2 (0.5%)	2 (0.5%)	0	2 (0.6%)	1 (0.3%)
Average daily volume voided > 3000 mL	1 (0.2%)	2 (0.5%)	2 (0.5%)	1 (0.3%)	2 (0.6%)	2 (0.7%)
Eligibility Violations Not Based on 3-Day Micturition Diary						
Symptomatic UTI, chronic inflammation or malignant disease of the pelvic organs	1 (0.2%)	0	3 (0.7%)	1 (0.3%)	0	2 (0.7%)
Nondrug treatment for OAB prior to screening	1 (0.2%)	0	0	1 (0.3%)	0	0
Error in Study Drug Administration Compared to Assigned Treatment						
Accidental intake of incorrect study drug during double-blind treatment period †	0	2 (0.5%)	1 (0.2%)	0	0	0
Poor Study Drug Compliance						
Poor study drug compliance (< 70%) during the double-blind treatment period	12 (2.8%)	8 (1.9%)	11 (2.7%)	8 (2.5%)	2 (0.6%)	7 (2.4%)
Inadequate Duration of Treatment						
Duration of placebo treatment in placebo run-in period was too short	2 (0.5%)	3 (0.7%)	3 (0.7%)	1 (0.3%)	3 (1.0%)	1 (0.3%)
Last diary day of the Final Visit was < 53 days	28 (6.5%)	27 (6.4%)	14 (3.4%)	21 (6.5%)	24 (7.7%)	11 (3.7%)

7.1.2.11. Baseline data

Baseline data in Study 047 is summarised in the tables below. Each group appeared reasonably well balanced in terms of demographics (Table 18), prior OAB history (Table 19) and characteristics of their OAB at the time of screening (Table 20).

Note that the FAS-I population included some patients who were designated as having 'frequency' rather than 'urgency incontinence' or 'mixed incontinence', and yet they had to have incontinence to enter the FAS-I population. This apparent contradiction arises from the fact that FAS-I was defined on the basis of the baseline micturition diary, whereas prior OAB history refers to the patients' previous reported experience of OAB. The same discrepancy was seen in Study 074, and it suggests that patients under-reported their incontinence when describing their prior OAB experience. The same effect is observed in all treatment groups, and does not undermine the basic conclusions of the studies.

Table 18. Summary of Patient Demographics and Baseline Characteristics, Study 047

	FAS			FAS-I		
		Mirabegron			Mirabegron	
Parameter	Placebo (n=433)	50 mg (n=425)	100 mg (n=412)	Placebo (n=325)	50 mg (n=312)	100 mg (n=296)
Sex (n, %)						
Male	101 (23.3%)	116 (27.3%)	103 (25.0%)	55 (16.9%)	61 (19.6%)	52 (17.6%)
Female	332 (76.7%)	309 (72.7%)	309 (75.0%)	270 (83.1%)	251 (80.4%)	244 (82.4%)
Age (years)						
Mean	60.1	59.6	60.8	60.8	60.7	61.7
SD	13.74	13.34	13.02	13.80	13.38	12.69
Age group (years) (n, %)						
< 65	261 (60.3%)	261 (61.4%)	244 (59.2%)	191 (58.8%)	179 (57.4%)	169 (57.1%)
≥ 65	172 (39.7%)	164 (38.6%)	168 (40.8%)	134 (41.2%)	133 (42.6%)	127 (42.9%)
< 75	366 (84.5%)	367 (86.4%)	345 (83.7%)	270 (83.1%)	264 (84.6%)	243 (82.1%)
≥ 75	67 (15.5%)	58 (13.6%)	67 (16.3%)	55 (16.9%)	48 (15.4%)	53 (17.9%)
Race (n, %)						
White	378 (87.3%)	378 (88.9%)	364 (88.4%)	289 (89.9%)	278 (89.1%)	263 (88.9%)
Black or African American	44 (10.2%)	29 (6.8%)	35 (8.5%)	29 (8.9%)	22 (7.1%)	27 (9.1%)
Asian	6 (1.4%)	11 (2.6%)	6 (1.5%)	3 (0.9%)	7 (2.2%)	1 (0.3%)
Other	5 (1.2%) †	7 (1.6%) ‡	7 (1.7%) §	4 (1.2%) ¶	5 (1.6%) ††	5 (1.7%) ‡‡
Ethnicity (n, %)						
Hispanic/Latino	23 (5.3%)	22 (5.2%)	31 (7.5%)	14 (4.3%)	17 (5.4%)	20 (6.8%)
Non-Hispanic/ Non-Latino	410 (94.7%)	403 (94.8%)	381 (92.5%)	311 (95.7%)	295 (94.6%)	276 (93.2%)
BMI (kg/m^2)						
n	432	425	412	325	312	296
Mean (SD)	30.4 (7.43)	30.0 (6.59)	30.3 (7.09)	30.8 (7.61)	30.2 (6.67)	30.9 (7.52)
Geographical region (n, %)						
Northeastern US	75 (17.3%)	72 (16.9%)	77 (18.7%)	50 (15.4%)	53 (17.0%)	50 (16.9%)
Midwestern US	57 (13.2%)	56 (13.2%)	48 (11.7%)	42 (12.9%)	39 (12.5%)	33 (11.1%)
Southern US	150 (34.6%)	140 (32.9%)	139 (33.7%)	118 (36.3%)	103 (33.0%)	104 (35.1%)
Western US	110 (25.4%)	113 (26.6%)	106 (25.7%)	83 (25.5%)	84 (26.9%)	80 (27.0%)
Canada	41 (9.5%)	44 (10.4%)	42 (10.2%)	32 (9.8%)	33 (10.6%)	29 (9.8%)

Table 19. Overactive Bladder History, Study 047

		Mirabegron			Mirabegron	
Parameter	Placebo (n=433)	50 mg (n=425)	100 mg (n=412)	Placebo (n=325)	50 mg (n=312)	100 mg (n=296)
Type of OAB (n, %) †						
Urgency incontinence	124 (28.6%)	135 (31.8%)	118 (28.6%)	98 (30.2%)	106 (34.0%)	88 (29.7%)
Frequency	133 (30.7%)	134 (31.5%)	139 (33.7%)	71 (21.8%)	68 (21.8%)	74 (25.0%)
Mixed	176 (40.6%)	156 (36.7%)	155 (37.6%)	156 (48.0%)	138 (44.2%)	134 (45.3%)
Prior OAB Surgery (n, %)						
Yes	49 (11.3%)	53 (12.5%)	46 (11.2%)	46 (14.2%)	45 (14.4%)	38 (12.8%)
Previous OAB drug (n, %)						
Yes	249 (57.5%)	242 (56.9%)	223 (54.1%)	198 (60.9%)	193 (61.9%)	169 (57.1%)
Reason for previous OAB drug discontinuation (n, %) ‡						
Insufficient effect - Yes	166 (66.7%)	161 (66.5%)	137 (61.4%)	128 (64.6%)	130 (67.4%)	103 (60.9%)
Poor tolerability - Yes	60 (24.1%)	49 (20.2%)	49 (22.0%)	47 (23.7%)	42 (21.8%)	35 (20.7%)
Duration of OAB symptoms (months)						
Mean (SD)	91.9 (108.52)	84.0 (94.61)	91.8 (108.44)	91.5 (100.98)	82.8 (88.16)	98.0 (112.01)
Median	52.4	51.9	52.0	59.1	52.3	60.0
Range	3 – 816	3 – 634	3 – 865	3 – 599	3 – 490	3 – 865

Table 20. Overactive Bladder-related Baseline Characteristics, Study 047

Parameter	Placebo (n=433)	Mirabegron 50 mg (n=425)	Mirabegron 100 mg (n=412)	Placebo (n=325)	Mirabegron 50 mg (n=312)	Mirabegron 100 mg (n=296)
Mean number of micturitions per 24 hours						
Mean (SD)	11.51 (3.269)	11.80 (3.458)	11.66 (3.389)	11.56 (3.344)	11.60 (3.240)	11.48 (3.172)
Range	3.7 – 40.3	5.7 – 33.3	7.3 – 35.3	3.7 – 40.3	5.7 – 28.7	7.7 – 30.3
Mean number of incontinence episodes per 24 hours	NA	NA	NA			
Mean (SD)				3.03 (3.077)	2.77 (2.648)	2.69 (2.438)
Range				0.3 – 25.7	0.3 – 18.0	0.3 – 15.3
Mean number of urgency incontinence episodes per 24 hours	NA	NA	NA			
Mean (SD)				2.51 (2.462)	2.30 (2.365)	2.38 (2.216)
Range				0.0 – 14.7	0.0 – 18.0	0.0 – 12.7
Mean volume voided per micturition (mL)						
Mean (SD)	157.5 (58.68)	156.0 (58.69)	157.6 (60.19)	159.6 (57.73)	157.9 (59.46)	158.5 (61.55)
Range	40 – 358	28 – 335	38 – 363	47 – 358	38 – 335	38 – 363
Mean number of urgency episodes (grade 3 or 4) per 24 hours						
Mean (SD)	5.61 (3.236)	5.88 (3.844)	5.95 (3.608)	6.24 (3.232)	6.11 (3.585)	6.50 (3.450)
Range	0.7 – 16.5	0.0 – 33.3	0.6 – 20.7	1.0 – 16.5	0.0 – 23.0	0.7 – 18.0
Mean level of urgency						
Mean (SD)	2.45 (0.537)	2.45 (0.534)	2.46 (0.544)	2.55 (0.536)	2.51 (0.537)	2.57 (0.526)
Range	0.7 – 4.0	0.3 – 4.0	0.9 – 4.0	0.7 – 4.0	0.8 – 4.0	1.1 – 3.9
Mean number of nocturia episodes per 24 hours						
Mean (SD)	1.93 (1.633)	1.90 (1.613)	2.04 (1.689)	1.97 (1.663)	1.82 (1.547)	2.03 (1.614)
Range	0.0 – 13.0	0.0 – 12.3	0.0 – 11.3	0.0 – 13.0	0.0 – 8.3	0.0 – 7.3

7.1.2.12. Results for the primary efficacy outcome

This study was positive for both of its co-primary endpoints. The major results for Study 047 are shown in the table below, including the two co-primary efficacy endpoints and key secondary endpoints. The results are broadly similar to those already discussed in Study 046, including the magnitude of the placebo response and the size of the placebo-subtracted treatment effect.

At baseline, subjects had a mean micturition frequency of about 12 episodes per 24 hours, and this was reduced during treatment in all groups. The placebo group showed a mean reduction of 1.05 episodes by the Final Visit. The mirabegron groups showed a significantly greater reduction, but the placebo subtracted difference was less than one voiding episode per day in both dose groups. For the 50mg dose, the placebo-subtracted treatment effect was 0.61 episodes per 24 hours (95%CI -0.98 to -0.24). For the 100mg dose, the treatment effect was 0.70 episodes per 24 hours (95%CI -1.07 to -0.33).

Table 21. Results for Coprimary and Key Secondary Endpoints, Study 047

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Statistic	Coprimary Efficacy Endpoints+		Key Secondary Efficacy Endpoints+		
			Change from BL to FV in Mean Number of Incontinence Episodes per 24 Hours (FAS-I)	Change from BL to FV in Mean Number of Micturitions per 24 Hours (FAS)	Change from BL to FV in Mean Volume Voided (mL) per Micturition (FAS)	Change from BL to Week 4 in Mean Number of Incontinence Episodes per 24 Hours (FAS-I)	Change from BL to Week 4 in Mean Number of Micturitions per 24 Hours (FAS)
178-CL-047 (ARIES)	Placebo 454/385	n	325	433	433	325	433
		Baseline	3.03 (0.171)	11.51 (0.157)	157.5 (2.82)	3.03 (0.171)	11.51 (0.157)
		Change from Baseline	-1.13 (0.112) (-1.35, -0.91)	-1.05 (0.132) (-1.31, -0.79)	7.0 (2.41) (2.3, 11.7)	-0.72 (0.116) (-0.95, -0.50)	-0.77 (0.127) (-1.02, -0.52)
	Mirabegron OCAS 50 mg 442/383	n	312	425	424	309	422
		Baseline	2.77 (0.150)	11.80 (0.168)	156.3 (2.84)	2.76 (0.149)	11.81 (0.169)
		Change from Baseline	-1.47 (0.114) (-1.69, -1.25)	-1.66 (0.133) (-1.92, -1.40)	18.2 (2.44) (13.4, 22.9)	-1.20 (0.119) (-1.43, -0.97)	-1.19 (0.129) (-1.44, -0.93)
		Difference from Placebo	-0.34 (0.160)# (-0.66, -0.03)	-0.61 (0.188)# (-0.98, -0.24)	11.1 (3.43)# (4.4, 17.9)	-0.48 (0.166)# (-0.80, -0.15)	-0.42 (0.182)# (-0.77, -0.06)
	Mirabegron OCAS 100 mg 433/380	n	296	412	412	293	409
		Baseline	2.69 (0.142)	11.66 (0.167)	157.6 (2.97)	2.69 (0.143)	11.65 (0.168)
		Change from Baseline	-1.63 (0.117) (-1.86, -1.40)	-1.75 (0.135) (-2.01, -1.48)	18.0 (2.47) (13.1, 22.8)	-1.18 (0.122) (-1.42, -0.94)	-1.37 (0.131) (-1.62, -1.11)
		Difference from Placebo	-0.50 (0.162)# (-0.82, -0.18)	-0.70 (0.189)# (-1.07, -0.33)	11.0 (3.45)# (4.2, 17.7)	-0.46 (0.168)# (-0.79, -0.13)	-0.60 (0.183)# (-0.96, -0.24)

For the more distressing endpoint of incontinence, a statistically significant treatment effect was also demonstrated, but the magnitude of the benefit was small. In the placebo group, incontinence reduced during the study by a mean of 1.13 episodes per 24 hours, from a baseline mean of 3.03 episodes. On average, active treatment with mirabegron helped prevent an additional episode every two to three days: the placebo-subtracted treatment effect was 0.34 episodes per 24 hours in the 50mg group, with the 95%CI narrowly excluding zero (95%CI -0.66 to -0.03); the placebo-subtracted treatment effect was 0.50 episodes per 24 hours in the 100mg group (95%CI -0.82 to -0.18). Given the mean baseline frequency of 2.77 episodes in the 100mg group, this means that mirabegron 100mg would be expected to prevent about one episode of incontinence every two days in subjects expected to have ~8 episodes in that period. For some patients, this modest improvement could be considered worthwhile, but most would consider it disappointing.

The results for both co-primary endpoints are displayed graphically below. Note, again, that the vertical axes have been scaled in a way that gives no reference to the modest proportional changes from baseline.

Figure 13. Adjusted Mean Change in Incontinence Frequency, Study 047

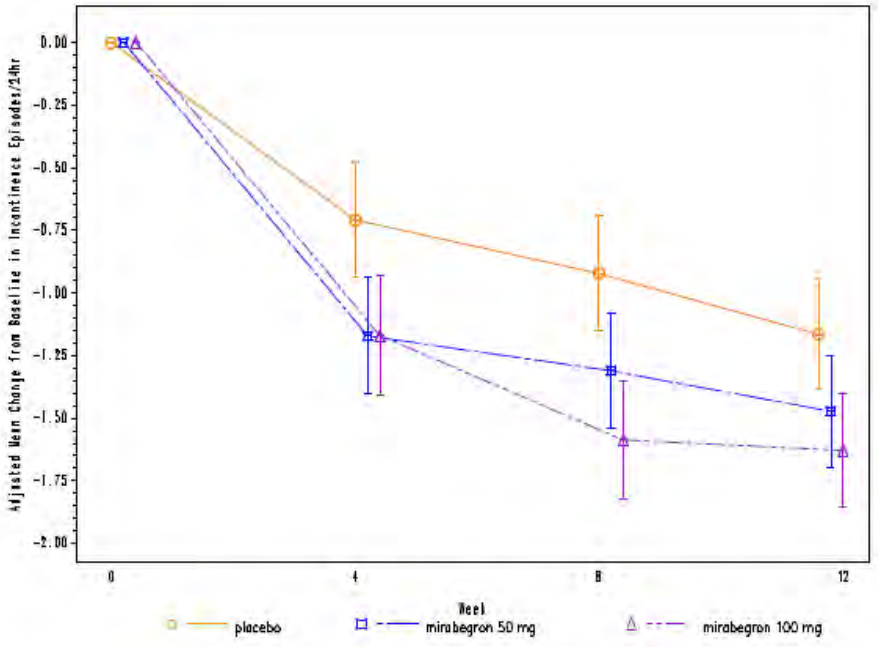
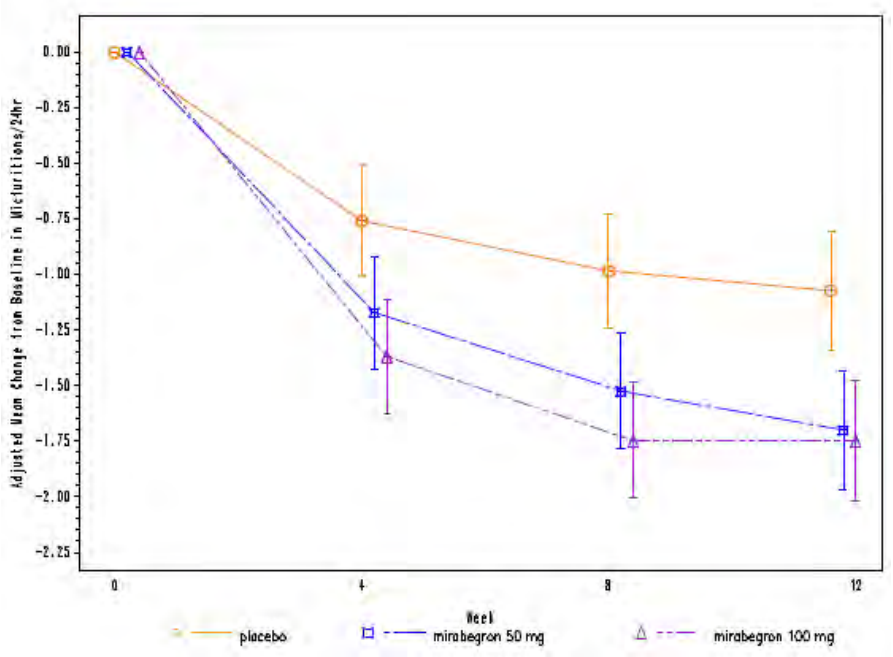


Figure 14. Adjusted Mean Change in Micturition Frequency, Study 047



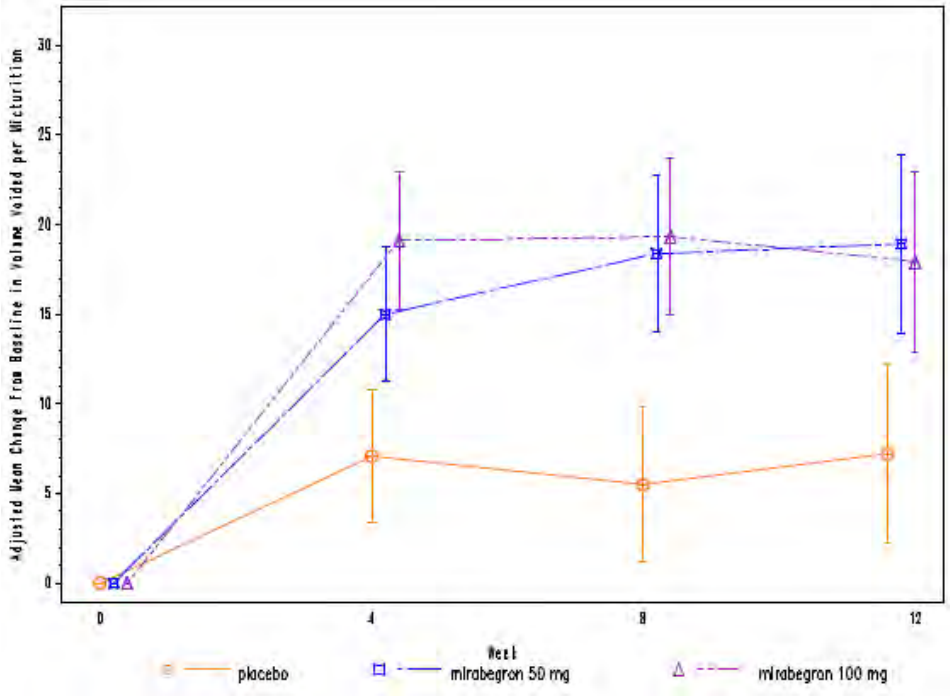
7.1.2.13. Results for other efficacy outcomes

Results for key secondary endpoints are shown in the table excerpt below. As in the previous study, active treatment was associated with an increase in voided volume by about 11 mL compared to placebo, which was statistically significant as shown by the 95%CIs, but of doubtful clinical value. The Week 4 results for the major variables of interest (micturition frequency and incontinence frequency) were similar to those observed at 12 weeks, in terms of the difference from placebo, and achieved statistical significance. For the 50mg group, the placebo-subtracted difference for micturition frequency was 0.42 at 4 weeks; the placebo-subtracted difference for incontinence was 0.48 at 4 weeks. For the 100mg group, the placebo-subtracted difference for micturition frequency was 0.60 at 4 weeks; the placebo-subtracted difference for incontinence was 0.46 at 4 weeks.

Table 22. Results for Key Secondary Endpoints, Study 047

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Statistic	Key Secondary Efficacy Endpoints†		
			Change from BL to FV in Mean Volume Voided (mL) per Micturition (FAS)	Change from BL to Week 4 in Mean Number of Incontinence Episodes per 24 Hours (FAS-I)	Change from BL to Week 4 in Mean Number of Micturitions per 24 Hours (FAS)
178-CL-047 (ARIES)	Placebo 454/385	n	433	325	433
		Baseline	157.5 (2.82)	3.03 (0.171)	11.51 (0.157)
		Change from Baseline	7.0 (2.41) (2.3, 11.7)	-0.72 (0.116) (-0.95, -0.50)	-0.77 (0.127) (-1.02, -0.52)
	Mirabegron OCAS 50 mg 442/383	n	424	309	422
		Baseline	156.3 (2.84)	2.76 (0.149)	11.81 (0.169)
		Change from Baseline	18.2 (2.44) (13.4, 22.9)	-1.20 (0.119) (-1.43, -0.97)	-1.19 (0.129) (-1.44, -0.93)
		Difference from Placebo	11.1 (3.43)# (4.4, 17.9)	-0.48 (0.166)# (-0.80, -0.15)	-0.42 (0.182)# (-0.77, -0.06)
	Mirabegron OCAS 100 mg 433/380	n	412	293	409
		Baseline	157.6 (2.97)	2.69 (0.143)	11.65 (0.168)
		Change from Baseline	18.0 (2.47) (13.1, 22.8)	-1.18 (0.122) (-1.42, -0.94)	-1.37 (0.131) (-1.62, -1.11)
		Difference from Placebo	11.0 (3.45)# (4.2, 17.7)	-0.46 (0.168)# (-0.79, -0.13)	-0.60 (0.183)# (-0.96, -0.24)

Figure 15. Adjusted Mean Change in Volume voided, Study 047



The other diary-derived secondary endpoints are displayed in the table below. All groups showed an improvement in the mean level of urgency, but the magnitude of the change was small: the placebo group showed a mean 0.08 reduction in the 5-point scale, and active treatment was associated with an additional reduction of about one eighth or one ninth of a scale point. The 95%CIs narrowly excluded zero. For the 50mg group, the placebo-subtracted change in urgency level was -0.11 (95%CI -0.18 to -0.04); for the 100mg group, the mean placebo-subtracted change was -0.13 (95%CI -0.20 to -0.05). The clinical value of this reduction is questionable.

The reduction in urgency incontinence was similar to the reduction in overall all-cause incontinence. The placebo group showed a mean reduction of 0.89 episodes per 24 hours, from a mean baseline of 2.56 episodes. The mirabegron 50mg group showed an additional placebo-subtracted reduction of 0.43 episodes (95%CI for change, -0.72 to -0.15); the 100mg group showed an additional reduction of 0.56 episodes (95%CI -0.85 to -0.28).

As shown in the table, there was also a significant reduction in the mean number of episodes of higher-grade (Grade 3-4) urgency episodes, with the placebo-subtracted differences suggesting that active treatment shifted a bit less than one episode of urgency per day into the lower urgency categories. (Note that this endpoint had been negative for the 100mg dose group in the previous pivotal study, 046). Nocturia was significantly reduced from a baseline of 2-3 episodes, but the placebo-subtracted difference was less than one fifth of an episode, meaning that less than one episode of nocturia would be prevented every five days by active treatment. This is of marginal clinical value, and was only marginally statistically significant – the 95%CIs closely approached zero, reaching -0.01 (one episode prevented every hundred days) in both dose groups.

Table 23. Results for Non-key Secondary Endpoints, Study 047

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Statistic	Change from BL to FV in Mean Level of Urgency (FAS) †	Change from BL to FV in Mean Number of Urgency Incontinence Episodes per 24 Hours (FAS-I) †	Change from BL to FV in Mean Number of Urgency Episodes (Grade 3 or 4) per 24 Hours (FAS) †	Change from BL to FV in Mean Number of Nocturia Episodes per 24 Hours (FAS) †
178-CL-047 (ARIES)	Placebo 454/385	n	432	319	432	366
		Baseline	2.45 (0.026)	2.56 (0.138)	5.61 (0.156)	2.28 (0.080)
		Change from Baseline	-0.08 (0.026) (-0.13, -0.03)	-0.89 (0.100) (-1.08, -0.69)	-0.82 (0.161) (-1.13, -0.50)	-0.38 (0.063) (-0.51, -0.26)
	Mirabegron OCAS 50 mg 442/383	n	425	297	424	348
		Baseline	2.45 (0.026)	2.42 (0.137)	5.90 (0.186)	2.32 (0.080)
		Change from Baseline	-0.19 (0.026) (-0.24, -0.13)	-1.32 (0.104) (-1.52, -1.12)	-1.57 (0.162) (-1.89, -1.25)	-0.57 (0.065) (-0.70, -0.44)
		Difference from Placebo	-0.11 (0.037)* (-0.18, -0.04)	-0.43 (0.145)* (-0.72, -0.15)	-0.75 (0.228)* (-1.20, -0.30)	-0.18 (0.091)* (-0.36, -0.01)
	Mirabegron OCAS 100 mg 433/380	n	411	291	411	356
		Baseline	2.46 (0.027)	2.42 (0.130)	5.96 (0.178)	2.36 (0.084)
		Change from Baseline	-0.21 (0.027) (-0.26, -0.15)	-1.45 (0.105) (-1.66, -1.24)	-1.76 (0.165) (-2.09, -1.44)	-0.57 (0.064) (-0.70, -0.45)
		Difference from Placebo	-0.13 (0.037)* (-0.20, -0.05)	-0.56 (0.145)* (-0.85, -0.28)	-0.94 (0.230)* (-1.40, -0.49)	-0.19 (0.090)* (-0.37, -0.01)

In subjects who used incontinence pads, there was a significant reduction with active treatment, as shown in the tables below, the placebo-subtracted difference was 0.41 pads per 24 hrs in the 50mg group and 0.46 in the 100mg group.

Table 24. Change from Baseline in Mean Number of Pads Used Per 24 Hours, Study 047

Study: mirabegron (YM178) 178-CL-047

Table 12.3.5.13
Change From Baseline to Each Visit in Mean Number of Pads Used Per 24-hour
Full Analysis Set

Visit	Statistics	placebo (N=433)	mirabegron 50mg (N=425)	mirabegron 100mg (N=412)
Week 8	Change from Baseline			
	Mean (SE)	-0.54 (0.148)	-0.96 (0.137)	-1.06 (0.133)
	Median	-0.33	-0.67	-0.67
	Min to Max	-14.7 to 5.3	-8.0 to 7.2	-7.3 to 5.0
	Adjusted Change from Baseline			
	Mean (SE)	-0.56 (0.116)	-0.96 (0.118)	-1.03 (0.119)
	95% Two-Sided CI	(-0.79, -0.33)	(-1.19, -0.73)	(-1.26, -0.80)
	Difference vs. Placebo			
	Mean (SE)		-0.40 (0.166)	-0.47 (0.166)
	95% Two-Sided CI		(-0.72, -0.07)	(-0.80, -0.14)
	p-value		0.016	0.005
Week 12	Baseline			
	n	152	145	147
	Mean (SE)	2.31 (0.165)	2.33 (0.152)	2.32 (0.171)
	Median	1.67	2.00	1.67
	Min to Max	0.3 to 14.7	0.3 to 10.0	0.3 to 11.3
	Mean (SE)	1.69 (0.159)	1.30 (0.136)	1.21 (0.169)
	Median	1.00	1.00	0.67
	Min to Max	0.0 to 11.7	0.0 to 14.0	0.0 to 19.3
	Change from Baseline			
	Mean (SE)	-0.62 (0.162)	-1.04 (0.132)	-1.10 (0.155)
	Median	-0.33	-1.00	-1.00
	Min to Max	-14.7 to 7.0	-8.0 to 5.0	-7.3 to 11.3
	Adjusted Change from Baseline			
	Mean (SE)	-0.63 (0.128)	-1.04 (0.131)	-1.09 (0.130)
	95% Two-Sided CI	(-0.88, -0.37)	(-1.30, -0.78)	(-1.35, -0.83)
	Difference vs. Placebo			
	Mean (SE)		-0.41 (0.184)	-0.46 (0.183)

Subjects who had at least one use of pad at baseline will be included in the analysis. Adjusted change from baseline are generated from the ANCOVA model with treatment group, gender, and geographic region as fixed factors and baseline as a covariate. Differences of the adjusted means are calculated by subtracting the adjusted mean of placebo from that of treatment group. P-values are from pairwise comparison vs. placebo within the ANCOVA model. Statistical significances are determined at 0.05 level.

Subjective endpoints are displayed below. The adjusted change from baseline was consistent with improvement for all subjective endpoints and for all treatment groups (for symptom bother and for PPBC, negative changes indicate a lessening of symptoms). The placebo-subtracted differences were modest. For the TS-VAS, the placebo-subtracted difference amounted to 0.85 and 1.39 for the 50mg and 100mg groups, respectively, on a 10-point scale. For the symptom bother subscale of the OAB-q, the placebo-subtracted difference from baseline was -6.2 and -9.3, respectively, in a 100-point scale. For HRQL, the placebo-subtracted improvements were 4.1 and 6.5, respectively, on a 100-point scale. For PPBC, mean reductions of just 0.2 and 0.3 were observed, on a 6-point scale. For most of these endpoints, the 95%CIs for the difference from placebo excluded zero, except the 95%CI for the PPBC changes in the 50mg group, which narrowly included zero.

For all of these subjective endpoints, it is difficult to know what the mean changes signify, in terms of actual clinical benefit. Given the modest improvements in the quantifiable endpoints of micturition and incontinence frequency, it seems likely that the quality-of-life benefits were also modest, though it is reassuring that the overall changes were in the beneficial direction.

Table 25. Subjective Endpoints, Study 047

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Statistic	Change from BL to FV in Treatment Satisfaction – Visual Analog Scale (FAS) †	Change from BL to FV in Symptom Bother Score (FAS) †	Change from BL to FV in HRQL Total Score (FAS) †	Change from BL to FV in PPBC (FAS) †
178-CL-047 (ARIES)	Placebo 454/385	n	390	356	355	392
		Baseline	5.45 (0.184)	48.1 (1.06)	63.4 (1.16)	3.8 (0.05)
		Adjusted Change from Baseline	0.70 (0.155) (0.4, 1.0)	-10.8 (0.97) (-12.7, -8.9)	10.7 (0.89) (9.0, 12.5)	-0.5 (0.05) (-0.6, -0.4)
	Mirabegron OCAS 50 mg 442/383	n	387	350	350	388
		Baseline	5.45 (0.189)	49.7 (1.08)	62.2 (1.18)	3.8 (0.05)
		Adjusted Change from Baseline	1.55 (0.156) (1.2, 1.9)	-17.0 (0.98) (-18.9, -15.1)	14.8 (0.90) (13.1, 16.6)	-0.7 (0.05) (-0.8, -0.6)
		Difference from Placebo	0.85 (0.22)* (0.4, 1.3)	-6.2 (1.38)* (-8.9, -3.5)	4.1(1.26)* (1.6, 6.6)	-0.2 (0.07)* (-0.3, -0.0)
	Mirabegron OCAS 100 mg 433/380	n	373	344	344	377
		Baseline	4.89 (0.190)	49.6 (1.09)	63.0 (1.17)	3.8 (0.05)
		Adjusted Change from Baseline	2.09 (0.159) (1.8, 2.4)	-20.2 (0.99) (-22.1, -18.2)	17.3 (0.90) (15.5, 19.0)	-0.8 (0.05) (-0.9, -0.7)
		Difference from Placebo	1.39 (0.22)* (1.0, 1.8)	-9.3 (1.38)* (-12.1, -6.6)	6.5 (1.27)* (4.1, 9.0)	-0.3 (0.07)* (-0.4, -0.2)

7.1.2.14. Subgroup analyses

Although the sponsor presented subgroup analyses for the co-primary endpoints, this analysis was relatively underpowered. A more meaningful subgroup analysis was performed on the pooled pivotal data, and this is presented in Section 7.4.

7.1.3. Pivotal Study 074

7.1.3.1. Study design, objectives, locations and dates

This was a phase 3, randomised, parallel-group, placebo-controlled, double-blind, multinational study conducted in female and male adults with symptoms of OAB (urinary frequency and urgency with or without incontinence) present for at least 3 months.

The study took place in multiple centres in Europe, Canada, and the United States from 28 April 2009 to 27 April 2010.

7.1.3.2. Inclusion and exclusion criteria

The inclusion criteria were the same as the other pivotal studies, as summarised below.

Inclusion criteria at screening

- Patient ≥ 18 years of age, of either gender.
- Had symptoms of OAB (urinary frequency and urgency *with or without* incontinence) for ≥ 3 months.
- Able to give written informed consent.
- Willing and able to complete the micturition diary and questionnaires.

Inclusion criteria at baseline

- Frequency of micturition on average ≥ 8 times per 24-hour period 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.

Exclusion criteria were essentially the same as those listed for study 046, and were aimed at excluding patients at high risk of adverse events and patients in whom the assessment of efficacy was likely to be compounded by other conditions or other treatments.

7.1.3.3. Study treatments

Study 074, like the other pivotal studies, used a single-blind placebo run-in period of 2 weeks. Following this, eligible patients were randomized in a 1:1:1 ratio to receive placebo, mirabegron 25mg or mirabegron 50mg orally daily for 12 weeks. Note that the proposed mirabegron dose

of 50mg was the higher dose assessed in this study, but it was the lower dose of Studies 046 and 047, and that this study was the only pivotal study to assess a dose of 25mg.

7.1.3.4. Efficacy variables and outcomes

The study used the same two co-primary endpoints assessed in the other pivotal studies:

- Change from baseline to end of treatment (final visit) in mean number of incontinence episodes per 24 hours based on a 3-day micturition diary
- Change from baseline to end of treatment (final visit) in mean number of micturitions per 24 hours based on a 3-day micturition diary

Key secondary efficacy variables (based on the 3-day micturition diary) included:

- Change from baseline to end of treatment (final visit) in mean volume voided per micturition
- Change from baseline to week 4 in mean number of incontinence episodes per 24 hours
- Change from baseline to week 4 in mean number of micturitions per 24 hours
- Change from baseline to end of treatment (final visit) in mean level of urgency
- Change from baseline to end of treatment (final visit) in mean number of urgency incontinence episodes per 24 hours
- Change from baseline to end of treatment (final visit) in mean number of urgency episodes (grades 3 or 4) per 24 hours

Additional secondary efficacy variables derived from the 3-day micturition diary:

- Change from baseline to week 8 and week 12 in mean number of micturitions perv24 hours
- Change from baseline to week 8 and week 12 in mean number of incontinence episodes per 24 hours
- Change from baseline to week 4, week 8 and week 12 in mean volume voided per micturition
- Change from baseline to week 4, week 8 and week 12 in mean number of urgency incontinence episodes per 24 hours
- Change from baseline to week 4, week 8 and week 12 in mean number of urgency episodes (grades 3 or 4) per 24 hours
- Change from baseline to week 4, week 8 and week 12 in mean level of urgency
- Change from baseline to week 4, week 8 week 12, and final visit in mean number of nocturia episodes per 24 hours
- Change from baseline to week 4, week 8 week 12 and final visit in mean number of pads used per 24 hours

Subjective assessments included the following:

- Change from baseline to week 4, week 8, week 12 and final visit in Symptom Bother and HRQL scores as assessed by the OAB-q questionnaire
- Change from baseline to week 12 and final visit in WPAI:SHP scores
- Change from baseline to week 4, week 8, week 12 and final visit in EQ-5D scores
- Change from baseline to week 4, week 8, week 12 and final visit in EQ-5D VAS scores
- Change from baseline to week 12 and final visit in PPBC

- Change from baseline to week 12 and final visit in TS-VAS
- Change from baseline to week 4, week 8, week 12 and final visit in number of physician visits for patient's bladder condition (excluding study-related visits)
- Change from baseline to week 12 and final visit on the Clinician Global Impression (CGI) scale (US only)
- Change from baseline to week 12 and final visit on the Patient Global Impression (PGI) scale (US only)

The last two scales (CGI and PGI) were not employed in the other pivotal studies. These were standard Likert scales similar to those used in many placebo-controlled drug studies, in which clinicians or patients assessed the change since baseline and recorded their impression in one of the following categories: 'Very much improved', 'Much improved', 'Minimally improved', 'No change', 'Minimally worse', 'Much worse', or 'Very much worse'. (The PGI also included a second question in which subjects rated their current status instead of their change since baseline.) These endpoints were not included in the European submission and are considered of minor importance, given that several other scales, including the TS-VAS, assessed similar information.

7.1.3.5. Randomisation and blinding methods

Randomisation was performed equally between the three treatment groups, using the same computerised system as in the other pivotal studies. Randomisation was stratified by centre.

Blinding was maintained with a double-dummy technique. For unclear reasons, unblinding may have occurred at one centre, affecting one patient in each treatment group (see Section 7.1.3.10). This low level of unblinding is unlikely to have altered the results.

7.1.3.6. Analysis populations

The analysis populations were as described for Study 046, and included the FAS, FAS-I, PPS and SAF.

7.1.3.7. Statistical methods

This study used the same co-primary endpoints as Study 046, and analysed these with the same statistical methods (see Section 7.1.1.7). Overall, the statistical methodology was appropriate.

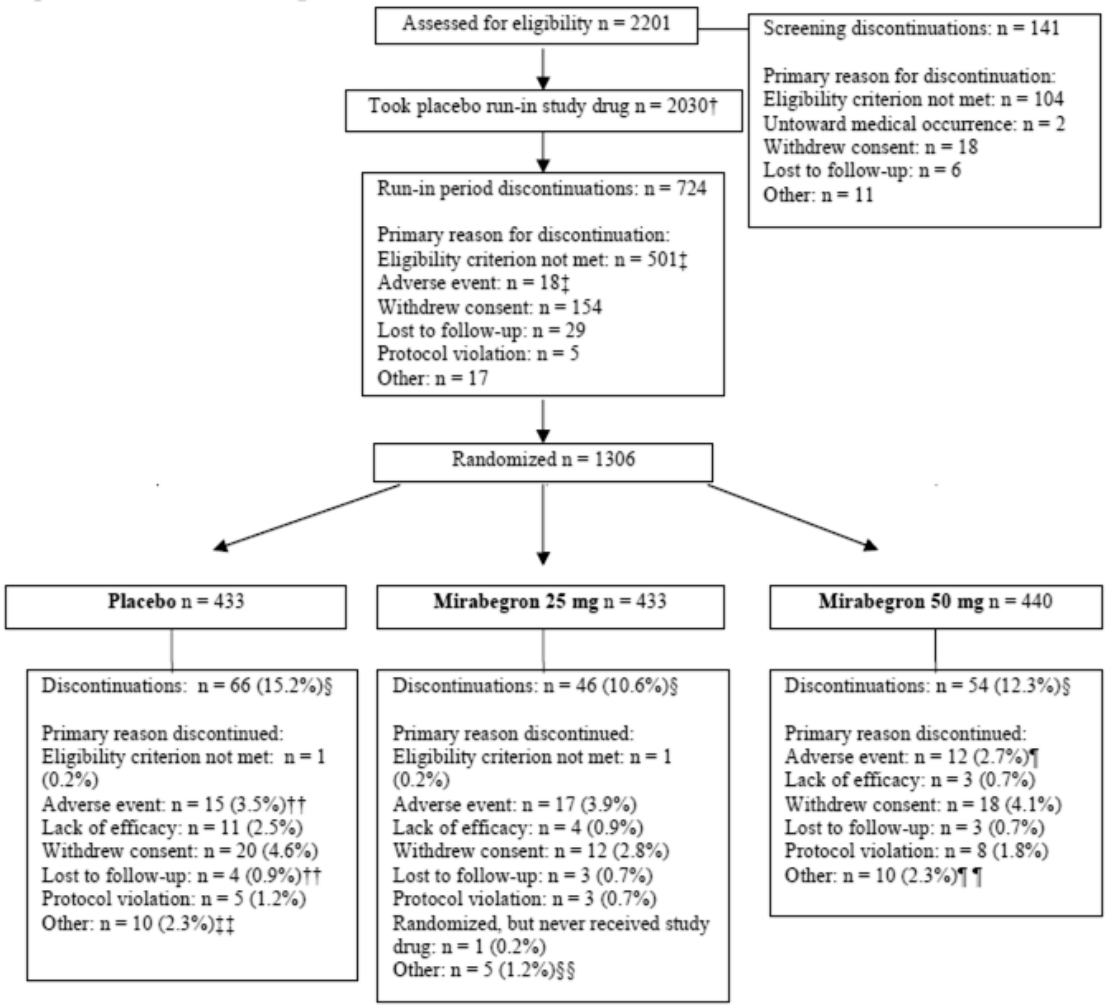
7.1.3.8. Sample size

Sample size considerations for Study 074 were essentially the same as those already described for Study 46. As with the other two pivotal studies, the study achieved its recruitment targets and demonstrated statistical significance for its primary endpoints, indicating an adequate sample size.

7.1.3.9. Participant flow

Patient disposition is summarised in the figure below. The discontinuation rate for randomised patients was 10.6% to 15.2% across the treatment groups, which is acceptable for a study of this nature. The discontinuation rate was slightly higher in the placebo group, and it does not appear likely that withdrawal bias contributed to the positive results of this study. Withdrawal due to AEs was seen in ~3-4% of subjects.

Figure 16. Patient Disposition, Study 074



7.1.3.10. Major protocol violations/deviations

Major protocol deviations included enrolment of 9 patients who had previously enrolled in the same or similar studies, as well as some violations of entry criteria. The main protocol deviations are summarised below. The most common deviation was an incomplete micturition diary.

Table 26. Reasons for Exclusion from the Per Protocol Set, Study 074

Parameter, n (%)	Placebo (n = 415)	Mirabegron 25 mg (n = 410)	Mirabegron 50 mg (n = 426)	Placebo (n = 262)	Mirabegron 25 mg (n = 254)	Mirabegron 50 mg (n = 257)
Total number of patients excluded, n (%)	48 (11.6%)	25 (6.1%)	38 (8.9%)	35 (13.4%)	18 (7.1%)	25 (9.7%)
Reasons						
Eligibility Violations Based on 3-Day Micturition Diary						
During 3-day baseline diary period:						
Average of < 8 micturitions per 24 hours	2 (0.5%)	3 (0.7%)	1 (0.2%)	2 (0.8%)	3 (1.2%)	1 (0.4%)
< 3 episodes of urgency (grade 3 or 4)	1 (0.2%)	0	1 (0.2%)	1 (0.4%)	0	0
Average daily volume voided > 3000 mL	0	2 (0.5%)	1 (0.2%)	0	1 (0.4%)	1 (0.4%)
Eligibility Violations Not Based on 3-Day Micturition Diary						
UTI, chronic inflammation or malignant disease of the pelvic organs	0	1 (0.2%)	0	0	1 (0.4%)	0
Nondrug treatment for OAB prior to screening	0	0	1 (0.2%)	0	0	1 (0.4%)
Error in Study Drug Administration Compared to Assigned Treatment						
Accidental intake of incorrect study drug during the double-blind treatment period †	1 (0.2%)	2 (0.5%)	0	1 (0.4%)	1 (0.4%)	0
Poor Study Drug Compliance						
Poor study drug compliance (< 70%) during the double-blind treatment period	5 (1.2%)	2 (0.5%)	3 (0.7%)	5 (1.9%)	0	2 (0.8%)
Inadequate Duration of Treatment						
Duration of placebo treatment in placebo run-in period was too short	0	1 (0.2%)	2 (0.5%)	0	1 (0.4%)	2 (0.8%)
Last diary day of the final visit was < 53 days	40 (9.6%)	16 (3.9%)	30 (7.0%)	27 (10.3%)	11 (4.3%)	19 (7.4%)
Unblinding of Study Drug						
Unblinding of treatment for double-blind study drug	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.4%)	1 (0.4%)	0
Participation in a Previous Mirabegron Study						
Participation in a previous mirabegron study	1 (0.2%)	1 (0.2%)	2 (0.5%)	1 (0.4%)	1 (0.4%)	1 (0.4%)

7.1.3.11. Baseline data

Baseline characteristics in the three treatment groups are summarised in the tables blow. Overall, the groups appeared well-matched in terms of demographics (Table 27), prior OAB history (Table 28) and OAB characteristics at screening (Table 29), with one exception: the proportion of patients with predominant urgency incontinence (as opposed to frequency without incontinence or mixed stress/urgency incontinence) was lower in the placebo group (28.2%) than the mirabegron 25mg group (38.0%) or mirabegron 50mg group (38.5%) of the FAS; similar differences were seen in the FAS-I population. The effects of this imbalance on the primary endpoints are difficult to predict. If the placebo group had less urge incontinence, then this might indicate milder urgency and a greater potential to reduce micturition frequency via non-pharmacological means, exaggerating the placebo effect, or it might indicate that there are less symptoms available for modification, lessening the placebo effect and enhancing the apparent treatment effect. It is unclear if the placebo response modifies mixed incontinence or stress incontinence to the same degree as urgency incontinence. Thus, the placebo response in this group might not be comparable to that in the active groups. Overall, this imbalance weakens the study slightly, but the same imbalance was not seen in the other pivotal studies, and the results across all three pivotal studies were similar, so it is unlikely to have had a major effect on the outcome.

Table 27. Patient Demographics and Baseline Characteristics, Study 074

	FAS			FAS-I		
		Mirabegron			Mirabegron	
Parameter	Placebo (n = 415)	25 mg (n = 410)	50 mg (n = 426)	Placebo (n = 262)	25 mg (n = 254)	50 mg (n = 257)
Sex (n, %)						
Male	127 (30.6%)	134 (32.7%)	133 (31.2%)	51 (19.5%)	55 (21.7%)	52 (20.2%)
Female	288 (69.4%)	276 (67.3%)	293 (68.8%)	211 (80.5%)	199 (78.3%)	205 (79.8%)
Age (years)						
Mean	58.2	58.8	60.4	58.8	59.9	61.4
SD	13.83	12.68	12.26	13.54	12.08	11.97
Age group (years) (n, %)						
< 65	261 (62.9%)	263 (64.1%)	262 (61.5%)	165 (63.0%)	155 (61.0%)	149 (58.0%)
≥ 65	154 (37.1%)	147 (35.9%)	164 (38.5%)	97 (37.0%)	99 (39.0%)	108 (42.0%)
< 75	371 (89.4%)	378 (92.2%)	378 (88.7%)	231 (88.2%)	234 (92.1%)	225 (87.5%)
≥ 75	44 (10.6%)	32 (7.8%)	48 (11.3%)	31 (11.8%)	20 (7.9%)	32 (12.5%)
Race (n, %)						
White	372 (89.6%)	373 (91.0%)	389 (91.3%)	229 (87.4%)	231 (90.9%)	236 (91.8%)
Black or African American	34 (8.2%)	31 (7.6%)	31 (7.3%)	27 (10.3%)	19 (7.5%)	19 (7.4%)
Asian	7 (1.7%)	5 (1.2%)	4 (0.9%)	5 (1.9%)	3 (1.2%)	2 (0.8%)
Other	2 (0.5%)†	1 (0.2%)‡	2 (0.5%)§	1(0.4%)¶	1(0.4%)††	0
Ethnicity (n, %)						
Hispanic/Latino	21 (5.1%)	22 (5.4%)	21 (4.9%)	14 (5.3%)	17 (6.7%)	18 (7.0%)
Non-Hispanic/ Non-Latino	394 (94.9%)	388 (94.6%)	405 (95.1%)	248 (94.7%)	237 (93.3%)	239 (93.0%)
BMI (kg/m^2)						
n	415	410	426	262	254	257
Mean (SD)	29.1 (6.27)	29.6 (6.32)	29.5 (6.52)	29.3 (6.51)	30.5 (6.70)	29.8 (6.71)
Geographical region (n, %)						
Eastern Europe	73 (17.6%)	75 (18.3%)	74 (17.4%)	37 (14.1%)	38 (15.0%)	40 (15.6%)
Western Europe	123 (29.6%)	117 (28.5%)	119 (27.9%)	77 (29.4%)	70 (27.6%)	72 (28.0%)
Northeastern US	39 (9.4%)	38 (9.3%)	41 (9.6%)	27 (10.3%)	29 (11.4%)	27 (10.5%)
Midwestern US	22 (5.3%)	24 (5.9%)	22 (5.2%)	13 (5.0%)	16 (6.3%)	13 (5.1%)
Southern US	67 (16.1%)	68 (16.6%)	74 (17.4%)	51 (19.5%)	47 (18.5%)	44 (17.1%)
Western US	60 (14.5%)	64 (15.6%)	65 (15.3%)	36 (13.7%)	42 (16.5%)	43 (16.7%)
Canada	31 (7.5%)	24 (5.9%)	31 (7.3%)	21 (8.0%)	12 (4.7%)	18 (7.0%)

Table 28. Overactive Bladder History, Study 074

		Mirabegron			Mirabegron	
Parameter	Placebo (n = 415)	25 mg (n = 410)	50 mg (n = 426)	Placebo (n = 262)	25 mg (n = 254)	50 mg (n = 257)
Type of OAB (n, %)†						
Urgency incontinence	117 (28.2%)	156 (38.0%)	164 (38.5%)	82 (31.3%)	109 (42.9%)	103 (40.1%)
Frequency	161 (38.8%)	130 (31.7%)	114 (26.8%)	60 (22.9%)	46 (18.1%)	33 (12.8%)
Mixed	137 (33.0%)	124 (30.2%)	148 (34.7%)	120 (45.8%)	99 (39.0%)	121 (47.1%)
Prior OAB Surgery (n, %)						
Yes	43 (10.4%)	25 (6.1%)	40 (9.4%)	37 (14.1%)	23 (9.1%)	34 (13.2%)
Previous OAB drug (n, %)						
Yes	217 (52.3%)	219 (53.4%)	206 (48.4%)	153 (58.4%)	147 (57.9%)	149 (58.0%)
Reason for previous OAB drug discontinuation (n, %)‡						
Insufficient effect						
Yes	141 (65.0%)	149 (68.0%)	143 (69.4%)	96 (62.7%)	98 (66.7%)	100 (67.1%)
Poor tolerability						
Yes	57 (26.3%)	48 (21.9%)	59 (28.6%)	43 (28.1%)	37 (25.2%)	46 (30.9%)
Duration of OAB symptoms (months)						
Mean (SD)	91.4 (96.08)	97.4 (115.14)	93.7 (98.94)	98.2 (99.61)	106.9 (124.41)	95.6 (94.76)
Median	63.0	59.8	62.7	64.6	61.1	64.0
Range	3 - 590	3 - 759	3 - 688	4 - 590	4 - 759	4 - 600

Table 29. Overactive Bladder-related Baseline Characteristics, Study 074

Parameter	Placebo (n = 415)	Mirabegron 25 mg (n = 410)	Mirabegron 50 mg (n = 426)	Placebo (n = 262)	Mirabegron 25 mg (n = 254)	Mirabegron 50 mg (n = 257)
Mean number of micturitions per 24 hours						
Mean	11.48	11.68	11.66	11.49	11.61	11.72
(SD)	(2.896)	(3.099)	(3.221)	(3.010)	(3.134)	(3.322)
Range	7.3 - 26.3	6.3 - 23.3	7.7 - 37.3	7.3 - 26.0	6.3 - 23.3	7.7 - 37.3
Mean number of incontinence episodes per 24 hours						
Mean	NA	NA	NA	2.43	2.65	2.51
(SD)				(2.349)	(2.544)	(2.347)
Range				0.3 - 13.7	0.3 - 21.0	0.3 - 13.5
Mean number of urgency incontinence episodes per 24 hours						
Mean	NA	NA	NA	2.19	2.39	2.27
(SD)				(2.202)	(2.155)	(2.221)
Range				0.0 - 13.7	0.0 - 13.0	0.0 - 12.5
Mean volume voided per micturition (mL)						
Mean	164.0	165.2	159.3	166.4	162.9	158.8
(SD)	(56.87)	(57.59)	(52.25)	(59.76)	(55.45)	(51.55)
Range	48 - 356	33 - 349	27 - 357	53 - 356	33 - 332	27 - 306
Mean number of urgency episodes (grade 3 or 4) per 24 hours						
Mean	5.40	5.57	5.80	6.13	6.28	6.63
(SD)	(3.310)	(3.617)	(3.567)	(3.398)	(3.717)	(3.695)
Range	0.3 - 26.0	1.0 - 21.7	1.0 - 18.7	0.3 - 26.0	1.0 - 21.7	1.0 - 18.7
Mean level of urgency						
Mean	2.36	2.37	2.41	2.47	2.51	2.56
(SD)	(0.551)	(0.563)	(0.561)	(0.579)	(0.572)	(0.533)
Range	0.8 - 4.0	0.4 - 4.0	0.7 - 4.0	0.8 - 4.0	0.7 - 4.0	0.7 - 4.0
Mean number of nocturia episodes per 24 hours						
Mean	1.78	1.96	2.03	1.79	1.99	1.92
(SD)	(1.274)	(1.516)	(1.537)	(1.273)	(1.539)	(1.544)
Range	0.0 - 6.7	0.0 - 9.0	0.0 - 12.0	0.0 - 6.7	0.0 - 9.0	0.0 - 12.0
Mean number of pads used per 24 hours						
Mean	0.92	0.77	0.83	1.41	1.20	1.32
(SD)	(1.804)	(1.486)	(1.706)	(2.092)	(1.735)	(2.008)
Range	0.0 - 12.3	0.0 - 11.0	0.0 - 12.0	0.0 - 12.3	0.0 - 11.0	0.0 - 12.0

7.1.3.12. Results for the primary efficacy outcome

Results for the two co-primary endpoints and key secondary endpoints are shown in the table below. As in the other pivotal studies, the mean baseline micturition frequency was 11-12 episodes per day, with little difference between groups at baseline. All groups experienced a reduction in micturition frequency through the study, amounting to just over one episode in the placebo group (mean change -1.18 episodes per 24 hours). Active treatment with mirabegron 25mg was associated with a placebo-subtracted reduction of 0.47 episodes per 24 hours, which was statistically significant (95% CI for placebo-subtracted change -0.82 to -0.13). The 50mg dose was associated with a smaller but still significant placebo-subtracted reduction of 0.42 episodes (95%CI -0.76 to -0.08). This is similar to the previous studies, and implies that active treatment would be expected to prevent less than one episode of voiding every two days, over a time period when about 23 voids would be expected from the baseline values. This is of marginal clinical value.

For the more distressing symptom of incontinence, baseline frequency was similar to the other pivotal studies, with about two and half episodes of incontinence per day. In the placebo group, the baseline incontinence frequency was 2.43 episodes per 24 hours and this improved during the study period by 0.96 episodes. Active treatment with mirabegron 25mg was associated with a placebo-subtracted reduction of 0.40 episodes of incontinence per 24 hours, which was

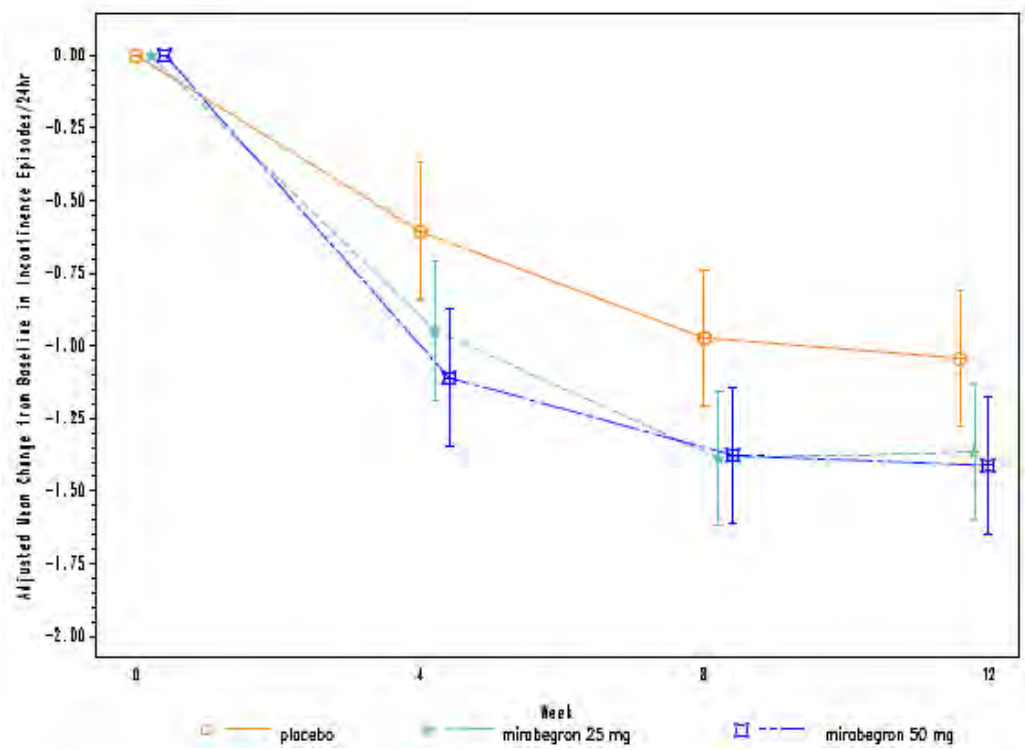
statistically significant (95%CI -0.74 to -0.06). The 50mg dose was associated with a similar placebo-subtracted reduction of 0.42 episodes (95%CI -0.76 to -0.08).*

Table 30. Results for Coprimary and Key Secondary Endpoints, Study 074

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Statistic	Coprimary Efficacy Endpoints †		Key Secondary Efficacy Endpoints †					
			Change from BL to FV in Mean Number of Incontinence Episodes per 24 Hours (FAS-I)	Change from BL to FV in Mean Number of Micturitions per 24 Hours (FAS)	Change from BL to FV in Mean Volume Voided (mL) per Micturition (FAS)	Change from BL to Week 4 in Mean Number of Incontinence Episodes per 24 Hours (FAS-I)	Change from BL to Week 4 in Mean Number of Micturitions per 24 Hours (FAS)	Change from BL to FV in Mean Level of Urgency (FAS)	Change from BL to FV in Mean Number of Urgency Incontinence Episodes per 24 Hours (FAS-I)	Change from BL to FV in Mean Number of Urgency Episodes (Grade 3 or 4) per 24 Hours (FAS)
178-CL-074 † (CAPRICORN)	Placebo 433/367	n	262	415	415	262	415	413	256	413
		Baseline	2.43 (0.145)	11.48 (0.142)	164.0 (2.79)	2.43 (0.145)	11.48 (0.142)	2.36 (0.027)	2.24 (0.138)	5.42 (0.163)
		Change from Baseline	-0.96 (0.122) (-1.19, -0.72)	-1.18 (0.124) (-1.42, -0.94)	8.3 (2.23) (3.9, 12.7)	-0.62 (0.120) (-0.85, -0.38)	-0.78 (0.124) (-1.02, -0.53)	-0.15 (0.028) (-0.21, -0.10)	-0.95 (0.110) (-1.16, -0.73)	-1.35 (0.154) (-1.66, -1.05)
	Mirabegron OCAS 25 mg 433/387	n	254	410	410	254	410	410	247	410
		Baseline	2.65 (0.160)	11.68 (0.153)	165.2 (2.84)	2.65 (0.160)	11.68 (0.153)	2.37 (0.028)	2.45 (0.137)	5.57 (0.179)
		Change from Baseline	-1.36 (0.124) (-1.60, -1.11)	-1.65 (0.125) (-1.90, -1.41)	12.8 (2.24) (8.4, 17.2)	-0.96 (0.122) (-1.20, -0.72)	-0.96 (0.124) (-1.20, -0.71)	-0.22 (0.029) (-0.28, -0.17)	-1.31 (0.112) (-1.53, -1.09)	-1.68 (0.155) (-1.99, -1.38)
		Difference from Placebo	-0.40 (0.174)# (-0.74, -0.06)	-0.47 (0.176)# (-0.82, -0.13)	4.6 (3.16) (-1.6, 10.8)	-0.34 (0.172) (-0.68, -0.01)	-0.18 (0.176) (-0.53, 0.16)	-0.07 (0.040) (-0.15, 0.01)	-0.36 (0.157) (-0.67, -0.05)	-0.33 (0.219) (-0.76, 0.10)
	Mirabegron OCAS 50 mg 440/386	n	257	426	426	255	424	426	251	426
		Baseline	2.51 (0.146)	11.66 (0.156)	159.3 (2.53)	2.52(0.147)	11.67 (0.157)	2.41 (0.027)	2.33 (0.140)	5.80 (0.173)
		Change from Baseline	-1.38 (0.123) (-1.62, -1.14)	-1.60 (0.122) (-1.84, -1.36)	20.7 (2.20) (16.4, 25.0)	-1.13 (0.122) (-1.36, -0.89)	-1.14 (0.122) (-1.38, -0.90)	-0.29 (0.028) (-0.35, -0.24)	-1.33 (0.111) (-1.55, -1.12)	-1.94 (0.152) (-2.24, -1.64)
		Difference from Placebo	-0.42 (0.175)# (-0.76, -0.08)	-0.42 (0.174)# (-0.76, -0.08)	12.4 (3.13)# (6.3, 18.6)	-0.51 (0.171)# (-0.85, -0.17)	-0.37 (0.174) (-0.71, -0.03)	-0.14 (0.040) (-0.22, -0.06)	-0.39 (0.156) (-0.69, -0.08)	-0.59 (0.217) (-1.01, -0.16)

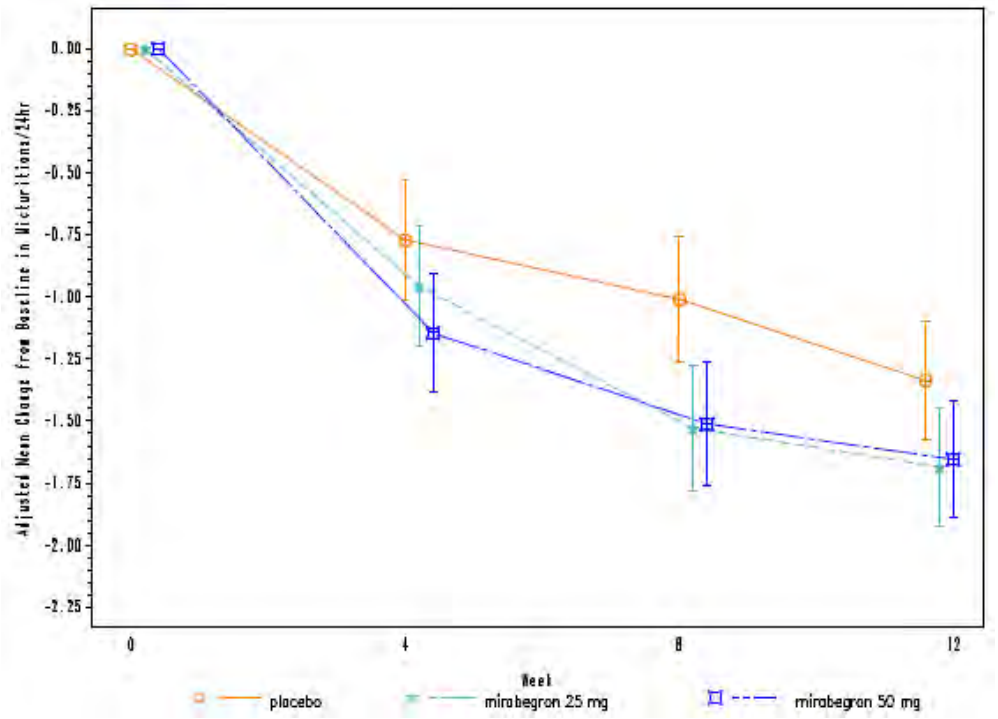
The results for the co-primary endpoints are displayed graphically below. As previously noted, the vertical scales of the graphs do not reflect the small proportional change from baseline.

Figure 17. Adjusted Change in Mean Incontinence Frequency, Study 074



*For the 50mg dose, the mean placebo-subtracted value and 95% confidence interval were reported with identical figures for both co-primary endpoints. The sponsor should be asked to confirm that there has not been an editing error producing this coincidence.

Figure 18. Adjusted Mean Change in Micturition Frequency, Study 074



7.1.3.13. Results for other efficacy outcomes

The key secondary endpoints are shown in the table-excerpt below. For the 50mg dose, a significant difference was observed compared to placebo for all of the key secondary endpoints. For the 25mg dose, several endpoints had 95%CIs that crossed zero: significance was achieved for change in incontinence episodes at week 4 and change in urgency incontinence at final visit, but not for change in mean volume voided, change in micturition frequency at week 4, change in mean level of urgency, or change in frequency of Grade 3 or 4 urgency episodes.

Table 31. Key Secondary Endpoints, Study 074

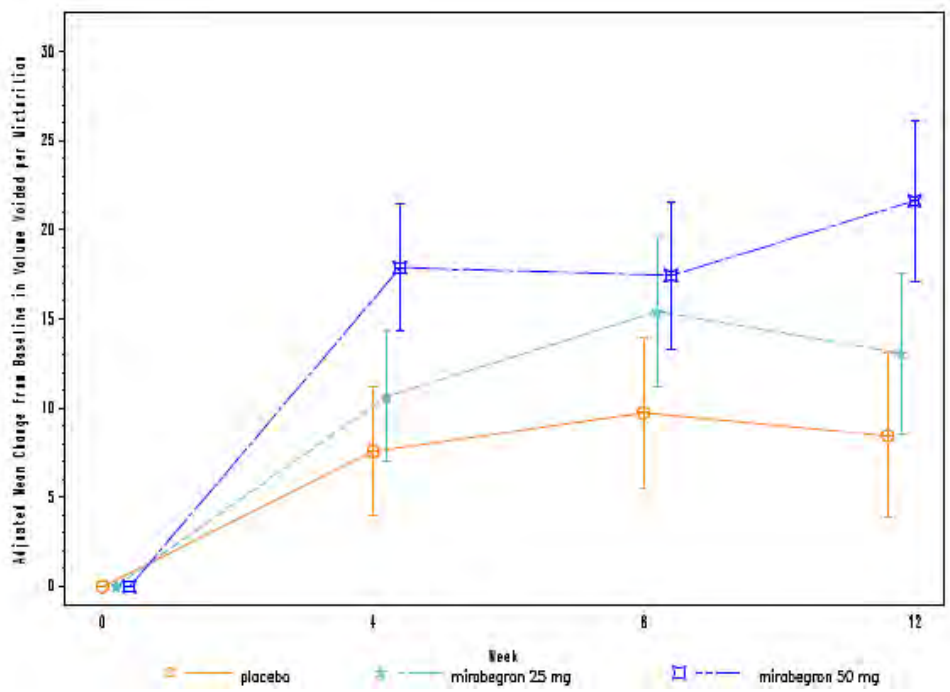
Study No.	Treatment Arm Number of Patients Randomized/ Completed	Statistic	Key Secondary Efficacy Endpoints †					
			Change from BL to FV in Mean Volume Voided (mL) per Micturition (FAS)	Change from BL to Week 4 in Mean Number of Incontinence Episodes per 24 Hours (FAS-I)	Change from BL to Week 4 in Mean Number of Micturitions per 24 Hours (FAS)	Change from BL to FV in Mean Level of Urgency (FAS)	Change from BL to FV in Mean Number of Urgency Incontinence Episodes per 24 Hours (FAS-I)	Change from BL to FV in Mean Number of Urgency Episodes (Grade 3 or 4) per 24 Hours (FAS)
178-CL-074 ‡ (CAPRICORN)	Placebo 433/367	n	415	262	415	413	256	413
		Baseline	164.0 (2.79)	2.43 (0.145)	11.48 (0.142)	2.36 (0.027)	2.24 (0.138)	5.42 (0.165)
		Change from Baseline	-8.3 (2.23) (-3.9, 12.7)	-0.62 (0.120) (-0.85, -0.38)	-0.78 (0.124) (-1.02, -0.53)	-0.15 (0.028) (-0.21, -0.10)	-0.95 (0.110) (-1.16, -0.73)	-1.35 (0.134) (-1.66, -1.05)
	Mirabegron OCAS 25 mg 433/387	n	410	254	410	410	247	410
		Baseline	165.2 (2.84)	2.65 (0.160)	11.68 (0.153)	2.37 (0.028)	2.45 (0.137)	5.57 (0.179)
		Change from Baseline	-12.8 (2.24) (-8.4, 17.2)	-0.96 (0.122) (-1.20, -0.72)	-0.96 (0.124) (-1.20, -0.71)	-0.22 (0.029) (-0.28, -0.17)	-1.31 (0.112) (-1.53, -1.09)	-1.68 (0.155) (-1.99, -1.38)
		Difference from Placebo	-4.6 (3.16) (-1.6, 10.8)	-0.34 (0.172) (-0.68, -0.01)	-0.18 (0.176) (-0.53, 0.16)	-0.07 (0.040) (-0.15, 0.01)	-0.36 (0.157) (-0.67, -0.05)	-0.33 (0.219) (-0.76, 0.10)
	Mirabegron OCAS 50 mg 440/386	n	426	255	424	426	251	426
		Baseline	159.3 (2.53)	2.52(0.147)	11.67 (0.157)	2.41 (0.027)	2.33 (0.140)	5.80 (0.173)
		Change from Baseline	-20.7 (2.20) (-16.4, 25.0)	-1.13 (0.122) (-1.36, -0.89)	-1.14 (0.122) (-1.38, -0.90)	-0.29 (0.028) (-0.35, -0.24)	-1.33 (0.111) (-1.55, -1.12)	-1.94 (0.152) (-2.24, -1.64)
		Difference from Placebo	-12.4 (3.13)≠ (-6.3, 18.6)	-0.51 (0.171)≠ (-0.85, -0.17)	-0.37 (0.174) (-0.71, -0.03)	-0.14 (0.040) (-0.22, -0.06)	-0.39 (0.156) (-0.69, -0.08)	-0.59 (0.217) (-1.01, -0.16)

For the 50mg dose, the placebo-subtracted change in volume voided was about 12 mL, as in the other studies (mean change 12.4, 95%CI 6.3 to 18.6). The placebo-subtracted changes at week 4 in micturition frequency and incontinence frequency for the 50mg group were similar to those seen at week 12. The mean level of urgency (placebo-subtracted) was reduced with mirabegron

50mg, by 0.14 in a 5-point scale, which narrowly achieved statistical significance (95% -0.22 to -0.06), but is of questionable clinical utility. With 50mg, urgency incontinence was also reduced by 0.39 episodes per 24 hours (placebo-subtracted), which was statistically significant (95%CI for placebo-subtracted change, -0.69 to -0.08). Episodes of higher-grade urgency (Grade 3 or 4) showed a similar reduction, as shown in the table.

For the 25mg dose group, changes were generally smaller and, as already noted, did not always achieve statistical significance. For details see the table.

Figure 19. Adjusted Mean Change in Volume Voided, Study 074



Nocturia was barely affected by active treatment, with very small mean placebo-subtracted changes (mean reductions of 0.01 and 0.04 episodes per 24 hours in the 25mg and 50mg dose groups, respectively), and this endpoint did not approach statistical significance.

Table 32. Change in Nocturia, Study 074

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Statistic	Change from BL to FV in Mean Number of Nocturia Episodes per 24 Hours (FAS) †
178-CL-074 (CAPRICORN)	Placebo 433/367	n	362
		Baseline	2.04 (0.061)
		Change from Baseline	-0.48 (0.058) (-0.60, -0.37)
	Mirabegron OCAS 25 mg 433/387	n	362
		Baseline	2.22 (0.075)
		Change from Baseline	-0.49 (0.058) (-0.61, -0.38)
		Difference from Placebo	-0.01 (0.082) (-0.17, 0.15)
	Mirabegron OCAS 50 mg 440/386	n	378
		Baseline	2.28 (0.074)
		Change from Baseline	-0.52 (0.057) (-0.63, -0.41)
		Difference from Placebo	-0.04 (0.081) (-0.20, 0.12)

For the secondary endpoint of pad use, the results of this study were negative. In all groups, there was a reduction in the mean number of pads used per 24 hours from baseline to final visit. The difference from placebo was positive in the 25mg group (+0.16, more pad use) and negative in the 50mg group (-0.17, less pad use), with no statistical difference from placebo in either group. The table excerpt below shows the results for the Final Visit.

Table 33. Change from Baseline in Mean Number of Pads Used Per 24 Hours, Study 074

Visit	Statistics	placebo (N=415)	mirabegron 25mg (N=410)	mirabegron 50mg (N=426)
Final Visit	Baseline			
	n	145	136	137
	Mean (SE)	2.63 (0.182)	2.32 (0.150)	2.58 (0.182)
	Median	2.33	2.00	2.00
	Min to Max	0.3 to 12.3	0.3 to 11.0	0.3 to 12.0
	Mean (SE)	1.57 (0.154)	1.58 (0.159)	1.39 (0.149)
	Median	1.00	1.00	1.00
	Min to Max	0.0 to 9.3	0.0 to 9.7	0.0 to 10.0
	Change From Baseline			
	Mean (SE)	-1.06 (0.155)	-0.74 (0.123)	-1.18 (0.147)
	Median	-0.67	-0.67	-1.00
	Min to Max	-10.0 to 3.3	-4.3 to 5.7	-8.7 to 3.3
	Adjusted Change From Baseline			
	Adjusted Mean (SE)	-0.99 (0.118)	-0.83 (0.122)	-1.16 (0.121)
	95% Two-Sided CI	(-1.22,-0.76)	(-1.07,-0.59)	(-1.39,-0.92)
	Difference vs. Placebo			
	Adjusted Mean (SE)		0.16 (0.171)	-0.17 (0.170)
	95% Two-Sided CI		(-0.18,0.49)	(-0.50,0.17)
	p-value		0.36	0.33

The subjective endpoints showed favourable changes in all groups including placebo, with minor numerical superiority seen with active treatment for most assessments (apart from the change in PPBC, which was the same in the placebo and mirabegron 50mg groups).

For the 25mg dose, statistical superiority over placebo was shown for the TS-VAS, but none of the other subjective endpoints in the table. For the 50mg dose, superiority was demonstrated for the TS-VAS and 'symptom bother' scores, but not the HRQL or PPBC. Even for measures in which a statistical effect was shown, the differences from placebo were of doubtful clinical value, with the TS-VAS showing a placebo-subtracted improvement of 0.49 for 25mg and 0.83 for 50mg, out of a 10-point scale, and the symptom bother score showing a placebo-subtracted reduction of 2.8 in a scale ranging to 100.

Table 34. Subjective Endpoints, Study 074

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Statistic	Change from BL to FV in Treatment Satisfaction – Visual Analog Scale (FAS) +	Change from BL to FV in Symptom Bother Score (FAS) +	Change from BL to FV in HRQL Total Score (FAS) +	Change from BL to FV in PPBC (FAS) +
178-CL-074 (CAPRICORN)	Placebo 433/367	n	377	405	406	376
		Baseline	5.13 (0.190)	49.1 (0.95)	64.5 (1.01)	4.0 (0.05)
		Adjusted Change from Baseline	1.05 (0.154) (0.75, 1.35)	-16.0 (0.90) (-17.8, -14.3)	13.0 (0.80) (11.5, 14.6)	-0.7 (0.06) (-0.8, -0.6)
	Mirabegron OCAS 25 mg 433/387	n	389	407	408	391
		Baseline	5.15 (0.185)	48.5 (0.97)	65.0 (1.04)	4.0 (0.05)
		Adjusted Change from Baseline	1.54 (0.152) (1.24, 1.84)	-17.9 (0.90) (-19.6, -16.1)	14.3 (0.79) (12.8, 15.9)	-0.8 (0.06) (-0.9, -0.6)
		Difference from Placebo	0.49 (0.216)* (0.07, 0.91)	-1.8 (1.27) (-4.3, 0.7)	1.3 (1.12) (-0.9, 3.5)	-0.1 (0.08) (-0.2, 0.1)
	Mirabegron OCAS 50 mg 440/386	n	388	422	419	395
		Baseline	5.13 (0.188)	50.6 (0.99)	63.7 (1.09)	4.0 (0.05)
		Adjusted Change from Baseline	1.88 (0.152) (1.58, 2.18)	-18.8 (0.88) (-20.5, -17.1)	14.2 (0.78) (12.7, 15.8)	-0.7 (0.06) (-0.8, -0.6)
		Difference from Placebo	0.83 (0.216)* (0.41, 1.25)	-2.8 (1.26)* (-5.3, -0.3)	1.2 (1.12) (-1.0, 3.4)	-0.0 (0.08) (-0.2, 0.1)

7.1.3.14. Subgroup analyses

Although the sponsor presented subgroup analyses for the co-primary endpoints, this analysis was relatively underpowered. A more meaningful subgroup analysis was performed on the pooled pivotal data, and this is presented in Section 7.3.

7.2. Supportive efficacy studies

In addition to the three pivotal phase 3 studies (Studies 046, 047 and 074), the sponsor performed a number of supportive studies, as follows:

- 1 supportive phase 3 study (178-CL-048),
- 2 supportive phase 2b studies (178-CL-045 and 178-CL-044),
- 1 phase 2a proof-of-concept study (178-CL-008),
- 1 phase 3 active-controlled long-term safety study (178-CL-049), and
- 1 phase 3 open label, long-term safety study (178-CL-051).

7.2.1. Supportive efficacy study 048

7.2.1.1. Design

Study 048 was a phase 3, a randomised, double-blind, placebo- and tolterodine-controlled, parallel-group, multi-centre study in which the efficacy of mirabegron was assessed in overactive bladder patients. The study consisted of a 2-week run-in period, a 12-week double-blind treatment period, and 2-week follow-up period.

Mirabegron was administered at the proposed dose of 50mg daily. Tolterodine was used at a standard dose of 4mg daily. Patients were randomised equally to mirabegron, tolterodine and placebo.

Entry criteria were generally similar to those in the pivotal studies, but patients were eligible if they had, on average, one episode of urgency per day in the baseline micturition diary; the requirement for Grade 3 or 4 urgency, which was an entry criteria for the pivotal studies, was not relevant to Study 048 because urgency was not graded in this study. Subjects *were* required to have at least one episode per day of episode of urge incontinence per day, however, so this population roughly corresponds to the FAS-I subgroup of the pivotal studies (rather than to the full pivotal population which included subjects without baseline incontinence).

From the study report, the entry criteria are listed as follows:

"Provisional enrolment

1. Outpatient of either sex, at least 20 years of age at time of consent
2. Continuous symptoms of overactive bladder for at least 24 weeks prior to start of the run-in period
3. Capable of walking to toilet unaided and measuring urine volume by him-/herself.
4. Has personally given written informed consent.

Formal enrolment (randomization)

Patients who satisfied inclusion criterion 3 above at provisional enrolment and all of the following criteria at formal enrolment progressed to the treatment period.

5. Averages at least 8 micturitions per 24 hours and satisfies at least one of the following conditions (confirmed from the 3-day diary entries for the run-in period).

- At least 1 urgency episode per 24 hours on average.

· At least 1 urge incontinence episode per 24 hours on average."

Primary endpoint

The primary endpoint was the change from baseline to the final visit in mean number of micturitions per 24 hours (which therefore matched one of the co-primary endpoints of the pivotal studies).

Secondary endpoints

The frequency of incontinence, which was a primary endpoint in the pivotal studies, was only a secondary endpoint Study 048.

Other secondary endpoints were:

· the mean volume voided per micturition

· the mean number of urgency incontinence episodes per 24 hours

· the mean number of urgency episodes per 24 hours

· the mean number of nocturia episodes per 24 hours

· QOL as assessed by the King's Health Questionnaire (KHQ)

The **King's Health Questionnaire** (KHQ) was the main QOL instrument used in this study. It is a disease-specific health-related QOL questionnaire designed to measure QOL of patients with urinary incontinence; it has been shown to be reliable and responsive to treatment-induced changes in clinical trials (Reese et al, 2003). Development, validation and instructions for conducting the questionnaire were described by Kelleher et al (1997) and updated in 2004 (Kelleher 2004). It includes questions in several domains, as summarised below: Incontinence impact, Role limitations, Physical limitations, Social limitations, Personal relationships, Emotions, Sleep and energy, Severity measures, General health perceptions, and Symptom severity. Decreases in scores represent improvements.

Table 35. King's Health Questionnaire

Domain No.	Domain	Question No.	Questions†
1	General health perception	1	General condition of health
2	Incontinence impact	2	Is your life in general affected?
3	Role limitations	3a	Are your household tasks affected?
		3b	Are your job or your normal daily activities outside the home affected?
4	Physical limitations	4a	Is your ability to exercise affected?
		4b	Is your use of transportation affected?
5	Social limitations	4c	Is your social life affected?
		4d	Is your ability to see and visit friends affected?
		5c	Is your family life affected?
6	Personal relationships	5a	Is your relationship with your partner affected?
		5b	Is your sex life affected?
7	Emotions	6a	Does your bladder problem ever make you feel depressed?
		6b	Does your bladder problem ever make you feel anxious or nervous?
		6c	Does your bladder problem ever make you feel bad about yourself?
8	Sleep/energy	7a	Is your sleep ever affected?
		7b	Do you ever feel tired and worn out?
9	Severity measures	8a	Do you ever wear pads?
		8b	Are you ever careful of how much fluid you drink?
		8c	Do you ever change your underclothes because they get wet?
		8d	Do you ever worry in case you smell?
		8e	Do you ever feel embarrassed?

† Questions are somewhat summarized.

7.2.1.1.1. Statistics

For analysis of the primary variable, the sponsor used the two-sample t-test to compare mirabegron and placebo for the change in mean number of micturitions per 24 hours (from baseline to final assessment). A standard, two-sided significance level of 5% was used.

For secondary variables, the Wilcoxon rank sum test was used for studying superiority to placebo in change in the mean number of incontinence episodes and change in the mean number of urge incontinence episodes. To estimate the adjusted difference in change from baseline between the placebo group and the respective treatment groups, and the two-sided 95% confidence interval for that difference, an ANOVA was used with treatment group as a factor and baseline as a covariate.

7.2.1.2. Differences between Study 048 and the pivotal studies

This study was conducted in Japan and had several design differences compared to the multi-centre, international pivotal studies. In Study 048, urinary urgency was based on whether a patient reported urgency or not with an episode of micturition; the 5-point PPIUS was not utilized. There was only one primary endpoint, micturition frequency, whereas incontinence frequency was considered a secondary endpoint. The subjective endpoints were also different, and included the QOL domain scores on King's Health Questionnaire (KHQ) instead of the OAB-q, which makes a comparison across studies difficult. The TS-VAS, which was considered a major secondary endpoint in the pivotal studies, was not used in this study. This study does not, therefore, conform to the EU note for Guidance on the performance of incontinence studies, because it did not include a global evaluation of the patient's subjective assessment of the benefits of therapy. Because of all these differences, the study was considered by the sponsor to be merely supportive, but it has a broadly acceptable phase 3 design and the results have a similar importance to the pivotal studies.

7.2.1.3. Results

7.2.1.3.1. Baseline data

The groups were acceptably matched at baseline, as shown in the table below.

Table 36. Demographic and Baseline Characteristics, Study 048

		Placebo (n = 368)	YM178 50 mg (n = 369)	Tolterodine 4 mg (n = 368)	P value
Sex	Male	58 (15.8%)	58 (15.7%)	64 (17.4%)	1.000†
	Female	310 (84.2%)	311 (84.3%)	304 (82.6%)	
Age (yr)	Mean ± SD	58.2 ± 14.18	58.3 ± 13.88	58.3 ± 13.69	0.948‡
	Median	60.0	60.0	60.0	
	(Minimum, maximum)	(20, 86)	(22, 88)	(20, 86)	
	< 65 yr of age	231 (62.8%)	233 (63.1%)	227 (61.7%)	–
	≥ 65 yr of age	137 (37.2%)	136 (36.9%)	141 (38.3%)	
Weight (kg)	Mean ± SD	55.32 ± 9.585	55.12 ± 9.840	56.54 ± 10.432	0.771‡
	Median	54.00	53.10	54.00	
	(Minimum, maximum)	(37.5, 105.0)	(35.7, 90.0)	(38.0, 104.5)	
Height (cm)	Mean ± SD	156.50 ± 7.875	156.62 ± 7.669	157.21 ± 7.677	0.827‡
	Median	156.00	155.70	157.00	
	(Minimum, maximum)	(138.0, 186.4)	(136.6, 184.5)	(132.0, 180.0)	
Duration of illness (mo)	Mean ± SD	76.5 ± 88.42	70.0 ± 66.91	75.6 ± 78.25	0.264‡
	Median	54.5	49.0	54.0	
	(Minimum, maximum)	(6, 813)	(6, 486)	(6, 608)	
	< 6 mo	0	0	0	–
	≥ 6 mo to < 1 yr	15 (4.1%)	23 (6.2%)	20 (5.4%)	
	≥ 1 yr to < 3 yr	101 (27.4%)	97 (26.3%)	112 (30.4%)	
	≥ 3 yr to < 5 yr	89 (24.2%)	99 (26.8%)	79 (21.5%)	
	≥ 5 yr to < 10 yr	93 (25.3%)	83 (22.5%)	76 (20.7%)	
	≥ 10 yr	68 (18.5%)	63 (17.1%)	80 (21.7%)	
	Unknown	2 (0.5%)	4 (1.1%)	1 (0.3%)	
OAB severity (mean number of micturitions) §	< 10	122 (33.2%)	140 (37.9%)	136 (37.0%)	–
	≥ 10 to < 15	220 (59.8%)	199 (53.9%)	202 (54.9%)	
	> 15	26 (7.1%)	30 (8.1%)	30 (8.2%)	
Type of incontinence	None	39 (10.6%)	31 (8.4%)	39 (10.6%)	0.352†
	Urge incontinence	236 (64.1%)	230 (62.3%)	235 (63.9%)	
	Mixed incontinence	93 (25.3%)	108 (29.3%)	94 (25.5%)	
Incontinence§	No	104 (28.3%)	103 (27.9%)	128 (34.8%)	0.935†
	Yes	264 (71.7%)	266 (72.1%)	240 (65.2%)	
Post-void residual volume (mL)	Mean ± SD	8.99 ± 12.868	8.45 ± 12.888	10.44 ± 16.560	0.567‡
	Median	3.90	3.60	3.50	
	(Minimum, maximum)	(0.0, 97.6)	(0.0, 84.0)	(0.0, 97.0)	
Medical history	No	311 (84.5%)	302 (81.8%)	322 (87.5%)	0.376†
	Yes	57 (15.5%)	67 (18.2%)	46 (12.5%)	
Complications	No	92 (25.0%)	98 (26.6%)	74 (20.1%)	0.674†
	Yes	276 (75.0%)	271 (73.4%)	294 (79.9%)	

The number of patients (the percentage in group)
† Fisher's exact test
‡ two-sample t-test
§ Based on baseline patients' diaries

7.2.1.3.2. Primary endpoint

The baseline micturition frequency in Study 048 was about 11 episodes per 24 hours, which is very similar to the three pivotal studies, despite some differences in entry criteria. Placebo treatment was associated with a mean reduction of 0.86 micturition episodes from a baseline of 11.29 episodes. Active treatment with mirabegron 50mg was associated with a further reduction of 0.86 (placebo-subtracted), and this was statistically significant (95%CI for the difference from placebo, -1.16 to -0.57). Tolterodine, the active control, showed a somewhat less beneficial change, with a mean placebo-subtracted change in micturition frequency of -0.61 episodes per 24 hours (95%CI -0.90 to -0.32).

Note that the magnitude of the placebo-subtracted change in micturition was modest, less than one voiding episode per day, but this was a slightly greater reduction than that seen in the pivotal studies.

Table 37. Results for Primary and Major Secondary Endpoints, Study 048

Study No.	Treatment Arm Number of Patients Randomized / Completed	Statistic	Primary Efficacy Endpoint (FAS)	Secondary Efficacy Endpoints (FAS) Change from Baseline to Final Visit in:				
			Mean Number of Micturitions per 24 Hours	Mean Number of Incontinence Episodes per 24 Hours	Mean Volume Voided (mL) per Micturition	Mean Number of Urgency Incontinence Episodes per 24 Hours	Mean Number of Urgency Episodes ¶ per 24 Hours	Mean Number of Nocturia Episodes per 24 Hours
178-CL-048	Placebo 381/350	n	368	264	364	258	368	322
		Baseline§	11.29 (2.748)	1.91 (1.760)	146.791(44.234)	1.67 (1.366)	4.42 (2.989)	1.81 (1.198)
		Change from Baseline†	-0.86 (2.354)	-0.66 (1.861)	9.72 (29.086)	-0.60 (1.745)	-1.37 (3.191)	-0.36 (1.062)
	Mirabegron OCAS 50 mg 380/349	n	369	266	368	254	369	323
		Baseline§	11.15 (2.650)	1.99 (2.054)	149.591 (46.376)	1.78 (1.752)	4.27 (2.848)	1.72 (0.998)
		Change from Baseline†	-1.67 (2.212)*	-1.12 (1.475)*	24.30 (35.477)*	-1.01 (1.338)*	-1.85 (2.555)*	-0.44 (0.933)
		Difference from Placebo‡	-0.86 (-1.16, -0.57)	-0.42 (-0.67, -0.17)	14.78 (9.97, 19.58)	-0.36 (-0.59, -0.12)	-0.54 (-0.90, -0.18)	-0.12 (-0.25, 0.01)
	Tolterodine ER 4 mg 378/355	n	368	240	367	230	368	332
		Baseline§	11.10 (2.567)	1.89 (1.826)	145.863 (46.897)	1.71 (1.571)	4.13 (2.810)	1.71 (1.075)
		Change from Baseline†	-1.40 (2.176)	-0.97 (1.612)	28.83 (34.720)	-0.95 (1.583)	-1.66 (2.560)	-0.42 (0.845)
		Difference from Placebo‡	-0.61 (-0.90, -0.32)	-0.32 (-0.57, -0.06)	19.05 (14.25, 23.85)	-0.32 (-0.56, -0.08)	-0.41 (-0.77, -0.05)	-0.10 (-0.23, 0.03)

7.2.1.3.3. Secondary endpoints

Results for the main secondary endpoints are shown in the table above. The findings in the mirabegron group were significantly different from the placebo group for all of the major secondary endpoints except nocturia.

Incontinence was about two episodes per day at baseline (mean 1.89 to 1.99 across the treatment groups), and this was reduced by 0.66 episodes per day in the placebo group. Active treatment with mirabegron 50mg was associated with a further reduction of 0.42 episodes (95%CI for placebo-subtracted change, -0.67 to -0.17), a similar value to that shown across the three pivotal studies. Tolterodine was associated with a similar but slightly smaller treatment effect (placebo-subtracted change -0.32 episodes per 24 hours, 95%CI -0.57 to -0.06).

The mean volume of micturition was increased by mirabegron treatment by ~15 mL over and above the placebo effect (+14.78 mL, 95%CI 9.97 to 19.58). Tolterodine was associated with a slightly greater increase (+19.05 mL, 95%CI 14.25 to 23.85).

Urgency incontinence showed similar changes to all-cause incontinence, with a placebo-subtracted change of -0.36 episodes per 24 hours in the mirabegron group (95%CI-0.59 to -0.12), and -0.32 in the tolterodine group (95%CI -0.56 to -0.08).

Urgency episodes were reduced by 0.54 episodes in the mirabegron group (placebo-subtracted), equivalent to about one episode every two days. Nocturia was not significantly changed by mirabegron, and the magnitude of the mean reduction was of doubtful clinical value (0.12 episodes per 24 hours). Tolterodine results for these two endpoints were similar (see table).

Overall, the results are broadly consistent with the pivotal studies and increase the external validity of the pivotal studies. The magnitude of the benefits was small, however, with primary endpoint showing that micturition is changed, on average, by less than one void per day.

Subjective endpoints consisted of responses to the King's Health Questionnaire. In most of the nine domains assessed, a significant and favourable difference was noted in the mirabegron group compared to placebo, as shown in the table below. Compared to placebo, the mirabegron group showed a statistically significant improvement in: domain 2 (incontinence impact), domain 3 (role limitations), domain 4 (physical limitations), domain 5 (social limitations), domain 7 (emotions), domain 8 (sleep/energy) and domain 9 (severity measures). As with most of the subjective endpoints described in this submission, it is difficult to assess what the

observed differences actually mean in terms of clinical utility, but it is at least encouraging that the overall trends were favourable.

Table 38. Change from Baseline in QOL Scores

	Placebo	YM178 50 mg	Tolterodine 4 mg
Domain 1 (general health perception)			
Baseline	32.3 ± 18.47	31.9 ± 17.81	33.8 ± 17.92
Final assessment	32.2 ± 18.34	29.7 ± 19.08	31.8 ± 19.00
Change	−0.1 ± 20.13 (368)	−2.2 ± 20.43 (365)	−2.1 ± 20.40 (365)
P value†	–	0.170	–
Domain 2 (incontinence impact)			
Baseline	49.1 ± 27.61	47.8 ± 26.77	49.5 ± 26.31
Final assessment	42.4 ± 25.74	33.8 ± 25.25	38.4 ± 25.52
Change	−6.7 ± 28.76 (368)	−13.9 ± 28.32 (365)	−11.0 ± 27.98 (365)
P value†	–	<0.001	–
Domain 3 (role limitations)			
Baseline	36.6 ± 25.21	34.7 ± 23.70	35.2 ± 23.15
Final assessment	31.9 ± 24.84	23.7 ± 22.02	26.6 ± 22.30
Change	−4.7 ± 25.99 (368)	−10.9 ± 23.55 (365)	−8.6 ± 23.91 (365)
P value†	–	<0.001	–
Domain 4 (physical limitations)			
Baseline	38.5 ± 25.79	37.1 ± 26.48	38.5 ± 27.04
Final assessment	33.4 ± 25.87	26.7 ± 22.64	30.4 ± 25.30
Change	−5.1 ± 23.48 (368)	−10.4 ± 25.32 (365)	−8.2 ± 24.88 (365)
P value†	–	0.004	–
Domain 5 (social limitations)			
Baseline	19.8 ± 22.58	19.4 ± 22.21	19.6 ± 20.92
Final assessment	18.0 ± 22.89	13.3 ± 20.06	13.7 ± 19.05
Change	−1.7 ± 20.57 (368)	−6.1 ± 21.43 (365)	−6.0 ± 19.32 (365)
P value†	–	0.005	–
Domain 6 (personal relationships)			
Baseline	9.3 ± 17.54	9.9 ± 18.52	7.9 ± 15.31
Final assessment	8.4 ± 18.25	6.6 ± 15.53	5.2 ± 12.98
Change	−0.9 ± 17.28 (259)	−3.3 ± 13.33 (263)	−2.7 ± 14.64 (278)
P value†	–	0.077	–
Domain 7 (emotions)			
Baseline	38.3 ± 26.16	36.6 ± 25.08	36.4 ± 25.40
Final assessment	33.0 ± 27.51	26.5 ± 23.80	27.5 ± 22.56
Change	−5.3 ± 25.07 (368)	−10.1 ± 24.77 (365)	−8.9 ± 23.03 (365)
P value†	–	0.009	–
Domain 8 (sleep/energy)			
Baseline	29.9 ± 24.98	27.8 ± 23.33	29.9 ± 23.76
Final assessment	24.9 ± 22.98	18.9 ± 20.68	21.9 ± 22.32
Change	−5.0 ± 21.54 (368)	−8.9 ± 22.01 (365)	−8.1 ± 21.84 (365)
P value†	–	0.016	–
Domain 9 (severity measures)			
Baseline	30.3 ± 19.48	30.5 ± 18.65	30.2 ± 18.44
Final assessment	27.0 ± 19.13	22.2 ± 17.45	22.3 ± 17.61
Change	−3.3 ± 15.52 (368)	−8.3 ± 16.83 (365)	−7.9 ± 16.51 (365)
P value†	–	<0.001	–

Mean ± SD. Parentheses contain the number of patients analyzed.
† Two-sample t-test vs placebo (significance level: 0.05, two-sided)

7.2.2. Supportive efficacy study 044

7.2.2.1. Design

Study 044 was a phase 2b study, designed to explore the dose-response relationship of mirabegron in the treatment of OAB. It was a multinational, multicentre, double-blind, randomised, parallel group, placebo- and tolterodine-controlled study with six treatment groups.

Like the pivotal studies, it employed a single-blind, 2-week placebo run-in period followed by a randomised, double-blind, placebo-controlled, 12-week treatment period.

At screening, patients received a micturition diary that was completed in the 3 days preceding Visit 2, and ambulatory blood pressure monitor to use for the 3-day diary period.

After the placebo run-in period, eligible patients were randomised to one of the following treatments:

- mirabegron OCAS 25mg qd
- mirabegron OCAS 50mg qd
- mirabegron OCAS 100mg qd
- mirabegron OCAS 200mg qd
- placebo
- tolterodine 4 mg qd.

In addition to micturition diaries, which were completed in the 3 days prior to each visit, patients measured vital signs (HR, SBP, DBP) 2 times per day in triplicate by means of ambulatory blood pressure monitoring, and symptom and Quality of Life Questionnaires were completed at baseline and approximately every two weeks thereafter. Post-void residual volume (the volume left in the bladder after voiding) was measured by ultra-sonography or bladder scan at baseline and the end of treatment.

The entry criteria were similar to the pivotal studies: men or women aged ≥ 18 years who had experienced symptoms of OAB (including urinary frequency, and urgency with or without urge incontinence) for at least 3 months prior to screening, who did not have major confounding illnesses or other treatments. To be eligible for randomisation, subjects had to experience frequency of micturition on average ≥ 8 times per 24-hour period during the 3-day micturition diary period, and at least 3 episodes of urgency with or without incontinence (grade 3 or 4), during the 3-day period.

The primary endpoint was the change from baseline to final visit in the mean micturition frequency (per 24 hours), based on the 3-day micturition diary.

Secondary efficacy variables as listed by the sponsor were:

- Change from baseline in mean volume voided per micturition
- Change from baseline in mean number of urgency episodes (grade 3 or 4) per 24 hours
- Change from baseline in level of urgency (using the same scale as in the pivotal studies, the Patient Perception of Intensity of Urgency Scale, or PPIUS).
- Change from baseline in mean number of urge incontinence episodes per 24 hours
- Change from baseline in mean number of incontinence episodes per 24 hours
- Change from baseline in mean number of nocturia episodes per 24 hours
- Change from baseline in symptom scores as assessed by International Consultation on Incontinence Questionnaire-Overactive Bladder (ICIQ-OAB)
- Change from baseline in quality of life scores as assessed by International Consultation on Incontinence Questionnaire-Overactive Bladder-Quality of Life (ICIQ-OABqol)
- Change from baseline in patient's perception of treatment benefit.

In most cases, these endpoints were derived from the micturition diaries and were similar to those employed in the pivotal studies. The OAB questionnaire referred to in the study report as the ICIQ-OAB is the same one referred to in the pivotal study reports as the OAB-q, and this contributed to a symptom bother score and a QOL estimate, as in the pivotal studies. The change from baseline in the patient's perception of treatment benefit was assessed with a 3-point scale, in contrast to the 10-point VAS used in the pivotal studies. This treatment assessment instrument had been used in a Phase 2a proof-of-concept study, and in one other

published OAB study (Sussman D, Garely A., 2002), but it has not been formally validated. Given that it only had 3 points, it would seem to lack the resolution required to characterise treatment benefit with any detail or subtlety, but this is acceptable in a minor supportive study.

7.2.2.1.1. Statistics

Changes from baseline in the mean number of micturitions per 24 hours were subjected to an analysis of covariance (ANCOVA) model, including mirabegron dose as a fixed factor and the baseline number of micturitions per 24 hours as a covariate.

Overall, the design of this study was acceptable for a phase 2 dose-ranging study.

7.2.2.2. Results

7.2.2.2.1. Baseline data

The groups were reasonably matched at baseline in terms of demographics and disease characteristics (data not shown).

7.2.2.2.2. Efficacy endpoints

The main efficacy results for Study 044 are shown in the table excerpt below (results for other Phase 2 studies have been cut from the table and will be included separately). For the primary endpoint of mean micturition frequency, all treatment groups had 11-12 micturitions per 24 hours at baseline, and all groups showed an improvement during the course of the study. In the placebo group, mean micturition frequency improved by 1.43 episodes from 11.67 at baseline. Active treatment with mirabegron caused an additional (placebo-subtracted and adjusted) improvement of 0.45, 0.64, 0.68, and 0.80 episodes per 24 hours in the 25mg, 50mg, 100mg and 200mg groups, respectively. Note that there was a dose trend across the range 25mg to 200mg, but the difference between 50mg and 100mg was minor, and the mean unadjusted changes from baseline were similar across dose groups without a dose trend. The tolterodine group showed a change from baseline that was similar to the mirabegron groups and greater than the change in the placebo group, but the sponsor did not estimate the placebo-subtracted change in the tolterodine group, making a comparison between active treatments difficult.

The 95%CIs for the placebo-subtracted change did not include zero for the 50mg, 100mg and 300mg doses, but did include zero for the 25mg group, which was therefore not significantly different from placebo.

The magnitude of the benefit at 50mg and 100mg is broadly similar to the phase 3 studies, and amounts to less than one void prevented by active treatment each day. The treatment effect at 200mg was slightly better (0.80 episodes per 24 hours), but the 95%CIs for the placebo-subtracted change with the 200mg dose overlapped those of other doses.

Table 39. Results for Primary and Key Secondary Endpoints, Study 044

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Statistic	Primary Efficacy Endpoint	Secondary Efficacy Endpoints				
				Change from Baseline to Final Visit in:				
			Mean Number of Micturitions per 24 Hours (FAS)	Mean Number of Incontinence Episodes per 24 Hours (FAS)	Mean Volume Voided (mL) per Micturition (FAS)	Mean Number of Urgency Episodes¶ per 24 Hours (FAS)	Mean Number of Urge Incontinence Episodes per 24 Hours (FAS)	Mean Number of Nocturia Episodes per 24 Hours (FAS)
178-CL-044 (DRAGON)	Placebo 169/157	n	166	106	165	165	106	144
		Baseline	11.67 (3.39)	2.45 (2.35)	161.38 (53.87)	5.75 (3.95)	2.21 (2.00)	1.77 (1.12)
		Change from Baseline	-1.43 (3.24)	-0.64 (2.54)	8.98 (39.66)	-1.26 (4.25)	-0.50 (2.26)	-0.36 (1.02)
	Mirabegron OCAS 25 mg 169/153	n	167	99	167	167	93	145
		Baseline	11.87 (2.88)	2.92 (3.23)	160.83 (55.04)	5.77 (4.12)	2.88 (3.09)	1.76 (1.17)
		Change from Baseline	-2.03 (2.59)	-1.77 (2.65)	16.79 (40.81)	-1.93 (3.44)	-1.76 (2.53)	-0.51 (0.95)
		Difference from Placebo	-0.45 (0.28) (-0.99, 0.10)	-0.84 (0.31)* (-1.45, -0.23)	8.03 (4.87) (-1.54, 17.60)	-0.70 (0.35)* (-1.38, -0.01)	-0.86 (0.26)* (-1.38, -0.35)	-0.15 (0.11) (-0.36, 0.07)
	Mirabegron OCAS 50 mg 169/153	n	167	108	167	166	106	142
		Baseline	11.85 (3.30)	2.41 (2.30)	153.62 (49.39)	5.94 (3.87)	2.21 (2.17)	1.70 (1.02)
		Change from Baseline	-2.14 (2.47)	-1.24 (2.00)	28.68 (45.48)	-1.79 (3.62)	-1.19 (1.94)	-0.57 (0.83)
		Difference from Placebo	-0.64 (0.28)* (-1.19, -0.10)	-0.62 (0.30)* (-1.22, -0.02)	20.05 (4.88)* (10.48, 29.63)	-0.60 (0.35) (-1.29, 0.08)	-0.69 (0.25)* (-1.18, -0.19)	-0.22 (0.11)* (-0.44, -0.01)
	Mirabegron OCAS 100 mg 169/161	n	168	111	168	168	107	141
		Baseline	11.81 (3.51)	2.49 (2.48)	152.67 (55.26)	5.92 (3.89)	2.39 (2.46)	1.82 (1.08)
		Change from Baseline	-2.14 (3.23)	-1.18 (2.90)	27.09 (47.03)	-2.40 (3.11)	-1.31 (2.21)	-0.41 (1.10)
		Difference from Placebo	-0.68 (0.28)* (-1.22, -0.13)	-0.53 (0.30) (-1.12, 0.06)	18.28 (4.90)* (8.66, 27.89)	-1.21 (0.35)* (-1.90, -0.52)	-0.74 (0.25)* (-1.23, -0.25)	-0.04 (0.11) (-0.26, 0.17)
	Mirabegron OCAS 200 mg 167/151	n	166	110	166	165	108	147
		Baseline	11.34 (2.41)	2.47 (2.23)	156.10 (50.17)	5.75 (3.57)	2.36 (2.02)	1.78 (1.17)
		Change from Baseline	-2.08 (2.67)	-1.21 (2.33)	34.10 (47.34)	-2.54 (3.22)	-1.38 (2.05)	-0.58 (0.99)
		Difference from Placebo	-0.80 (0.28)* (-1.34, -0.25)	-0.58 (0.30) (-1.16, 0.01)	26.06 (4.87)* (16.49, 35.62)	-1.42 (0.35)* (-2.10, -0.73)	-0.80 (0.25)* (-1.29, -0.31)	-0.21 (0.11) (-0.43, 0)
	Tolterodine ER 4 mg 85/82	n	85	53	85	85	52	72
		Baseline	12.31 (3.68)	2.85 (2.76)	157.00 (64.40)	5.83 (3.72)	2.63 (2.53)	1.78 (0.98)
		Change from Baseline	-2.23 (3.03)	-1.15 (2.71)	26.25 (46.83)	-1.65 (3.78)	-1.10 (2.40)	-0.56 (0.91)
		Difference from Placebo	ND	ND	ND	ND	ND	ND

Other endpoints did not show statistically significant treatment effect across the doses. The mean number of incontinence episodes was significantly improved by the two lower dose groups, 25mg and 50mg, but not by the higher doses, 100mg and 200mg, based on the 95%CIs for the placebo-subtracted change from baseline. The placebo group showed an improvement of 0.64 incontinence episodes per 24 hours, from a baseline of 2.45, and active treatment was associated with an additional improvement of 0.84, 0.62, 0.53 and 0.58 episodes across the dose groups from lowest to highest, respectively. Although not significant, the magnitude of the placebo-subtracted changes observed at 100mg was consistent with the larger Phase 3 studies, where statistical significance *was* achieved. The results in the tolterodine group were similar to those seen with mirabegron.

The mean volume voided was increased with active treatment, and the difference was significant for the 50mg, 100mg and 200mg doses. The mean number of urgency episodes was improved with mirabegron treatment in all dose groups, and this was significant for the 25mg, 100mg and 200mg doses but not for the proposed dose of 50mg. The magnitude of the benefit at the proposed dose of 50mg was a reduction of 0.60 episodes or urgency (95%CI for placebo-subtracted change was -1.29 to +0.08), whereas for 100mg the estimated benefit was 1.21 episodes per 24 hours.

The frequency of urgency incontinence was reduced by a similar amount as the all-cause incontinence, and the placebo-subtracted change was significant for the 25mg, 50mg, 100mg and 200mg doses, as shown by the table above. For the proposed 50mg dose, an additional 0.69 episodes were prevented per 24 hours (95%CI -1.18 to -0.19).

Nocturia was significantly reduced with active treatment for the 50mg dose, but for none of the other doses. The statistical significance for the 50mg dose was marginal (placebo-subtracted change from baseline -0.22 episodes, 95%CI -0.44 to -0.1). The magnitude of the treatment effect (one episode of nocturia prevented every 5 days) was similar to other studies, and would be expected to be of minor clinical utility.

The results for subjective endpoints are shown in the tables below (YM178 = mirabegron). Although not adequately explained by the sponsor, the questions referred to in the table headings appear to correspond to the following categories:

- Questions 3a, 4a, 5a, 6a - Bladder Symptoms

- Questions 3b, 4b, 5b, 6b - Symptom Bother
- Questions 3-27 – Quality of Life

The actual questions of the OAB questionnaire are reproduced in an appendix to this report.

In general, there were significant benefits for active treatment over placebo in terms of Bladder Symptoms and Symptom Bother, with an apparent dose trend (the 25mg dose group did not achieve significance for Symptom Bother). The clinical meaning of the observed difference is, however, unclear. There was *not* a significant benefit for overall QOL, as assessed by questions 3 to 27 of the OAB-q. This information is therefore merely supportive of the more objective efficacy measures.

Table 40. ANCOVA Modelling Result for ICIQ-OAB, Study 044, Questions 3a, 4a, 5a, 6a

	Placebo	25 mg qd	50 mg qd	100 mg qd	200 mg qd
Adjusted mean CFB	-1.82	-2.40	-2.51	-2.72	-3.02
Estimated difference to placebo		-0.58	-0.69	-0.90	-1.20
95% CI		-1.13; -0.02	-1.24; -0.13	-1.45; -0.34	-1.76; -0.65
P-value		0.0410*	0.0150*	0.0016*	< 0.0001*

CFB = change from baseline
* Statistically significant at the 0.05 level

Table 41. ANCOVA Modelling Results for ICIQ-OAB, Study 044, Questions 3b, 4b, 5b, 6b

	Placebo	25 mg qd	50 mg qd	100 mg qd	200 mg qd
Adjusted mean CFB	-6.01	-7.83	-8.38	-8.47	-10.02
Estimated difference to placebo		-1.82	-2.37	-2.46	-4.01
95% CI		-4.15; 0.52	-4.70; -0.03	-4.80; -0.12	-6.34; -1.68
P-value		0.1273	0.0474*	0.0396*	0.0008*

CFB = change from baseline
* Statistically significant at the 0.05 level

Table 42. ANCOVA Modelling Results for QOL, Study 044, Questions 3 to 27

	Placebo	25 mg qd	50 mg qd	100 mg qd	200 mg qd
Adjusted mean CFB	-16.11	-17.09	-20.36	-20.57	-22.19
Estimated difference to placebo		-0.98	-4.25	-4.46	-6.08
95% CI		-5.88; 3.92	-9.13; 0.62	-9.37; 0.46	-11.0; -1.19
P-value		0.6943	0.0872	0.0754	0.0149*

CFB = change from baseline
* Statistically significant at the 0.05 level

Finally, the results for the patent perception of benefit are shown below. This endpoint was listed in the study synopsis as one of the secondary endpoints, but not subsequently mentioned in the results section of the synopsis or the main study report. The excerpt below shows results for the last visit, Visit 6. About a third of placebo recipients (32.3%) thought their treatment had benefited them "very much", and the results in the mirabegron 50mg group were slightly better than this (38.8%), implying that about 6.5% (38.8%-32.3%) of mirabegron recipients had an attributable improvement in the "very much" category. For the overall category of any improvement, the 50mg dose was associated with at least "a little" improvement in 81.7% of subjects, compared to 67.1% of placebo recipients. This result was not subjected to a statistical analysis, but appears to be of sufficient magnitude that a trial of mirabegron treatment would be considered clinically worthwhile. The problem is that, on the basis of these numbers, of all the patients reporting they were "very much" improved on mirabegron 50mg, only a small proportion (6.5/38.8, or 17% of the "very much" responders) are likely to have had an attributable response and there is no way of distinguishing these from the much larger number of subjects reporting a placebo response.

Table 43. Frequencies of Patients' Perception of Treatment Benefit and Responders, Study 044

		Visit 6					
Characteristic	Statistic	Placebo	YM178 OCAS 25 mg qd n (%)	YM178 OCAS 50 mg qd n (%)	YM178 OCAS 100 mg qd n (%)	YM178 OCAS 200 mg qd n (%)	Tolterodine 4mg qd n (%)
Number of patients	N	159	155	155	163	154	82
Patients assessment of treatment benefit (PTB)	None	52 (32.9%)	28 (18.3%)	32 (21.1%)	29 (18.2%)	15 (9.9%)	15 (18.6%)
	A little	55 (34.8%)	70 (46.8%)	61 (40.1%)	68 (42.8%)	73 (48.0%)	44 (54.3%)
	Very much	51 (32.3%)	55 (36.9%)	59 (38.8%)	62 (39.0%)	64 (42.1%)	22 (27.2%)
	Missing	1	2	3	4	2	1
Number of evaluable patients		146	142	142	150	147	78
Number of responders on PTB		77 (52.7%)	87 (61.3%)	96 (67.6%)	100 (66.7%)	109 (74.1%)	43 (55.1%)

7.2.3. Supportive efficacy study 045

7.2.3.1. Design

This study was a randomised, placebo-controlled dose-ranging study assessing the efficacy of mirabegron in the treatment of OAB.

The entry criteria were broadly similar to the pivotal studies, but subjects had to have some urgency incontinence – not necessarily confirmed in the 3-day diary. The listed entry criteria were:

- Male or female outpatient aged between 20 and 80 years at the time of informed consent
- Symptoms of OAB for at least 24 weeks before initiation of the run-in period
- Capable of walking to the lavatory and measuring urine volume unassisted
- Written informed consent
- An average frequency of micturition of 8 or more times per 24 hours period and meeting at least one of the following diary conditions:
  - On average, at least one episode of urgency per 24 hours
  - On average, at least one episode of urge incontinence per 24 hours

The exclusion criteria were similar to the pivotal studies, but included a lack of urgency incontinence.

The study was performed from 11 September 2007 (first signed consent) to 3 April 2008 (last subject evaluation).

Subjects underwent a single-blind placebo run-in period, followed by a randomised, controlled double-blind treatment period of 12 weeks.

The randomised treatments were:

- placebo group: Two mirabegron placebo tablets/day
- mirabegron 25mg group: mirabegron (extended-release tablet) 25mg/day
- mirabegron 50mg group: mirabegron (extended-release tablet) 50mg/day
- mirabegron 100mg group: mirabegron (extended-release tablet) 100mg/day

The major endpoints were the same as described above for Study 044.

The primary efficacy endpoint was change in the mean number of micturitions per 24 hours from baseline to the end of study.

The secondary endpoints were:

- Change from baseline in mean number of urgency episodes per 24 hours
- Change from baseline in mean number of incontinence episodes per 24 hours

- Change from baseline in mean number of urge incontinence episodes per 24 hours
- Change from baseline in mean volume voided per micturition
- Change from baseline in mean number of nocturia episodes
- Change from baseline in the quality of life domain scores assessed by the King's Health Questionnaire.

7.2.3.2. Statistics

The primary analysis of the main endpoint was conducted using a Williams' multiple comparison between the placebo group and each mirabegron treatment group, using a one-sided significance level of 0.025. Sample size was chosen to provide adequate power to show superiority of mirabegron over placebo and to allow demonstration of the dose-response relationship; prospective sample sizes were assessed using the Williams' multiple comparison method, using data from Study 044 to guide assumptions about potential treatment effect and standard deviations. The sponsor concluded that 165 cases were needed to show superiority of the mirabegron 100mg group over the placebo group with more than 80% power of detection at a significance level of 0.025. Allowing for possible dropouts, an enrolment target of ≥ 180 subjects was set for each group.

7.2.3.3. Results

7.2.3.3.1. Baseline data

The groups were acceptably matched at baseline in terms of demographics and disease characteristics (data not shown).

7.2.3.3.2. Efficacy endpoints

The results for the primary endpoint were consistent with other studies of mirabegron in OAB. At baseline, the micturition frequency was about 11-12 episodes per 24 hours, and during the treatment study period this fell by one to two episodes. In the placebo group, from a mean baseline of 11.17 episodes per 24 hours, subjects experienced a mean change of -1.18 episodes. In the active groups, additional (placebo-subtracted) changes were observed, ranging from 0.66 episodes in the 25mg group, to 0.74 in the 50mg group and 0.78 in the 100mg group. As shown in the table below, the 95%CIs for the placebo-subtracted changes did not include zero and were consistent with a statistically significant treatment effect ($p<0.001$ in all active groups by ANOVA). As in all of the other studies, the magnitude of the benefit amounted to less than one episode of voiding per day, and was therefore of modest clinical utility.

The primary endpoint showed a dose-response trend in the mean placebo-subtracted change, but there was a great deal of overlap in the 95%CIs, as shown in the table, and the differences between groups were relatively minor (just 0.12 of an episode difference in the placebo-subtracted treatment effect from the highest dose to the lowest).

Table 44. Results for Primary Endpoint and Key Secondary Endpoints, Study 045

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Statistic	Primary Efficacy Endpoint	Secondary Efficacy Endpoints					
				Change from Baseline to Final Visit in:					
			Mean Number of Micturitions per 24 Hours (FAS)	Mean Number of Incontinence Episodes per 24 Hours (FAS)	Mean Volume Voided (mL) per Micturition (FAS)	Mean Number of Urgency Episodes¶ per 24 Hours (FAS)	Mean Number of Urge Incontinence Episodes per 24 Hours (FAS)	Mean Number of Nocturia Episodes per 24 Hours (FAS)
178-CL-045	Placebo 214/198	n	211	140	211	211	132	168
		Baseline	11.17 (2.526)	1.68 (1.471)	148.953 (42.962)	4.57 (3.160)	1.55 (1.376)	1.62 (1.135)
		Change from Baseline	-1.18 (2.155)	-0.64 (1.360)	11.18 (36.931)	-1.83 (2.965)	-0.68 (1.358)	-0.24 (0.977)
	Mirabegron OCAS 25 mg 211/200	n	209	134	209	208	128	179
		Baseline	11.47 (2.835)	2.20 (2.499)	147.746 (50.455)	4.68 (3.209)	1.97 (2.378)	1.74 (1.043)
		Change from Baseline	-1.94 (2.158) §	-1.29 (1.938) §	23.78 (41.667) #	-2.15 (2.731)	-1.14 (1.809) §	-0.49 (0.907)
		Difference from Placebo	-0.66 (-1.04, -0.28)	-0.39 (-0.67, -0.11)	12.52 (4.97, 20.07)	-0.27 (-0.75, 0.21)	-0.24 (-0.51, 0.02)	-0.20 (-0.36, -0.04)
	Mirabegron OCAS 50 mg 208/195	n	208	144	208	208	137	176
		Baseline	11.77 (2.606)	2.00 (2.228)	151.570 (49.464)	4.84 (3.255)	1.82 (2.098)	1.56 (1.028)
		Change from Baseline	-2.12 (2.383) §	-1.20 (1.455) §	27.25 (39.514) #	-2.24 (3.120)	-1.09 (1.345) §	-0.38 (0.814)
		Difference from Placebo	-0.74 (-1.12, -0.36)	-0.40 (-0.67, -0.13)	16.20 (8.64, 23.77)	-0.29 (-0.77, 0.19)	-0.27 (-0.53, -0.01)	-0.16 (-0.33, 0)
	Mirabegron OCAS 100 mg 209/196	n	207	150	207	207	142	180
		Baseline	11.20 (2.761)	1.86 (1.666)	152.697(46.526)	4.53 (3.093)	1.77 (1.640)	1.61 (0.994)
		Change from Baseline	-1.97 (1.970) §	-1.28 (1.355) §	31.23 (39.452) #	-2.48 (2.605) §	-1.24 (1.278) §	-0.39 (0.849)
		Difference from Placebo	-0.78 (-1.16, -0.40)	-0.54 (-0.81, -0.28)	20.23 (12.66, 27.80)	-0.67 (-1.15, -0.19)	-0.45 (-0.70, -0.19)	-0.15 (-0.32, 0.01)

Additional endpoints are shown in the table, and were also consistent with the other efficacy studies. Incontinence, which is the most distressing symptom for OAB patients and the most important of the secondary endpoints, was significantly reduced with active treatment. Interpretation of this endpoint is difficult, however, because of a marked difference between groups at baseline. In the placebo group, incontinence was reduced by a mean of 0.64 episodes from a baseline of 1.68 episodes per 24 hours. In the mirabegron 25mg group, treatment was associated with a reduction of 1.29 episodes from a baseline of 2.20 episodes. The placebo-subtracted change was 0.39 episodes, but it is unclear if some of the between-group difference was due to the fact that a higher number of episodes were present at baseline, giving more chance for regression to the mean and the placebo effect to prevent episodes independently of any true treatment effect. In the 50mg group, the placebo-subtracted change was -0.40 episodes and in the 100mg group, -0.54 episodes, with confidence intervals showing a significant difference between active treatments and placebo but no significant difference between active groups. The dose trend showed a numerical increase across doses, but with small differences between the mean treatment effects.

As shown in the table, the mean volume voided per micturition was significantly higher in the active groups, but the actual volume difference was only 13-20 mL across the active groups, compared to placebo. Urgency episodes were reduced, relative to placebo, by 0.27, 0.29 and 0.67 episodes per 24 hours, in the 25mg, 50mg and 100mg dose groups, respectively, but only in the highest dose group did the 95%CI exclude zero difference. At the proposed dose of 50mg, the mean benefit was about one episode of urgency prevented every 3 to 4 days. Urgency incontinence was reduced by 0.24, 0.27 and 0.45 episodes per 24 hours, relative to placebo, with the 50mg and 100mg doses showing statistical separation from placebo. The 95%CI for 50mg dose included the possibility that only one episode of urgency incontinence was prevented every 100 days. Nocturia was not significantly reduced with 50mg or 100mg, but the 25mg dose group did show a significant reduction, relative to placebo. The magnitude of the mean benefit for nocturia was modest: placebo-subtracted changes were -0.20, -0.16 and -0.15 in the 25mg, 50mg and 100mg dose groups, respectively; note that this is the opposite of the expected dose trend.

The sponsor performed a number of additional analyses, including one which considered the proportion of subjects normalised for the main symptoms of urgency, incontinence and nocturia. For the proposed dose, 6% of subjects (20.2%-14.2%) had an *attributable* normalisation of urgency, 2.9% (45.8%-42.9%) had an attributable normalisation of incontinence, and 2.9% (14.8%-11.9%) had an attributable normalisation of nocturia. Treatment was therefore associated with a fairly low yield of good responses.

Table 45. Percentage of Subjects Whose Symptoms for Secondary Endpoints (other than QOL) Disappeared at End of Study 045

Item	Placebo	YM178		
		25 mg	50 mg	100 mg
Mean number of urgency episodes	30/211 (14.2%)	45/208 (21.6%)	42/208 (20.2%)	52/207 (25.1%)
Mean number of incontinence episodes	60/140 (42.9%)	58/134 (43.3%)	66/144 (45.8%)	84/150 (56.0%)
Mean number of nocturia episodes	20/168 (11.9%)	26/179 (14.5%)	26/176 (14.8%)	35/180 (19.4%)

Number of resolved subjects/total number of subjects (percentage)

Assessments of quality of life showed that active treatment was associated with some significant benefits in some domains. For the proposed dose of 50mg, a significant reduction (improvement) in KHQ domain scores was observed for Incontinence Impact, Role Limitations, Physical Limitations, Emotions and Severity Measures.

Table 46. QOL Scores, Study 045

Item	Placebo (n=201)	YM178		
		25 mg (n=204)	50 mg (n=200)	100 mg (n=200)
General health perception (Domain 1)				
Baseline	33.3 ± 20.21	32.1 ± 19.34	31.4 ± 19.25	33.5 ± 17.44
End of study	31.1 ± 21.44	28.8 ± 19.40	31.6 ± 20.43	29.1 ± 17.14
Change	−2.2 ± 20.49	−3.3 ± 21.01	0.3 ± 21.70	−4.4 ± 19.96
P value†	–	–‡	–‡	0.194
Incontinence impact (Domain 2)				
Baseline	48.3 ± 25.79	52.3 ± 26.47	49.7 ± 27.55	50.0 ± 25.88
End of study	41.0 ± 26.82	35.9 ± 24.84	36.5 ± 26.86	34.8 ± 25.95
Change	−7.3 ± 26.70	−16.3 ± 29.50	−13.2 ± 29.49	−15.2 ± 29.47
P value†	–	<0.001	0.005	0.004
Role limitations (Domain 3)				
Baseline	37.1 ± 24.63	38.4 ± 25.92	36.8 ± 26.49	36.9 ± 23.38
End of study	30.3 ± 22.90	25.9 ± 21.26	25.4 ± 23.15	24.3 ± 22.41
Change	−6.7 ± 24.73	−12.5 ± 27.29	−11.3 ± 25.49	−12.6 ± 25.70
P value†	–	–‡	0.025	0.013
Physical limitations (Domain 4)				
Baseline	39.4 ± 26.52	40.6 ± 26.88	40.2 ± 26.48	36.8 ± 25.25
End of study	33.7 ± 24.55	28.0 ± 23.87	29.4 ± 24.10	26.2 ± 24.70
Change	−5.7 ± 25.48	−12.6 ± 26.62	−10.8 ± 24.55	−10.6 ± 25.07
P value†	–	0.003	0.011	0.016
Social limitations (Domain 5)				
Baseline	21.9 ± 25.32	22.0 ± 23.84	20.7 ± 23.60	20.3 ± 22.02
End of study	18.7 ± 23.08	14.3 ± 20.51	16.0 ± 21.26	13.0 ± 20.16
Change	−3.2 ± 21.03	−7.8 ± 21.94	−4.7 ± 17.98	−7.3 ± 18.39
P value†	–	–‡	0.070	0.021
Personal relationships (Domain 6)§				
Baseline	8.8 ± 16.82	10.0 ± 18.10	10.8 ± 20.16	10.0 ± 18.43
End of study	7.3 ± 14.41	6.3 ± 13.83	8.0 ± 17.98	6.8 ± 16.92
Change	−0.8 ± 14.38	−3.5 ± 15.49	−2.6 ± 13.45	−3.2 ± 17.19
P value†	–	–‡	–‡	0.104
Emotions (Domain 7)				
Baseline	40.0 ± 29.08	42.9 ± 28.55	38.8 ± 25.52	40.5 ± 26.36
End of study	32.6 ± 24.95	29.0 ± 27.31	28.8 ± 25.65	26.8 ± 24.46
Change	−7.4 ± 23.76	−13.9 ± 24.19	−10.0 ± 21.19	−13.7 ± 23.76
P value†	–	–‡	0.029	0.004
Sleep/energy (Domain 8)				
Baseline	28.3 ± 25.07	31.2 ± 25.54	29.9 ± 24.11	26.9 ± 23.90
End of study	21.9 ± 20.86	19.8 ± 22.28	21.5 ± 22.33	17.4 ± 21.22
Change	−6.4 ± 21.13	−11.4 ± 22.13	−8.4 ± 19.84	−9.5 ± 19.16
P value†	–	–‡	–‡	0.060
Severity measures (Domain 9)				
Baseline	28.0 ± 18.36	30.0 ± 19.26	32.0 ± 21.42	31.5 ± 19.40
End of study	23.3 ± 18.32	22.1 ± 19.64	23.4 ± 19.89	21.2 ± 18.64
Change	−4.7 ± 13.09	−7.9 ± 15.91	−8.5 ± 15.58	−10.3 ± 16.44
P value†	–	0.020	0.007	<0.001

n = Number of subjects at Visit 2 (baseline)
Mean ± SD

7.2.4. Supportive efficacy study 008

7.2.4.1. Design

Study 008 was a small randomised, double-blind, parallel group, proof-of-concept study of the efficacy of mirabegron in comparison with placebo and tolterodine in patients with symptomatic OAB. It only had 63-65 subjects per dose group, and therefore lacked the statistical power of most of the other supportive studies. It was also very short. A 2-week single-blind placebo run-in period was followed by a 4-week double-blind treatment period, and then a 2-week single-blind placebo follow-up period. The doses employed (100mg bid and 150mg bid) were also well in excess of the recommended dose of 50mg daily, being 4 and 6 times the

recommended daily dose, respectively. For all of these reasons, it is only weakly supportive of the proposed usage of mirabegron.

The main entry criteria were similar to those in the pivotal studies: eligible subjects were of either gender, aged ≥ 18 years, with symptoms of OAB (urinary frequency and urgency with or without incontinence) for ≥ 3 months. Patients had to have a micturition frequency of ≥ 8 episodes per 24-hours on average during the 3-day diary period, and at least 3 episodes of urgency (grade 3 or 4), with or without incontinence, during the 3-day diary period.

Subjects were randomised to one of the following treatments, with sufficient placebo tablets provided to maintain the blind:

- Group I - mirabegron 100mg bid
- Group II - mirabegron 150mg bid
- Group III - tolterodine 4 mg od
- Group IV - placebo

The primary endpoint was the same as other supportive studies: change from baseline in mean number of micturitions per 24 hours.

Secondary efficacy endpoints were:

- Change from baseline in mean volume voided per micturition
- Change from baseline in mean number of incontinence episodes/24 hours
- Change from baseline in mean number of nocturia episodes/24 hours
- Change from baseline in mean number of urge incontinence episodes/24 hours
- Change from baseline in mean number of urgency episodes/24 hours
- Change from baseline in severity of urgency
- Change from baseline in patient perception of bladder condition
- Patient perception of treatment benefit

The two subjective endpoints were assessed with simple categorical scales. A 3-point scale was used for assessment of treatment benefit and a 6-point scale for the patients' perception of their bladder condition.

For the patients' assessment of treatment benefit, the question "Has the treatment been of any benefit to you?" had the three possible outcomes:

1. No
2. Yes, a little
3. Yes, very much

For the patients' perception of bladder condition, the stem "My bladder condition…" had the following six possible completions:

1. Does not cause me any problems at all
2. Causes me some very minor problems
3. Causes me some minor problems
4. Causes me (some) moderate problems
5. Causes me severe problems
6. Causes me many severe problems

7.2.4.1.1. Statistics

Changes in mean number of micturitions per 24 hours were analysed by ANCOVA, with treatment as a fixed factor, and centre as a random factor. Baseline micturition frequency was included in the model as covariate. Comparisons were tested with a two-sided significance level 0.05. Sample size was not based on statistical considerations as this was a proof-of-concept study.

7.2.4.2. Results

7.2.4.2.1. Baseline data

The groups were acceptably matched at baseline for a minor supportive study, apart from baseline incontinence frequency (see table below), which was greater in the 150mg BID group.

7.2.4.2.2. Efficacy endpoints

Results for the primary endpoint of micturition frequency were positive. The magnitude of the estimated placebo-subtracted treatment benefit was greater than in the pivotal studies, and was slightly more than one episode of micturition, from a baseline of 11 to 12 episodes per 24 hours. This could reflect the use of high total daily doses (4 or 6 times the proposed daily dose). For the 100mg bid dose, the placebo-subtracted change in micturition frequency was -1.02, and for 150mg bid it was -1.03, with 95%CIs excluding zero as shown in the table below. The active control, tolterodine, showed a lesser treatment effect that was not significantly different from placebo.

For the major secondary endpoint, incontinence frequency, the estimated treatment effect amounted to more than one episode of incontinence in the 100mg bid dose group, which is better than the results obtained in the larger pivotal studies, which used once daily dosing. The dose trend in Study 008, however, was the reverse of the expected trend and the higher dose group did not show a significant effect, which is likely to reflect the relatively low patient numbers in combination with a fairly modest treatment effect, so that the treatment effect was easily swamped by random variation. In the 100mg bid dose group, the reduction in incontinence was 1.16 episodes over and above the placebo effect (95%CI -1.93 to -0.38), from a baseline of 2.5 episodes per 24 hours. In the 150mg bid group, the placebo-subtracted reduction in incontinence was only 0.57 episodes (95%CI -1.34 to +0.20), from a baseline of 3.57 episodes per 24 hours.

Table 47. Results for Primary and Key Secondary Endpoints, Study 008

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Statistic	Primary Efficacy Endpoint	Secondary Efficacy Endpoints				
				Change from Baseline to Final Visit in:				
			Mean Number of Micturitions per 24 Hours (FAS)	Mean Number of Incontinence Episodes per 24 Hours (FAS)	Mean Volume Voided (mL) per Micturition (FAS)	Mean Number of Urgency Episodes¶ per 24 Hours (FAS)	Mean Number of Urge Incontinence Episodes per 24 Hours (FAS)	Mean Number of Nocturia Episodes per 24 Hours (FAS)
178-CL-008‡‡ (BLOSSOM)	Placebo 66/62	n	64	41	64	63	40	57
		Baseline	12.34 (3.51)	2.41 (1.69)	151.8 (58.34)	5.83 (3.39)	2.10 (1.54)	1.88 (1.16)
		Change from Baseline	-1.32 (2.49)	-0.80 (1.47)	10.9 (35.99)	-1.01 (3.03)	-0.78 (1.43)	-0.25 (0.93)
	Mirabegron IR 100 mg, bid 65/61	n	65	37	65	65	37	58
		Baseline	11.30 (2.65)	2.50 (2.53)	164.7 (62.86)	5.52 (3.47)	2.41 (2.50)	1.84 (0.97)
		Change from Baseline	-2.00 (1.76)	-2.01 (2.30)	26.7 (51.20)	-2.19 (3.01)	-1.92 (2.28)	-0.59 (0.73)
		Difference from Placebo	-1.02@ (-1.67, -0.36)	-1.16@ (-1.93, -0.38)	15.56 (-0.14, 31.25)	-1.27@ (-2.32, -0.22)	-0.97@ (-1.73, -0.21)	-0.39@ (-0.65, -0.12)
	Mirabegron IR 150 mg, bid 65/60	n	63	41	63	62	39	54
		Baseline	12.25 (3.62)	3.57 (3.47)	150.7 (53.49)	6.58 (4.34)	3.47 (3.39)	1.92 (1.08)
		Change from Baseline	-2.30 (2.12)	-1.96 (2.64)	32.4 (47.67)	-2.55 (3.80)	-1.89 (2.70)	-0.42 (0.83)
		Difference from Placebo	-1.03@ (-1.69, -0.37)	-0.57 (-1.34, 0.20)	22.25@ (6.48, 38.02)	-1.27@ (-2.34, -0.21)	-0.35 (-1.12, 0.42)	-0.17 (-0.44, 0.10)
	Tolterodine ER 4 mg, qd 66/62	n	63	41	63	63	39	58
		Baseline	11.00 (3.06)	2.95 (2.52)	179.9 (65.21)	5.55 (3.64)	2.70 (2.11)	1.84 (1.08)
		Change from Baseline	-1.27 (1.99)	-1.70 (2.26)	23.2 (42.18)	-1.98 (2.84)	-1.55 (1.89)	-0.37 (0.87)
		Difference from Placebo	-0.40 (-1.06, 0.26)	-0.61 (-1.34, 0.12)	13.10 (-2.71, 28.91)	-1.09 (-2.11, -0.06)*	-0.44 (-1.16, 0.28)	-0.20 (-0.47, 0.07)

For the other diary-related endpoints, a significant benefit for mirabegron 100mg bid was shown for the mean number of urgency episodes, the mean number of urgency incontinence episodes, and the mean number of nocturia episodes, but not for the mean volume voided. For

the 150mg bid dose, a significant benefit was shown for volume voided and mean number of urgency episodes, but not for mean number of urgency incontinence episodes or nocturia episodes, as determined from the 95%CIs which are shown in the table. The achievement of some endpoints but not others, with no consistent trend across doses, is likely to reflect the relative low patient numbers. In broad terms, the magnitudes of the observed mean changes for these secondary endpoints were consistent with the pivotal studies, where the majority of these endpoints were achieved.

The distributions of responses for the subjective endpoints, as assessed at the final visit, are shown in the tables below. Recipients of mirabegron were more likely to report that they had responded to treatment "very much", compared to placebo recipients. Tolterodine recipients were even more likely to report that they had improved "very much". In the sponsor's report, neither the table reproduced below nor the accompanying text indicated clearly what definition of responder was being used in the final line of the table, but it appears to have been patients showing a positive shift in category.

Logistic regression of the proportion of responders showed that there was a statistically significant difference between mirabegron 100mg bid and placebo (p=0.0150), and between mirabegron 150mg bid and placebo (p=0.0038) for this endpoint. The difference between tolterodine 4mg od and placebo was also statistically significant (p=0.0001), but the difference between the tolterodine and mirabegron groups was not statistically significant.

Table 48. Patients' Assessment of Treatment Benefit, Study 008

Characteristic	Statistic	Placebo	YM178 100 mg bid	YM178 150 mg bid	Pooled YM178 group	Tolterodine 4 mg od
		n (%)	n (%)	n (%)	n (%)	n (%)
Number of patients	N	64	65	63	128	63
Patients assessment of treatment benefit	No	18 (28.1%)	7 (10.8%)	8 (12.7%)	15 (11.7%)	3 (4.8%)
	Yes, a little	33 (51.6%)	37 (56.9%)	32 (50.8%)	69 (53.9%)	33 (52.4%)
	Yes, very much	13 (20.3%)	21 (32.3%)	23 (36.5%)	44 (34.4%)	27 (42.9%)
Number of responders on patients' assessment of treatment benefit		32 (50.0%)	39 (60.0%)	45 (71.4%)	84 (65.6%)	47 (74.6%)

Table 49. Patient Perception of Bladder Condition, Study 008

Characteristic	Statistic	Placebo	YM178 100 mg bid	YM178 150 mg bid	Pooled YM178 group	Tolterodine 4 mg od
		n (%)	n (%)	n (%)	n (%)	n (%)
Number of patients	N	64	65	63	128	63
Patients perception of bladder condition (PBC)	Does not cause me any problems at all	3 (4.7%)	4 (6.2%)	5 (7.9%)	9 (7.0%)	6 (9.5%)
	Causes me some very minor problems	7 (10.9%)	10 (15.4%)	11 (17.5%)	21 (16.4%)	15 (23.8%)
	Causes me some minor problems	8 (12.5%)	14 (21.5%)	16 (25.4%)	30 (23.4%)	12 (19.0%)
	Causes me (some) moderate problems	22 (34.4%)	28 (43.1%)	17 (27.0%)	45 (35.2%)	18 (28.6%)
	Causes me severe problems	18 (28.1%)	7 (10.8%)	11 (17.5%)	18 (14.1%)	12 (19.0%)
	Causes me many severe problems	6 (9.4%)	2 (3.1%)	3 (4.8%)	5 (3.9%)	0
PBC_resp_V2(1)		34 (53.1%)	36 (55.4%)	43 (68.3%)	79 (61.7%)	38 (60.3%)
PBC_resp_V2(2)		11 (17.2%)	18 (27.7%)	21 (33.3%)	39 (30.5%)	20 (31.7%)

There was a corresponding in shift in responses for patient perception of bladder condition (PBC), with placebo recipients being more likely to report moderate or severe bladder problems, and mirabegron recipients more likely to report moderate or mild problems, as

shown in the table above. Inspection of the proportions responding with an improvement (reduction) by one category (PBC_resp_V2(1)) and of those with a favourable shift of two categories (PBC_resp_V2(1)) suggested that active treatment was more likely to produce a favourable shift. Formal logistic regression of this endpoint showed that there was no statistically significant difference between mirabegron 100mg and placebo (p=0.0618). The mirabegron 150mg group *was* statistically significantly different from placebo (p=0.0135), however, and the difference between tolterodine and placebo was also statistically significant (p=0.0165). The difference between tolterodine and the mirabegron groups was not significant.

Overall, the results in this study are broadly consistent with the pivotal results, and add to external validity of the pivotal studies, but have limited applicability because of the doses used, the low patient numbers, and the short duration of treatment.

7.2.5. Long-term study 049

7.2.5.1. Design

Study 049 was a long-term safety study with no placebo group, though it did employ tolterodine as an active control. The assessment of efficacy was a secondary focus, and the study was not powered or designed to show superiority of mirabegron over the active control; it is therefore only weakly supportive of the efficacy of mirabegron.

Patients were eligible if they were adults of either gender with symptoms of OAB for ≥ 3 months and recorded an average frequency of micturition ≥ 8 times per 24-hour period during the 3-day micturition diary period, with at least 3 episodes of urgency (grade 3 or 4) with or without incontinence, during the 3-day diary period.

The study consisted of a single-blind placebo run-in period of 2 weeks, followed by a randomised double-blind, active-controlled treatment period of 12 months. Patients were randomly assigned with equal likelihood to receive mirabegron 50mg, mirabegron 100mg or tolterodine ER 4 mg once daily for 12 months. The randomised, double-blind, active-controlled, treatment period consisted of assessment visits at months 1, 3, 6, 9 and 12.

The sponsor listed a large number of efficacy endpoints, all of which were considered secondary.

- Change in mean number of micturitions per 24 hours
- Change in mean number of incontinence episodes per 24 hours
- Change in mean volume voided per micturition
- Change in mean number of urgency incontinence episodes per 24 hours
- Change in mean number of urgency episodes (grade 3 and/or 4) per 24 hours
- Change in mean level of urgency
- Change in the mean number of pads used per 24 hours
- Change in mean number of nocturia episodes per 24 hours
- Change in Symptom Bother and HRQL scores as assessed by the OAB-q
- Change from baseline to month 12 and Final Visit in PPBC
- Change from baseline to month 12 and Final Visit in the TS-VAS
- Change in scores as assessed by WPAI:SHP
- Change in scores as assessed by the EQ-5D questionnaire
- Change in the number of non-study physician visits for the patient's bladder condition

In addition, for the change from baseline in PPBC, an analysis was performed at month 12 and Final Visit based on the following improvement from baseline definitions:

- Improvement: ≥ 1 point improvement from baseline
- Major improvement: ≥ 2 point improvement from baseline

Unless stated otherwise, the endpoints were assessed as changes from baseline to months 3, 6, 9, 12 and Final Visit, sometimes with a month 1 assessment as shown in the tables.

7.2.5.1.1. Statistics

Results in each group were compared with ANCOVA.

7.2.5.2. Results

7.2.5.2.1. Baseline data

The groups were reasonably well-matched at baseline (data not shown).

7.2.5.2.2. Efficacy endpoints

As shown in the table below, favourable changes were observed in all three treatment groups, with reductions in incontinence frequency, micturition frequency, and mean volume voided from baseline to the final visit. It is unclear how much of the observed improvement was due to the placebo effect and regression to the mean, but the mean reductions in both incontinence (1.01 to 1.24 across the mirabegron dose groups) and micturition frequency (1.27 to 1.41 episodes) were broadly comparable to the changes seen in the placebo groups of the pivotal studies. For instance, in Study 046, the mean reduction in incontinence for placebo recipients was 1.17 episodes from a baseline incontinence frequency of 2.67 episodes per 24 hrs, and the mean improvement in micturition frequency was 1.34 episodes per 24 hrs from a baseline of 11.7 episodes per 24 hrs. Although a comparison across studies is inherently unreliable, the strong placebo response demonstrated in the pivotal studies suggests that a large proportion of the observed changes in the table below could have been due to factors other than the active pharmacological treatment.

Table 50. Results for Major Efficacy Endpoints, Study 049

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Statistic	Efficacy Endpoints				
			Change from Baseline to Final Visit in:			Change from Baseline to Month 1 in:	
			Mean Number of Incontinence Episodes per 24 Hours (FAS-I)	Mean Number of Micturitions per 24 Hours (FAS)	Mean Volume Voided (mL) per Micturition (FAS)	Mean Number of Incontinence Episodes per 24 Hours (FAS-I)	Mean Number of Micturitions per 24 Hours (FAS)
178-CL-049 (TAURUS)	Mirabegron OCAS 50 mg 815/629	n	479	789	789	478	786
		Baseline	2.66 (0.120)	11.13 (0.100)	160.1 (2.09)	2.67 (0.120)	11.12 (0.099)
		Adjusted Change from Baseline	-1.01 (0.087) (-1.18, -0.84)	-1.27 (0.083) (-1.44, -1.11)	17.5 (1.65) (14.3, 20.7)	-0.94 (0.079) (-1.09, -0.78)	-0.94 (0.069) (-1.07, -0.80)
	Mirabegron OCAS 100 mg 824/645	n	483	802	802	479	797
		Baseline	2.49 (0.113)	11.16 (0.102)	164.9 (2.06)	2.51 (0.114)	11.17 (0.103)
		Adjusted Change from Baseline	-1.24 (0.086) (-1.41, -1.07)	-1.41 (0.082) (-1.57, -1.25)	21.5 (1.63) (18.3, 24.7)	-1.03 (0.079) (-1.18, -0.87)	-1.10 (0.068) (-1.24, -0.97)
	Tolterodine ER 4 mg 813/621	n	488	791	791	485	786
		Baseline	2.42 (0.107)	10.94 (0.093)	160.1 (2.01)	2.42 (0.108)	10.94 (0.093)
		Adjusted Change from Baseline	-1.26 (0.086) (-1.43, -1.10)	-1.39 (0.083) (-1.56, -1.23)	18.1 (1.64) (14.8, 21.3)	-0.96 (0.078) (-1.12, -0.81)	-1.02 (0.069) (-1.15, -0.88)

Results for some other endpoints are displayed in the tables below but note that the same difficulties of interpretation apply to these minor endpoints, and that most or all of the observed changes could be due to the placebo effect. For many diary-based endpoints, the sponsor did not produce convenient summary tables, so the data is not reproduced here. Consulting the long, unabridged tables in the appendix of the study report did not raise any significant new issues, but merely emphasized the difficulties of interpretation that arise without a placebo group.

The Treatment Satisfaction VAS showed that, on average, patients in all three groups had an improvement in satisfaction compared to baseline, with the greatest improvement seen in the tolterodine group. Similarly, all groups showed a mean decrease in Symptom Bother scores and

a mean increase in QOL scores, but this could reflect the placebo effect or some degree of spontaneous improvement unrelated to active treatment.

Table 51. Change from Baseline in TS-VAS, Study 049

Parameter	Mirabegron 50 mg (n=789)	Mirabegron 100 mg (n= 802)	Tolterodine ER 4 mg (n= 791)
Baseline			
n	654	676	676
Mean (SE)	4.87 (0.138)	4.88 (0.133)	5.01 (0.131)
Median	4.60	4.80	4.90
Range	0.0 to 10.0	0.0 to 10.0	0.0 to 10.0
Final Visit			
Mean (SE)	6.98 (0.165)	7.03 (0.114)	7.21 (0.212)
Median	8.00	8.15	8.00
Range	0.0 to 80.0	0.0 to 10.0	0.0 to 95.0
Change from Baseline			
Mean (SE)	2.10 (0.195)	2.15 (0.151)	2.20 (0.230)
Median	1.30	1.35	1.25
Range	-10.0 to 77.7	-9.7 to 10.0	-9.7 to 90.5
ANCOVA Model †			
Adjusted mean change from baseline (SE)	2.08 (0.167)	2.11 (0.164)	2.27 (0.164)
95% two-sided CI	(1.75, 2.41)	(1.79, 2.43)	(1.94, 2.59)

Table 52. Change from Baseline in Symptom Bother and QOL, Study 049

Scale	Mirabegron 50 mg (n=789)	Mirabegron 100 mg (n= 802)	Tolterodine ER 4 mg (n=791)
	Adjusted mean change from baseline †		
Symptom Bother Score	-13.1	-14.8	-14.3
HRQL Total Score	10.7	11.7	11.4
Coping	12.2	13.6	13.3
Concern	11.8	13.3	12.5
Sleep	10.7	10.8	11.2
Social	6.5	7.2	7.2

The best that can be said of the efficacy results in this study is that, if treatment was associated with any efficacy, there was no obvious waning of that efficacy with continued use. The graphs below show that the main efficacy variables were fairly stable after the first month. Unfortunately, this is of limited reassurance given that the improvements in micturition frequency and incontinence could be due to the placebo effect and regression to the mean. Without a placebo group, the results are essentially uninterpretable.

Figure 20. Adjusted Mean Change from Baseline in Incontinence Frequency, Study 049

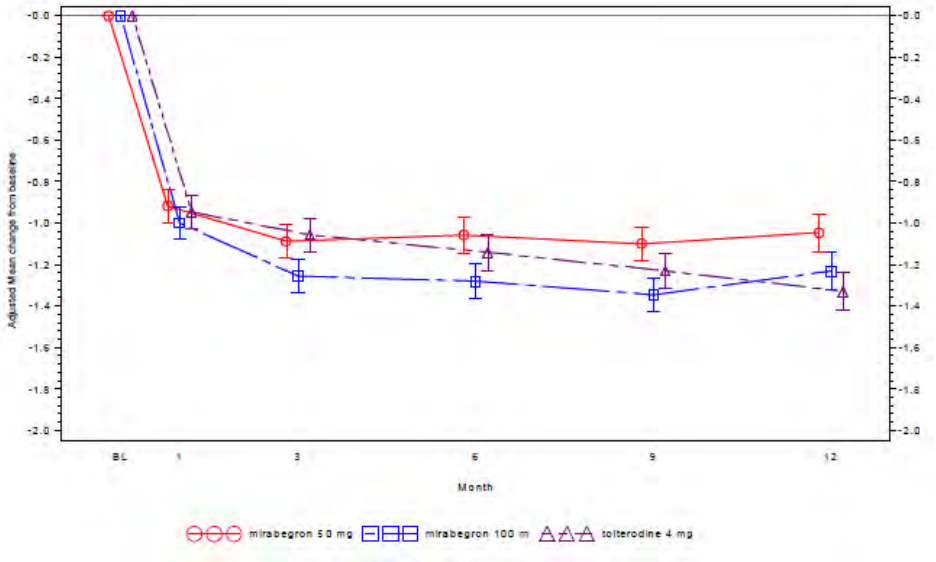
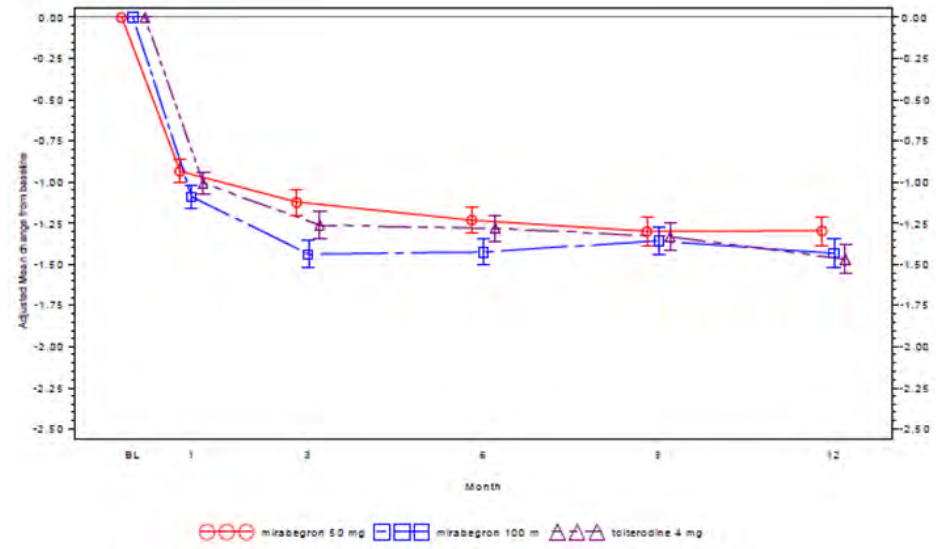


Figure 21. Adjusted Mean Change from Baseline in Micturition Frequency, Study 049



7.2.6. Long-term study 051

7.2.6.1. Design

Study 051 was another long-term safety study in OAB patients. It assessed two doses of mirabegron (50mg daily and 100mg daily), but it did not randomise between the dose groups, and it had no control group of non-mirabegron recipients. It is primarily useful for assessing safety and provides only very weak support for the claim of mirabegron efficacy.

The study consisted of a 1-week run-in period and a 52-week treatment period. After the 1-week run-in period, subjects who satisfied the inclusion criteria were enrolled for treatment. They all started with mirabegron 50mg, taken orally once daily. An optional increase in dose to 100mg daily was available at the week 8 visit, provided that 50mg was found to provide insufficient efficacy, the investigator concluded that the subject's safety was not at risk, and the subject desired the increased dosage. When dose was increased to 100mg, this dose was generally maintained until treatment completion unless adverse events occurred.

Because subjects who had not responded to 50mg were the ones who escalated therapy to 100mg, the final dose groups were selected on their basis of treatment responsiveness, and it is impossible to compare the efficacy at the two doses. Furthermore, without a placebo group, it is impossible to determine what changes were due to the placebo effect and regression to the mean and what changes, if any, were due to active treatment.

To be eligible, patients had to be adults ≥ 20 years with OAB and average at least 8 micturitions per 24 hours in their 3-day baseline micturition diary, with at least 1 urgency episode per 24 hours on average, or at least 1 urge incontinence episode per 24 hours on average. Other entry criteria were similar to the pivotal studies.

The efficacy endpoints were as follows:

- Change from baseline in mean number of micturitions per 24 hours
- Change from baseline in mean number of urgency episodes per 24 hours
- Change from baseline in mean number of incontinence episodes per 24 hours
- Change from baseline in mean number of urge incontinence episodes per 24 hours
- Change from baseline in mean number of nocturia episodes
- Change from baseline in quality of life domain scores on King's Health Questionnaire

None of these was considered primary, as the study's main focus was long-term safety.

7.2.6.1.1. Statistics

Because this was an uncontrolled study, the results were primarily reported with descriptive statistics.

7.2.6.2. Results

7.2.6.2.1. Baseline data

The baseline demographics and disease characteristics were typical of an OAB population (data not shown).

7.2.6.2.2. Efficacy endpoints

The main efficacy results are shown in the table excerpt below (results for Study 049 have been removed). The table shows results for those who only received 50mg, versus those who used 100mg in addition to 50mg. For some endpoints, the changes were greater in the lower dose group, and for others the changes were greater in the higher dose group. Because the subjects were not randomly assigned to groups, it is not possible to draw any conclusions about the relative efficacy of the two different groups, and it is not known whether the changes listed in the table reflect efficacy, the placebo effect or regression to the mean. The changes from baseline appear broadly comparable to changes observed in the placebo groups of other studies, so the study does not provide evidence of a strong therapeutic effect.

Table 53. Results for Major Efficacy Endpoints, Study 050

Study No.	Treatment Arm	Statistic	Efficacy Endpoints Change from Baseline to Final Visit in:				
			Mean Number of Incontinence Episodes per 24 Hours (FAS)	Mean Number of Micturitions per 24 Hours (FAS)	Mean Number of Urgency Episodes per 24 Hours (FAS)	Mean Number of Urge Incontinence Episodes per 24 Hours (FAS)	Mean Number of Nocturia Episodes (FAS)
178-CL-051	Mirabegron OCAS 50 mg [only]	n	104	146	146	103	122
		Baseline	1.95 (1.632)	11.11 (2.600)	4.79 (2.993)	1.79 (1.581)	1.52 (0.881)
		Change from Baseline	-1.30 (1.400)	-2.16 (2.673)	-3.31 (2.948)	-1.32 (1.401)	-0.49 (0.832)
	Mirabegron OCAS 100 mg [used]	n	45	50	50	44	43
		Baseline	2.40 (2.259)	11.27 (2.702)	5.43 (3.512)	2.11 (2.076)	1.73 (1.082)
		Change from Baseline	-1.56 (2.143)	-1.57 (2.341)	-2.72 (2.884)	-1.33 (1.909)	-0.47 (1.077)

When viewed graphically, it is clear that the main efficacy variables, including mean number of micturitions (Figure 22) and mean number of incontinence episodes (Figure 23), showed substantial spread in terms of standard deviations, and did not convincingly depart from baseline.

Figure 22. Change from Baseline in Mean Number of Micturitions Per 24 Hours, Study 050

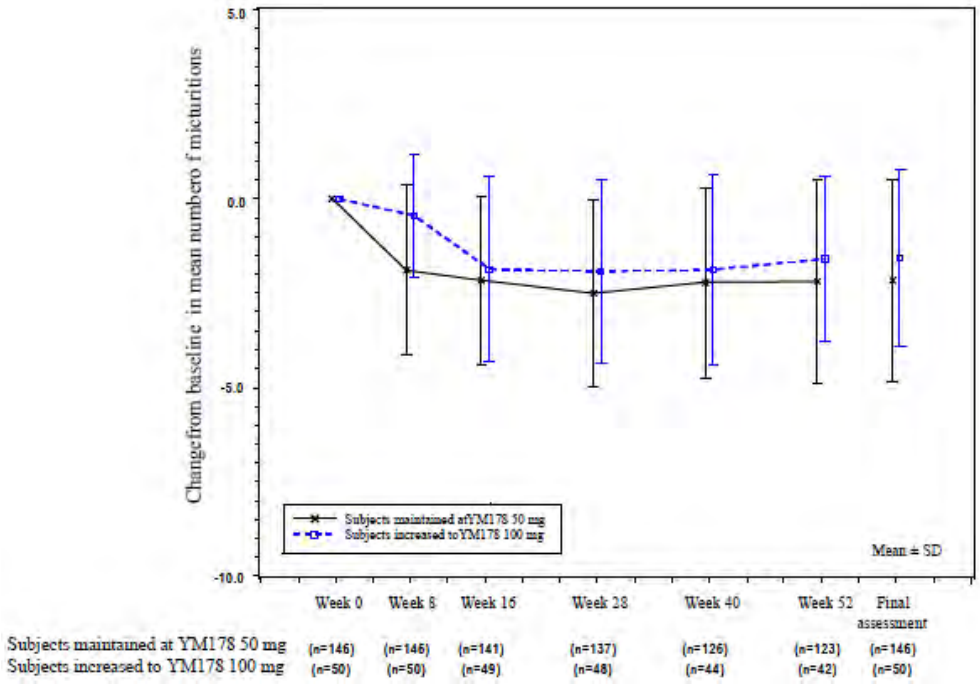
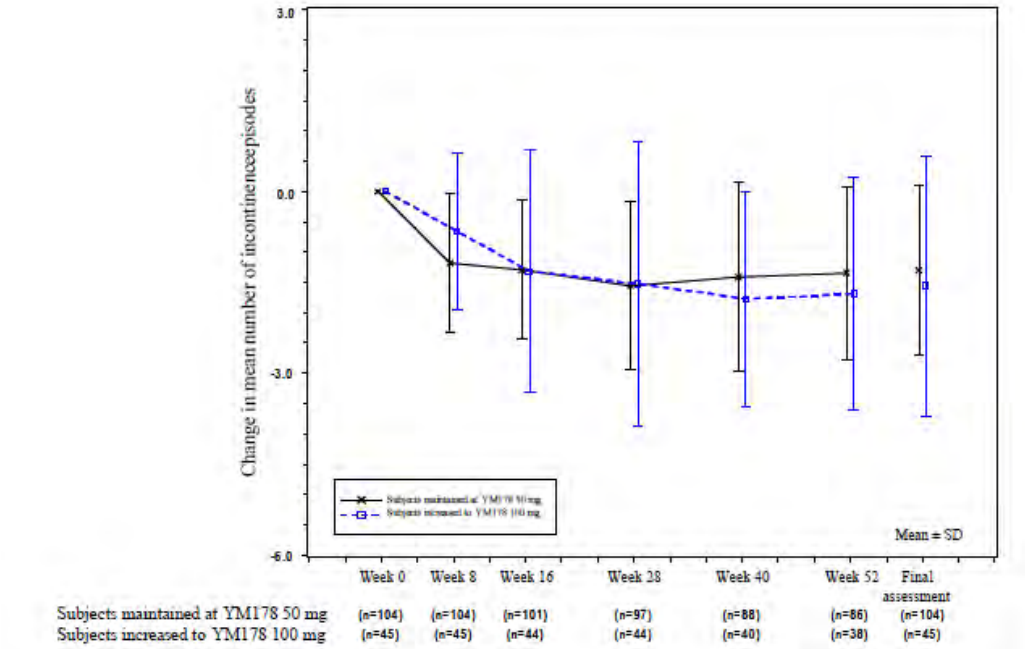


Figure 23. Change from Baseline in Mean Number of Incontinence Episodes Per 24 Hours, Study 050



The KHQ results are shown below. Decreases (improvements) were observed in all domains, but without a placebo group it is impossible to know to what extent this is due to the placebo effect and regression to the mean.

Table 54. Change in QOL Scores, Study 050

	All subjects	Subjects Maintained at 50 mg	Subjects Increased to 100 mg
General health perception (Domain 1)			
Week 28 visit	−4.5 ± 22.99 (182)	−5.7 ± 23.65 (135)	−1.1 ± 20.82 (47)
Week 52 visit	−7.8 ± 21.37 (164)	−8.4 ± 22.87 (122)	−6.0 ± 16.39 (42)
Final assessment	−6.3 ± 21.86 (192)	−6.9 ± 23.36 (144)	−4.2 ± 16.58 (48)
Incontinence impact (Domain 2)			
Week 28 visit	−27.1 ± 29.49 (182)	−29.4 ± 28.23 (135)	−20.6 ± 32.27 (47)
Week 52 visit	−22.8 ± 27.82 (164)	−23.8 ± 27.27 (122)	−19.8 ± 29.50 (42)
Final assessment	−22.7 ± 28.50 (192)	−24.3 ± 27.66 (144)	−18.1 ± 30.72 (48)
Role limitations (Domain 3)			
Week 28 visit	−23.2 ± 25.06 (182)	−25.3 ± 24.84 (135)	−17.0 ± 24.94 (47)
Week 52 visit	−19.5 ± 27.79 (164)	−21.6 ± 26.56 (122)	−13.5 ± 30.63 (42)
Final assessment	−19.3 ± 27.38 (192)	−21.5 ± 26.14 (144)	−12.5 ± 30.07 (48)
Physical limitations (Domain 4)			
Week 28 visit	−22.1 ± 26.45 (182)	−23.7 ± 26.66 (135)	−17.4 ± 25.53 (47)
Week 52 visit	−17.5 ± 28.29 (164)	−18.6 ± 29.24 (122)	−14.3 ± 25.39 (42)
Final assessment	−17.9 ± 28.00 (192)	−19.3 ± 29.08 (144)	−13.5 ± 24.23 (48)
Social limitations (Domain 5)			
Week 28 visit	−11.6 ± 21.21 (182)	−13.1 ± 20.98 (135)	−7.3 ± 21.52 (47)
Week 52 visit	−9.7 ± 22.82 (164)	−10.5 ± 23.94 (122)	−7.3 ± 19.26 (42)
Final assessment	−9.9 ± 22.90 (192)	−10.9 ± 24.01 (144)	−7.1 ± 19.10 (48)
Personal relationships (Domain 6)			
Week 28 visit	−4.9 ± 13.12 (128)	−4.7 ± 12.55 (95)	−5.6 ± 14.83 (33)
Week 52 visit	−4.7 ± 16.52 (114)	−3.6 ± 15.96 (84)	−7.8 ± 17.90 (30)
Final assessment	−4.7 ± 15.99 (135)	−4.2 ± 15.32 (102)	−6.1 ± 18.07 (33)
Emotions (Domain 7)			
Week 28 visit	−19.2 ± 22.68 (182)	−19.3 ± 24.24 (135)	−18.9 ± 17.63 (47)
Week 52 visit	−17.6 ± 24.33 (164)	−18.1 ± 26.00 (122)	−16.1 ± 18.88 (42)
Final assessment	−17.5 ± 24.66 (192)	−18.2 ± 26.40 (144)	−15.5 ± 18.58 (48)
Sleep / energy (Domain 8)			
Week 28 visit	−13.4 ± 18.58 (182)	−13.0 ± 18.85 (135)	−14.5 ± 17.93 (47)
Week 52 visit	−12.3 ± 20.46 (164)	−13.3 ± 18.17 (122)	−9.5 ± 26.07 (42)
Final assessment	−13.0 ± 20.21 (192)	−14.1 ± 18.31 (144)	−9.7 ± 24.99 (48)
Severity measures (Domain 9)			
Week 28 visit	−14.4 ± 16.91 (182)	−15.8 ± 16.76 (135)	−10.6 ± 16.95 (47)
Week 52 visit	−14.4 ± 16.11 (164)	−15.5 ± 16.04 (122)	−11.3 ± 16.10 (42)
Final assessment	−14.1 ± 16.57 (192)	−15.6 ± 16.32 (144)	−9.4 ± 16.61 (48)

Mean ± SD. The number of subjects is shown within parentheses.

In conclusion, because it lacked a randomised, controlled design, this study provides almost no insight into the long term efficacy of mirabegron.

7.3. Analyses performed across trials

Because the three pivotal studies shared entry criteria and endpoints, they were suitable for a pooled analysis, which is reproduced below. Note that the studies were all slightly different in terms of the treatments being assessed, with Study 046 using a tolterodine control group as well assessing mirabegron 50mg and 100mg, Study 047 just assessing mirabegron 50mg and 100mg, and Study 074 assessing 50mg and 25mg, but not 100mg. The pooled results therefore involve all three studies, for the proposed 50mg dose, but only Studies 046 and 047 for the 100mg dose.

In general, the results for the proposed 50mg dose in the pooled analysis were consistent with the individual studies. The results in the 25mg group were derived from only one study, so the confidence intervals were broader. The magnitude of the effects at this dose also appeared inferior to the pooled 50mg results.

Table 55. Overview of Efficacy Results, Individual and Pooled Pivotal Studies

	Study 178-CL-046			Study 178-CL-047		Study 178-CL-074		Pooled Primary Studies	
	Mirabegron 50 mg	Mirabegron 100 mg	Tolterodine ER 4 mg	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron 25 mg	Mirabegron 50 mg	Mirabegron 50 mg	Mirabegron 100 mg
Coprimary Efficacy Results									
Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 hours (FAS-I)									
n	293	281	300	312	296	254	257	862	577
Adjusted mean difference vs placebo (SE)	-0.41 (0.160)	-0.29 (0.162)	-0.10 (0.159)	-0.34 (0.160)	-0.50 (0.162)	-0.40 (0.17)	-0.42 (0.17)	-0.40 (0.09)	-0.41 (0.11)
95% 2-sided CI	(-0.72, -0.09)	(-0.61, 0.03)	(-0.42, 0.21)	(-0.66, -0.03)	(-0.82, -0.18)	(-0.74, -0.06)	(-0.76, -0.08)	(-0.58, -0.21)	(-0.62, -0.19)
P value ‡	0.003#	0.010#	0.11	0.026#	< 0.001#	0.005#	0.001#	<0.001#	<0.001#
Change from Baseline to Final Visit in Mean Number of Micturitions per 24 hours (FAS)									
n	473	478	475	425	412	410	426	1324	890
Adjusted mean difference vs placebo (SE)	-0.60 (0.156)	-0.44 (0.156)	-0.25 (0.156)	-0.61 (0.188)	-0.70 (0.189)	-0.47 (0.18)	-0.42 (0.17)	-0.55 (0.10)	-0.54 (0.12)
95% 2-sided CI	(-0.90, -0.29)	(-0.74, -0.13)	(-0.55, 0.06)	(-0.98, -0.24)	(-1.07, -0.33)	(-0.82, -0.13)	(-0.76, -0.08)	(-0.75, -0.36)	(-0.77, -0.31)
P value †	< 0.001#	0.005#	0.11	0.001#	< 0.001#	0.007#	0.015#	<0.001#	<0.001#
Key Secondary Efficacy Results									
Change from Baseline to Final Visit in Mean Volume Voided per Micturition (mL) (FAS)									
n	472	478	475	424	412	410	426	1322	890
Adjusted mean difference vs placebo (SE)	11.9 (2.83)	13.2 (2.82)	12.6 (2.83)	11.1 (3.43)	11.0 (3.45)	4.6 (3.16)	12.4 (3.13)	11.9 (1.82)	12.3 (2.12)
95% 2-sided CI	(6.3, 17.4)	(7.7, 18.7)	(7.1, 18.2)	(4.4, 17.9)	(4.2, 17.7)	(-1.6, 10.8)	(6.3, 18.6)	(8.3, 15.5)	(8.1, 16.5)
P value †	< 0.001#	< 0.001#	< 0.001*	0.001#	0.002#	0.15§	<0.001#§	<0.001#	<0.001#
Change from Baseline to Week 4 in Mean Number of Incontinence Episodes per 24 hours (FAS-I)									
n	293	281	299	309	293	254	255	857	574
Adjusted mean difference vs placebo (SE)	-0.39 (0.167)	-0.38 (0.169)	-0.35 (0.166)	-0.48 (0.166)	-0.46 (0.168)	-0.34 (0.17)	-0.51 (0.17)	-0.45 (0.10)	-0.42 (0.12)
95% 2-sided CI	(-0.71, -0.06)	(-0.71, -0.05)	(-0.68, -0.03)	(-0.80, -0.15)	(-0.79, -0.13)	(-0.68, -0.01)	(-0.85, -0.17)	(-0.64, -0.26)	(-0.65, -0.20)
P value ‡	0.002#	0.002#	0.019*	0.003#	< 0.001#	0.039§	<0.001#§	<0.001#	<0.001#
Change from Baseline to Week 4 in Mean Number of Micturitions per 24 hours (FAS)									
n	471	477	474	422	409	410	424	1317	886
Adjusted mean difference vs placebo (SE)	-0.40 (0.136)	-0.52 (0.136)	-0.33 (0.136)	-0.42 (0.182)	-0.60 (0.183)	-0.18 (0.176)	-0.37 (0.17)	-0.40 (0.09)	-0.56 (0.11)
95% 2-sided CI	(-0.66, -0.13)	(-0.79, -0.26)	(-0.60, -0.06)	(-0.77, -0.06)	(-0.96, -0.24)	(-0.53, 0.16)	(-0.71, -0.03)	(-0.59,-0.22)	(-0.78, -0.35)
P value †	0.004#	<0.001#	0.016*	0.022#	0.001#	0.30§	0.035§	<0.001#	<0.001#
Key Secondary Efficacy Results for Study 178-CL-074 and Pooled Primary Studies; Additional Secondary Efficacy Results for Studies 178-CL-046 and 178-CL-047									
Change from Baseline to Final Visit in Mean Level of Urgency (FAS)									
n	472	475	473	425	411	410	426	1323	886
Adjusted mean difference vs placebo (SE)	-0.09 (0.040)	-0.08 (0.040)	-0.07 (0.040)	-0.11 (0.037)	-0.13 (0.037)	-0.07 (0.04)	-0.14 (0.04)	-0.11 (0.02)	-0.11 (0.03)
95% 2-sided CI	(-0.17, -0.02)	(-0.16, -0.01)	(-0.15, 0.01)	(-0.18, -0.04)	(-0.20, -0.05)	(-0.15, 0.01)	(-0.22, -0.06)	(-0.16, -0.07)	(-0.16, -0.06)
P value †	0.018*	0.037*	0.085	0.004*	< 0.001*	0.083§	<0.001§	<0.001#	<0.001#

	Study 178-CL-046			Study 178-CL-047		Study 178-CL-074		Pooled Primary Studies	
	Mirabegron 50 mg	Mirabegron 100 mg	Tolterodine ER 4 mg	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron 25 mg	Mirabegron 50 mg	Mirabegron 50 mg	Mirabegron 100 mg
Change from Baseline to Final Visit in Mean Number of Urgency Incontinence Episodes per 24 hours (FAS-I)									
n	286	276	289	297	291	247	251	834	567
Adjusted mean difference vs placebo (SE)	-0.35 (0.155)	-0.22 (0.156)	-0.07 (0.154)	-0.43 (0.145)	-0.56 (0.145)	-0.36 (0.16)	-0.39 (0.16)	-0.40 (0.09)	-0.40 (0.10)
95% 2-sided CI	(-0.65, -0.05)	(-0.53, 0.09)	(-0.38, 0.23)	(-0.72, -0.15)	(-0.85, -0.28)	(-0.67, -0.05)	(-0.69, -0.08)	(-0.57, -0.23)	(-0.60, -0.20)
P value ‡	0.003*	0.024*	0.26	0.005*	< 0.001*	0.004§	0.002§	<0.001#	<0.001#
Change from Baseline to Final Visit in Mean Number of Urgency Episodes (Grade 3 or 4) per 24 hours (FAS)									
n	470	474	472	424	411	410	426	1320	885
Adjusted mean difference vs placebo (SE)	-0.60 (0.214)	-0.31 (0.214)	-0.42 (0.214)	-0.75 (0.228)	-0.94 (0.230)	-0.33 (0.22)	-0.59 (0.22)	-0.64 (0.13)	-0.60 (0.15)
95% 2-sided CI	(-1.02, -0.18)	(-0.73, 0.11)	(-0.84, -0.00)	(-1.20, -0.30)	(-1.40, -0.49)	(-0.76, 0.10)	(-1.01, -0.16)	(-0.89, -0.39)	(-0.89, -0.31)
P value †	0.005*	0.14	0.050*	0.001*	< 0.001*	0.13§	0.007§	<0.001#	<0.001#

Pooled primary studies include 178-CL-046, 178-CL-047, and 178-CL-074. All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). All randomized patients who took at least one dose of double-blind study drug and who had a micturition measurement and at least one incontinence episode in the baseline diary and at least one postbaseline visit diary with a micturition measurement (Full Analysis Set-Incontinence [FAS-I]). ER: extended release. For the pooled primary studies and Studies 178-CL-046, 178-CL-047 and 178-CL-074 individually, a stepwise parallel gate keeping procedure was performed to control the Type I error rate at the 0.05 significance level for the coprimary and key secondary efficacy endpoints. Since 2 mirabegron treatment groups were compared with placebo, the Hochberg procedure was used to adjust for multiplicity within each stage. Since the comparison between tolterodine and placebo was a secondary analysis in Study 178-CL-046, no adjustment for multiplicity was necessary. In the pooled primary studies, the adjusted mean difference versus placebo for change from baseline and corresponding 95% CI were generated from an ANCOVA model with treatment group, gender and study as fixed factors and baseline as a covariate. In Studies 178-CL-046, 178-CL-047, and 178-CL-074, the adjusted mean difference versus placebo for change from baseline and corresponding 95% CI were generated from an analysis of covariance (ANCOVA) model with treatment group, gender and geographical region as fixed factors and baseline as a covariate. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from that of treatment groups.

† Nominal P values are from pairwise comparisons versus placebo within the ANCOVA model, a parametric analysis.

‡ Nominal P values are from pairwise comparison versus placebo within the stratified rank ANCOVA, a nonparametric analysis.

Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustment.

* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment.

§ Study 178-CL-074 only: Since the mirabegron 25 mg group did not meet statistical significance with multiplicity adjustment for mean volume voided (P=0.15), subsequent key secondary efficacy endpoints for the mirabegron 25 mg group were excluded from further hypothesis testing as part of the gatekeeping procedure. Mean volume voided per micturition and subsequent key secondary efficacy endpoints for the mirabegron 50

mg group were evaluated at the 0.025 significance level. Since the mirabegron 50 mg group did not meet statistical significance with multiplicity adjustment for change from baseline to Week 4 in mean number of micturitions per 24 hours (P=0.035), subsequent key secondary efficacy endpoints for the mirabegron 50 mg group were excluded from further hypothesis testing as part of the gatekeeping procedure.

Figure 24. Change in Incontinence Episodes Per 24 Hours, Pivotal Studies

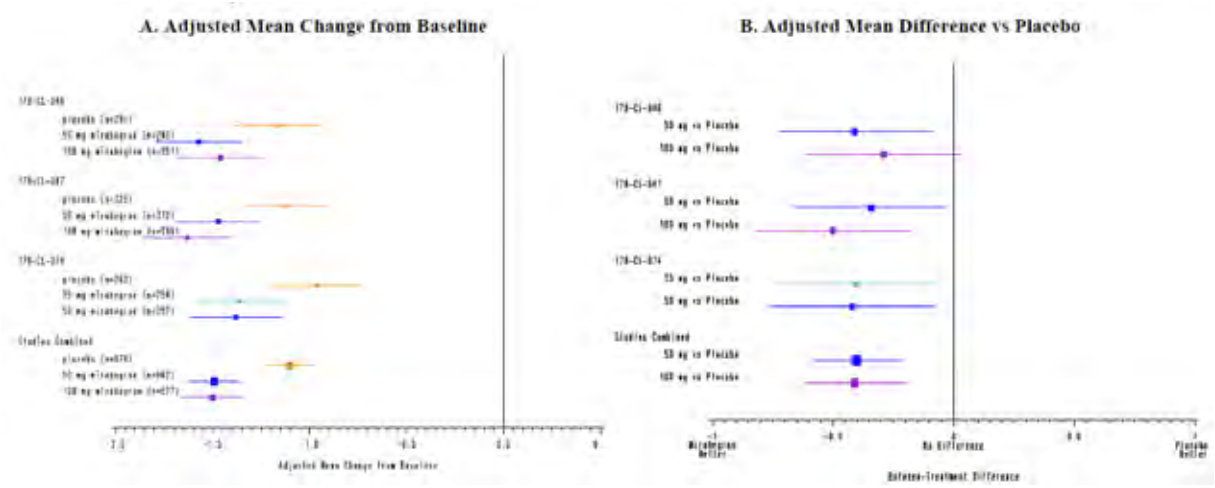


Figure 25. Change in Micturition Episodes Per 24 Hours, Pivotal Studies

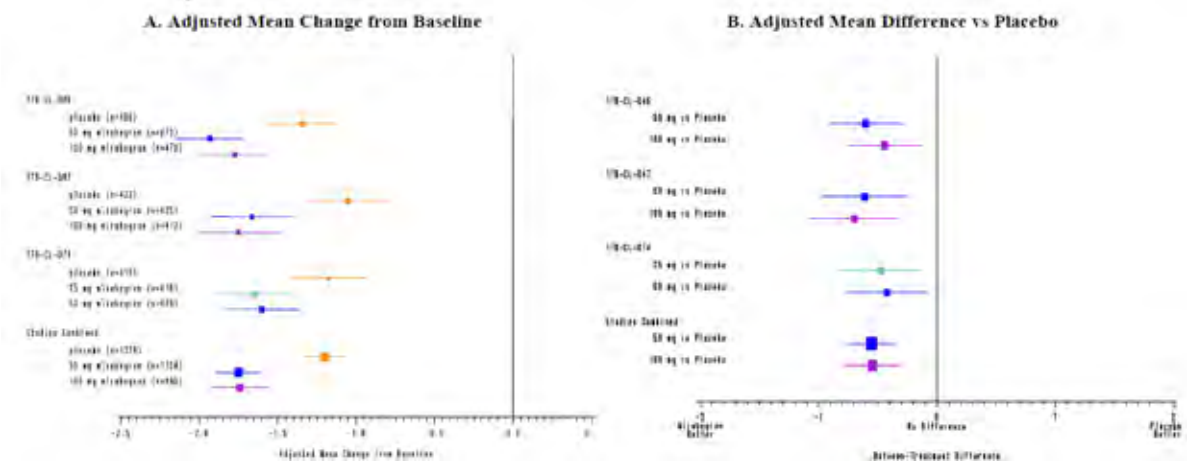


Figure 26. Change in Volume Voided per Micturition, Pivotal Studies

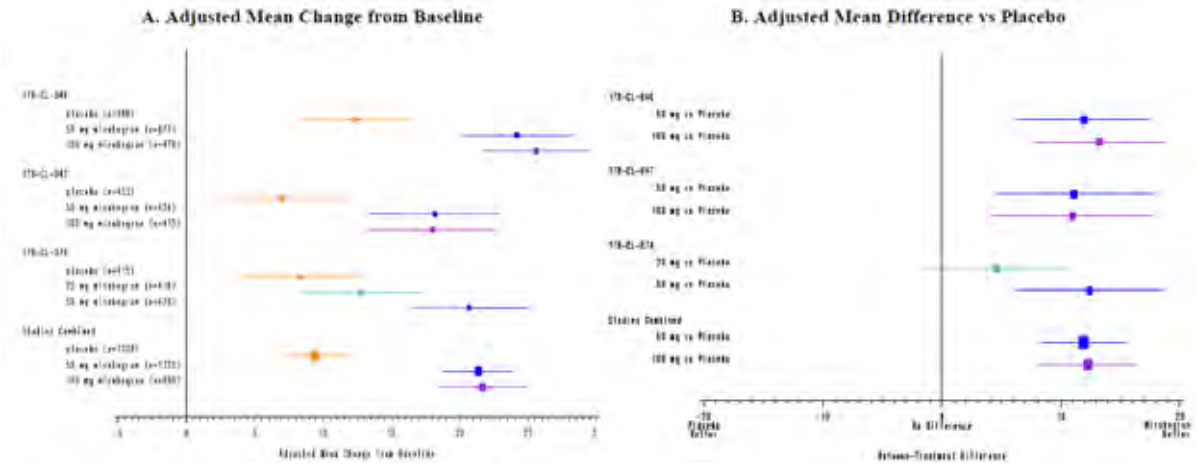


Figure 27. Adjusted Change in Mean Number Incontinence Episodes, Pooled Pivotal Studies

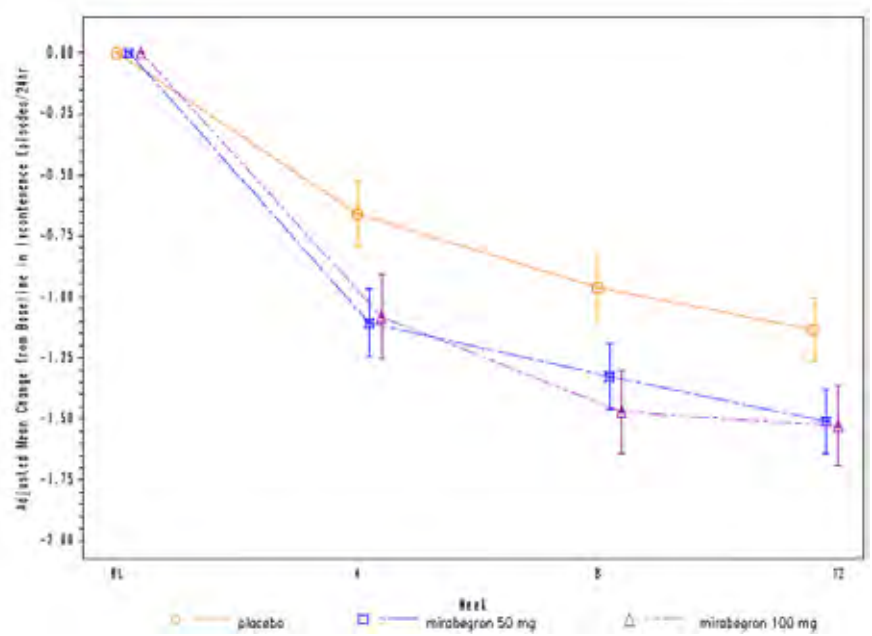
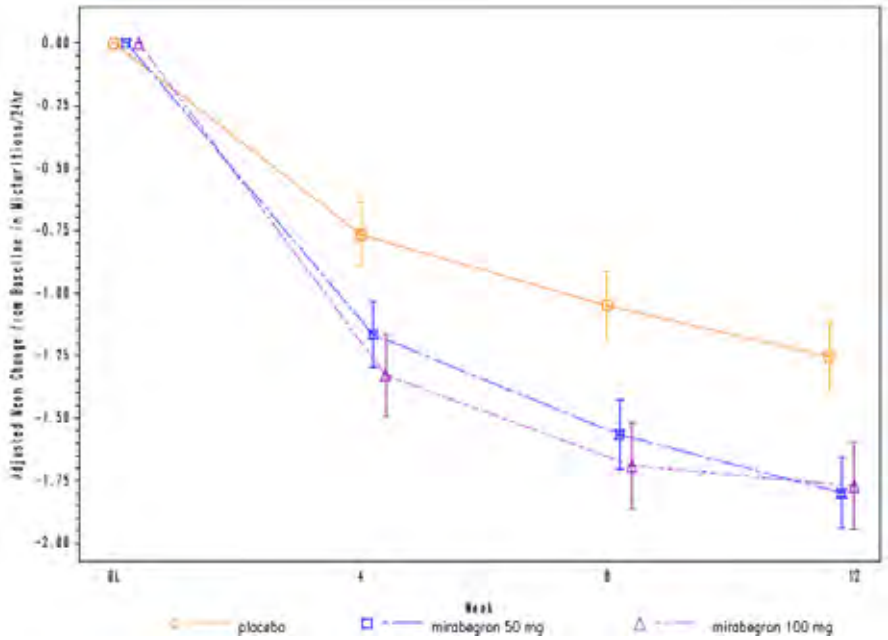


Figure 28. Adjusted Change in Mean Number of Micturition Episodes, Pooled Pivotal Studies



The sponsor presented responder analyses based on 1) the achievement of zero incontinence episodes at final visit, or 2) a reduction of at least 50% from baseline incontinence. These results are shown below. Note the very high responder rates in the placebo group, which reflects the inclusion of patients who only had one or very few episodes of incontinence at baseline. At the proposed dose, the attributable (placebo-subtracted) difference in responder rate for both definitions was modest, amounting to 6.3% for zero incontinence and 9.9% for ≥ 50% reduction. Although this difference in response rate was statistically significant, the data suggests that the *majority* of responders responded because of the placebo effect and regression to the mean. Without a clear method of identifying attributable responses, there is a substantial

risk that clinicians will continue the drug in subjects who appear to have 'responded' but would have responded to placebo.

Table 56. Responder Analysis for Zero Incontinence Episodes at Final Visit, Pooled Pivotal Studies

	Placebo (n = 878)	Mirabegron 50 mg (n = 862)	Mirabegron 100 mg (n = 577)
Final Visit			
Responders (n [%])	332 (37.8%)	380 (44.1%)	268 (46.4%)
Difference vs Placebo (%)		6.3%	8.6%
95% 2-sided CI for Difference†		(1.7%, 10.9%)	(3.5%, 13.8%)
Odds Ratio‡		1.32	1.58
95% 2-sided CI for Odds Ratio	--	(1.08, 1.61)	(1.25, 2.00)
P value		0.008*	< 0.001*

Table 57. Responder Analysis for ≥ 50% Reduction from Baseline in Incontinence Episodes at Final Visit, Pooled Pivotal Studies

	Placebo (n = 878)	Mirabegron 50 mg (n = 862)	Mirabegron 100 mg (n = 577)
Final Visit			
Responders (n [%])	523 (59.6%)	599 (69.5%)	407 (70.5%)
Difference vs Placebo (%)		9.9%	11.0%
95% 2-sided CI for Difference†		(5.5%, 14.4%)	(6.0%, 15.9%)
Odds Ratio‡		1.54	1.64
95% 2-sided CI for Odds Ratio	--	(1.26, 1.89)	(1.29, 2.07)
P value		< 0.001*	< 0.001*

Finally, the sponsor performed a pooled analysis of the change in treatment satisfaction as measured by the TS-VAS. This was a minor endpoint, but relatively important in view of the European guidelines on the conduct of urological studies, which suggest that subjective endpoints should be major endpoints. It is therefore reassuring to observe that there was a statistically significant improvement in treatment satisfaction ($p<0.01$) at the proposed dose, in comparison to placebo.

Table 58. Adjusted Mean Difference from Baseline in TS-VAS, Pooled Pivotal Studies

	Mirabegron 50 mg (n = 1324)	Mirabegron 100 mg (n = 890)
TS-VAS - *Adjusted Mean Difference vs Placebo†*		
Mean (SE)	0.76 (0.125)	1.08 (0.145)
95% 2-sided CI	(0.52, 1.01)	(0.80, 1.37)
P value‡	< 0.001*	< 0.001*

The higher statistical power of the pooled analysis allowed a number of subgroup analyses, which are shown below. There was no evidence that the efficacy of mirabegron was significantly different in subgroups defined by baseline demographics, OAB history or concomitant drug use.

Table 59. Change from Baseline to Final Visit for the Coprimary Efficacy Endpoints by Subpopulation, Demographics, Pooled Pivotal Studies

Sub-population and Category				Mean Number of Incontinence Episodes per 24 hours, FAS-I			Mean Number of Micturitions per 24 hours, FAS		
				Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
Gender	Male	Adjusted Change from Baseline	n	154	168	94	362	382	241
			Mean (SE)	-1.41 (0.159)	-1.48 (0.152)	-1.52 (0.205)	-0.92 (0.135)	-1.29 (0.131)	-1.62 (0.166)
			95% 2-sided CI	(-1.72, -1.10)	(-1.78, -1.18)	(-1.92, -1.12)	(-1.18, -0.66)	(-1.55, -1.04)	(-1.95, -1.29)
		Adjusted Diff vs Placebo	Mean	--	-0.07	-0.11	--	-0.37	-0.70
			95% 2-sided CI		(-0.50, 0.36)	(-0.62, 0.40)		(-0.74, -0.01)	(-1.12, -0.28)
	Female	Adjusted Change from Baseline	n	724	694	483	966	942	649
			Mean (SE)	-1.03 (0.074)	-1.50 (0.075)	-1.50 (0.093)	-1.31 (0.082)	-1.93 (0.084)	-1.79 (0.103)
			95% 2-sided CI	(-1.17, -0.89)	(-1.65, -1.35)	(-1.68, -1.32)	(-1.47, -1.15)	(-2.09, -1.77)	(-1.99, -1.59)
		Adjusted Diff vs Placebo	Mean	--	-0.47	-0.47	--	-0.62	-0.48
			95% 2-sided CI		(-0.67, -0.26)	(-0.70, -0.23)		(-0.85, -0.39)	(-0.74, -0.22)
		Interaction P value:			**0.22**			**0.16**	
Age Group	< 65 years	Adjusted Change from Baseline	n	533	507	342	824	825	550
			Mean (SE)	-1.19 (0.086)	-1.41 (0.088)	-1.41 (0.109)	-1.29 (0.089)	-1.80 (0.089)	-1.70 (0.112)
			95% 2-sided CI	(-1.36, -1.02)	(-1.58, -1.24)	(-1.63, -1.20)	(-1.47, -1.11)	(-1.97, -1.62)	(-1.92, -1.48)
		Adjusted Diff vs Placebo	Mean	--	-0.22	-0.22	--	-0.51	-0.41
			95% 2-sided CI		(-0.46, 0.02)	(-0.50, 0.05)		(-0.75, -0.26)	(-0.69, -0.12)
	≥ 65 years	Adjusted Change from Baseline	n	345	355	235	504	499	340
			Mean (SE)	-0.96 (0.106)	-1.61 (0.105)	-1.63 (0.131)	-1.05 (0.114)	-1.68 (0.115)	-1.81 (0.141)
			95% 2-sided CI	(-1.16, -0.75)	(-1.82, -1.41)	(-1.89, -1.38)	(-1.28, -0.83)	(-1.90, -1.45)	(-2.08, -1.53)
		Adjusted Diff vs Placebo	Mean	--	-0.66	-0.68	--	-0.62	-0.75
			95% 2-sided CI		(-0.95, -0.37)	(-1.01, -0.35)		(-0.94, -0.30)	(-1.11, -0.40)
		Interaction P value:			**0.036**			**0.31**	
	< 75 years	Adjusted Change from Baseline	n	766	751	493	1174	1175	780
			Mean (SE)	-1.13 (0.072)	-1.49 (0.072)	-1.47 (0.092)	-1.18 (0.075)	-1.72 (0.075)	-1.69 (0.095)
			95% 2-sided CI	(-1.27, -0.99)	(-1.63, -1.35)	(-1.65, -1.29)	(-1.32, -1.03)	(-1.87, -1.58)	(-1.87, -1.50)
		Adjusted Diff vs Placebo	Mean	--	-0.36	-0.34	--	-0.55	-0.51
			95% 2-sided CI		(-0.56, -0.16)	(-0.57, -0.11)		(-0.75, -0.34)	(-0.75, -0.27)
	≥ 75 years	Adjusted Change from Baseline	n	112	111	84	154	149	110
			Mean (SE)	-0.87 (0.187)	-1.51 (0.187)	-1.67 (0.217)	-1.37 (0.206)	-1.96 (0.210)	-2.11 (0.245)
			95% 2-sided CI	(-1.23, -0.50)	(-1.88, -1.15)	(-2.10, -1.25)	(-1.78, -0.97)	(-2.38, -1.55)	(-2.59, -1.63)
		Adjusted Diff vs Placebo	Mean	--	-0.65	-0.81	--	-0.59	-0.73
			95% 2-sided CI		(-1.17, -0.13)	(-1.37, -0.25)		(-1.17, -0.02)	(-1.36, -0.11)
		Interaction P value:			**0.30**			**0.79**	
Race	White	Adjusted Change from Baseline	n	806	804	541	1227	1235	838
			Mean (SE)	-1.06 (0.070)	-1.50 (0.070)	-1.49 (0.088)	-1.15 (0.073)	-1.76 (0.073)	-1.76 (0.092)
			95% 2-sided CI	(-1.19, -0.92)	(-1.64, -1.37)	(-1.66, -1.32)	(-1.30, -1.01)	(-1.90, -1.61)	(-1.94, -1.58)
		Adjusted Diff vs Placebo	Mean	--	-0.45	-0.43	--	-0.60	-0.61
			95% 2-sided CI		(-0.64, -0.25)	(-0.66, -0.21)		(-0.81, -0.40)	(-0.84, -0.37)
	Black or African American	Adjusted Change from Baseline	n	58	41	28	80	61	36
			Mean (SE)	-1.54 (0.261)	-1.44 (0.310)	-1.60 (0.376)	-1.74 (0.287)	-1.66 (0.329)	-1.21 (0.429)
			95% 2-sided CI	(-2.05, -1.03)	(-2.04, -0.83)	(-2.34, -0.87)	(-2.31, -1.18)	(-2.31, -1.02)	(-2.06, -0.37)
		Adjusted Diff vs Placebo	Mean	--	0.10	-0.06	--	0.08	0.53
			95% 2-sided CI		(-0.68, 0.89)	(-0.96, 0.83)		(-0.77, 0.93)	(-0.48, 1.54)
	Asian	Adjusted Change from Baseline	n	8	11	2	13	17	8
			Mean (SE)	-1.60 (0.698)	-0.81 (0.595)	-1.14 (1.394)	-2.29 (0.709)	-2.25 (0.620)	-1.28 (0.905)
			95% 2-sided CI	(-2.97, -0.23)	(-1.97, 0.36)	(-3.87, 1.59)	(-3.68, -0.90)	(-3.46, -1.03)	(-3.05, 0.50)
		Adjusted Diff vs Placebo	Mean	--	0.79	0.46	--	0.04	1.02
			95% 2-sided CI		(-1.01, 2.59)	(-2.60, 3.52)		(-1.80, 1.89)	(-1.24, 3.27)

Table 59 continued. Change from Baseline to Final Visit for the Coprimary Efficacy Endpoints by Subpopulation, Demographics, Pooled Pivotal Studies

Sub-population and Category				Mean Number of Incontinence Episodes per 24 hours, FAS-I			Mean Number of Micturitions per 24 hours, FAS		
				Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
Race	Other	Adjusted Change from Baseline	n	6	6	6	8	11	8
			Mean (SE)	-1.83 (0.805)	-1.82 (0.806)	-1.89 (0.807)	-1.61 (0.903)	-1.06 (0.770)	-2.32 (0.905)
			95% 2-sided CI	(-3.41, -0.25)	(-3.40, -0.24)	(-3.48, -0.31)	(-3.38, 0.16)	(-2.57, 0.45)	(-4.09, -0.55)
		Adjusted Diff. vs Placebo	Mean	--	0.01	-0.07	--	0.55	-0.71
			95% 2-sided CI		(-2.23, 2.24)	(-2.30, 2.17)		(-1.78, 2.87)	(-3.22, 1.79)
		Interaction P value:			**0.38**			**0.070**	
Ethnicity	Non-Hispanic or Latino	Adjusted Change from Baseline	n	559	534	276	804	808	381
			Mean (SE)	-1.04 (0.086)	-1.43 (0.088)	-1.60 (0.129)	-1.08 (0.096)	-1.65 (0.096)	-1.76 (0.148)
			95% 2-sided CI	(-1.21, -0.87)	(-1.60, -1.26)	(-1.85, -1.34)	(-1.27, -0.90)	(-1.83, -1.46)	(-2.05, -1.47)
		Adjusted Diff. vs Placebo	Mean	--	-0.39	-0.55	--	-0.56	-0.67
			95% 2-sided CI		(-0.63, -0.15)	(-0.86, -0.24)		(-0.82, -0.30)	(-1.02, -0.32)
	Hispanic or Latino	Adjusted Change from Baseline	n	28	35	20	44	43	31
			Mean (SE)	-0.97 (0.383)	-1.46 (0.343)	-1.23 (0.455)	-1.53 (0.407)	-1.29 (0.412)	-1.80 (0.487)
			95% 2-sided CI	(-1.73, -0.22)	(-2.14, -0.79)	(-2.12, -0.34)	(-2.33, -0.73)	(-2.10, -0.49)	(-2.75, -0.84)
		Adjusted Diff. vs Placebo	Mean	--	-0.49	-0.25	--	0.24	-0.26
			95% 2-sided CI		(-1.50, 0.52)	(-1.42, 0.91)		(-0.90, 1.38)	(-1.51, 0.98)
		Interaction P value:			**0.79**			**0.40**	
BMI Group	< 25 kg/m²	Adjusted Change from Baseline	n	223	234	143	373	370	236
			Mean (SE)	-1.18 (0.132)	-1.64 (0.129)	-1.48 (0.166)	-1.36 (0.132)	-2.04 (0.133)	-1.81 (0.168)
			95% 2-sided CI	(-1.43, -0.92)	(-1.89, -1.39)	(-1.81, -1.16)	(-1.61, -1.10)	(-2.30, -1.78)	(-2.14, -1.48)
		Adjusted Diff. vs Placebo	Mean	--	-0.47	-0.31	--	-0.68	-0.46
			95% 2-sided CI		(-0.83, -0.10)	(-0.73, 0.11)		(-1.05, -0.32)	(-0.88, -0.04)
	25 to < 30 kg/m²	Adjusted Change from Baseline	n	304	306	193	461	499	326
			Mean (SE)	-1.21 (0.113)	-1.47 (0.113)	-1.72 (0.144)	-1.15 (0.119)	-1.85 (0.115)	-2.02 (0.144)
			95% 2-sided CI	(-1.44, -0.99)	(-1.69, -1.25)	(-2.00, -1.44)	(-1.38, -0.91)	(-2.07, -1.63)	(-2.31, -1.74)
		Adjusted Diff. vs Placebo	Mean	--	-0.25	-0.51	--	-0.70	-0.88
			95% 2-sided CI		(-0.57, 0.06)	(-0.87, -0.14)		(-1.03, -0.38)	(-1.24, -0.51)
	≥ 30 kg/m²	Adjusted Change from Baseline	n	351	322	241	493	455	327
			Mean (SE)	-0.95 (0.106)	-1.41 (0.110)	-1.34 (0.129)	-1.13 (0.115)	-1.41 (0.120)	-1.41 (0.143)
			95% 2-sided CI	(-1.15, -0.74)	(-1.63, -1.19)	(-1.60, -1.09)	(-1.35, -0.90)	(-1.64, -1.17)	(-1.69, -1.13)
		Adjusted Diff. vs Placebo	Mean	--	-0.46	-0.39	--	-0.28	-0.28
			95% 2-sided CI		(-0.76, -0.16)	(-0.72, -0.07)		(-0.61, 0.04)	(-0.65, 0.08)
		Interaction P value:			**0.59**			**0.11**	
Geographical Region	Europe	Adjusted Change from Baseline	n	405	405	281	676	666	478
			Mean (SE)	-1.11 (0.096)	-1.57 (0.096)	-1.42 (0.119)	-1.37 (0.089)	-1.90 (0.090)	-1.78 (0.109)
			95% 2-sided CI	(-1.29, -0.92)	(-1.76, -1.38)	(-1.65, -1.18)	(-1.54, -1.19)	(-2.08, -1.73)	(-2.00, -1.57)
		Adjusted Diff. vs Placebo	Mean	--	-0.46	-0.31	--	-0.53	-0.42
			95% 2-sided CI		(-0.73, -0.20)	(-0.62, -0.01)		(-0.78, -0.29)	(-0.70, -0.13)
	North America	Adjusted Change from Baseline	n	473	457	296	652	658	412
			Mean (SE)	-1.09 (0.093)	-1.43 (0.095)	-1.59 (0.122)	-1.02 (0.110)	-1.59 (0.110)	-1.70 (0.144)
			95% 2-sided CI	(-1.27, -0.90)	(-1.62, -1.24)	(-1.83, -1.35)	(-1.24, -0.81)	(-1.81, -1.38)	(-1.98, -1.42)
		Adjusted Diff. vs Placebo	Mean	--	-0.34	-0.51	--	-0.57	-0.68
			95% 2-sided CI		(-0.60, -0.08)	(-0.81, -0.20)		(-0.87, -0.27)	(-1.04, -0.32)
		Interaction P value:			**Not applicable†**			**Not applicable†**	

Table 60. Change from Baseline for the Coprimary Efficacy Endpoints by Subpopulation, Characteristics of OAB, Pooled Pivotal Studies

Sub-population and Category				Mean Number of Incontinence Episodes per 24 hours, FAS-I			Mean Number of Micturitions per 24 hours, FAS		
				Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
Type of OAB	Urge Incontinence	Adjusted Change from Baseline	n	336	352	228	442	491	297
			Mean (SE)	-1.20 (0.108)	-1.39 (0.106)	-1.51 (0.133)	-1.25 (0.122)	-1.82 (0.116)	-2.06 (0.150)
			95% 2-sided CI	(-1.41, -0.99)	(-1.60, -1.18)	(-1.77, -1.25)	(-1.49, -1.01)	(-2.05, -1.59)	(-2.35, -1.77)
		Adjusted Diff. vs Placebo	Mean	–	-0.19	-0.31	--	-0.57	-0.81
			95% 2-sided CI		(-0.49, 0.10)	(-0.64, 0.03)		(-0.90, -0.25)	(-1.19, -0.43)
	Mixed	Adjusted Change from Baseline	n	364	350	232	415	412	271
			Mean (SE)	-1.06 (0.106)	-1.58 (0.107)	-1.41 (0.132)	-1.05 (0.129)	-1.84 (0.128)	-1.61 (0.159)
			95% 2-sided CI	(-1.26, -0.85)	(-1.79, -1.37)	(-1.67, -1.15)	(-1.30, -0.80)	(-2.09, -1.59)	(-1.92, -1.30)
		Adjusted Diff. vs Placebo	Mean	–	-0.52	-0.36	--	-0.79	-0.56
			95% 2-sided CI		(-0.81, -0.23)	(-0.69, -0.03)		(-1.14, -0.44)	(-0.96, -0.17)
	Frequency	Adjusted Change from Baseline	n	178	160	117	471	421	322
			Mean (SE)	-0.99 (0.150)	-1.53 (0.158)	-1.68 (0.185)	-1.29 (0.119)	-1.59 (0.127)	-1.55 (0.146)
			95% 2-sided CI	(-1.28, -0.69)	(-1.84, -1.22)	(-2.04, -1.31)	(-1.53, -1.06)	(-1.83, -1.34)	(-1.83, -1.26)
		Adjusted Diff. vs Placebo	Mean	–	-0.55	-0.69	--	-0.29	-0.25
			95% 2-sided CI		(-0.97, -0.12)	(-1.16, -0.23)		(-0.63, 0.04)	(-0.62, 0.11)
	Interaction P value:				**0.33**			**0.10**	
Duration of OAB Symptoms	< 12 months	Adjusted Change from Baseline	n	67	66	63	122	128	115
			Mean (SE)	-1.21 (0.241)	-1.58 (0.243)	-1.82 (0.249)	-1.79 (0.231)	-1.93 (0.226)	-1.99 (0.239)
			95% 2-sided CI	(-1.69, -0.74)	(-2.06, -1.11)	(-2.31, -1.34)	(-2.24, -1.34)	(-2.37, -1.49)	(-2.46, -1.52)
		Adjusted Diff. vs Placebo	Mean	–	-0.37	-0.61	--	-0.14	-0.20
			95% 2-sided CI		(-1.04, 0.30)	(-1.29, 0.07)		(-0.77, 0.49)	(-0.85, 0.45)
	≥1 to < 60 months	Adjusted Change from Baseline	n	345	370	212	561	568	361
			Mean (SE)	-1.22 (0.106)	-1.55 (0.103)	-1.50 (0.137)	-1.19 (0.108)	-1.78 (0.107)	-1.85 (0.137)
			95% 2-sided CI	(-1.43, -1.02)	(-1.75, -1.35)	(-1.77, -1.23)	(-1.40, -0.98)	(-1.99, -1.57)	(-2.12, -1.58)
		Adjusted Diff. vs Placebo	Mean	–	-0.33	-0.27	--	-0.59	-0.66
			95% 2-sided CI		(-0.62, -0.04)	(-0.62, 0.07)		(-0.89, -0.29)	(-1.00, -0.32)
	≥1 60 month	Adjusted Change from Baseline	n	466	426	302	645	628	414
			Mean (SE)	-0.99 (0.092)	-1.42 (0.096)	-1.45 (0.116)	-1.09 (0.101)	-1.69 (0.103)	-1.58 (0.128)
			95% 2-sided CI	(-1.17, -0.81)	(-1.61, -1.24)	(-1.67, -1.22)	(-1.29, -0.90)	(-1.89, -1.49)	(-1.83, -1.33)
		Adjusted Diff. vs Placebo	Mean	–	-0.44	-0.46	--	-0.59	-0.49
			95% 2-sided CI		(-0.70, -0.18)	(-0.75, -0.17)		(-0.87, -0.31)	(-0.81, -0.17)
	Interaction P value:				**0.86**			**0.62**	
Prior OAB Surgery	Previous OAB surgery	Adjusted Change from Baseline	n	97	108	60	114	126	74
			Mean (SE)	-0.77 (0.202)	-1.34 (0.191)	-1.39 (0.256)	-1.02 (0.241)	-1.85 (0.229)	-1.58 (0.299)
			95% 2-sided CI	(-1.16, -0.37)	(-1.71, -0.96)	(-1.90, -0.89)	(-1.49, -0.54)	(-2.30, -1.40)	(-2.17, -0.99)
		Adjusted Diff. vs Placebo	Mean	–	-0.57	-0.63	--	-0.83	-0.56
			95% 2-sided CI		(-1.11, -0.03)	(-1.27, 0.01)		(-1.48, -0.18)	(-1.31, 0.19)
	No Previous OAB surgery	Adjusted Change from Baseline	n	781	754	517	1214	1198	816
			Mean (SE)	-1.14 (0.071)	-1.52 (0.072)	-1.52 (0.090)	-1.22 (0.074)	-1.74 (0.074)	-1.76 (0.093)
			95% 2-sided CI	(-1.28, -1.00)	(-1.66, -1.37)	(-1.69, -1.34)	(-1.36, -1.07)	(-1.89, -1.59)	(-1.94, -1.57)
		Adjusted Diff. vs Placebo	Mean	–	-0.38	-0.38	--	-0.52	-0.54
			95% 2-sided CI		(-0.57, -0.18)	(-0.61, -0.15)		(-0.73, -0.32)	(-0.77, -0.30)
	Interaction P value:				**0.72**			**0.62**	

Table 60 continued. Change from Baseline for the Coprimary Efficacy Endpoints by Subpopulation, Characteristics of OAB, Pooled Pivotal Studies

Sub-population and Category				Mean Number of Incontinence Episodes per 24 hours			Mean Number of Micturitions per 24 hours		
				Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
Previous OAB Antimuscarinic Medication	Previous OAB med	Adjusted Change from Baseline	n	518	506	336	704	688	460
			Mean (SE)	-0.92 (0.087)	-1.49 (0.088)	-1.42 (0.110)	-0.93 (0.097)	-1.67 (0.098)	-1.61 (0.122)
			95% 2-sided CI	(-1.09, -0.75)	(-1.66, -1.32)	(-1.64, -1.21)	(-1.12, -0.74)	(-1.86, -1.48)	(-1.85, -1.37)
		Adjusted Diff. vs Placebo	Mean	–	-0.57	-0.50	--	-0.74	-0.69
			95% 2-sided CI		(-0.81, -0.33)	(-0.77, -0.22)		(-1.01, -0.47)	(-0.99, -0.38)
	No Previous OAB med	Adjusted Change from Baseline	n	360	356	241	624	636	430
			Mean (SE)	-1.35 (0.104)	-1.50 (0.105)	-1.62 (0.129)	-1.51 (0.103)	-1.84 (0.102)	-1.87 (0.126)
			95% 2-sided CI	(-1.55, -1.14)	(-1.71, -1.29)	(-1.87, -1.36)	(-1.71, -1.31)	(-2.04, -1.64)	(-2.12, -1.63)
		Adjusted Diff. vs Placebo	Mean	–	-0.15	-0.27	--	-0.33	-0.36
			95% 2-sided CI		(-0.44, 0.14)	(-0.60, 0.06)		(-0.62, -0.05)	(-0.68, -0.04)
	Interaction P value:				**0.095**			**0.10**	
Reason for Discontinuing	Insufficient Effect Yes	Adjusted Change from Baseline	n	336	335	224	466	464	296
			Mean (SE)	-0.86 (0.113)	-1.56 (0.114)	-1.50 (0.142)	-0.86 (0.115)	-1.54 (0.116)	-1.65 (0.148)
			95% 2-sided CI	(-1.09, -0.64)	(-1.78, -1.34)	(-1.78, -1.22)	(-1.09, -0.64)	(-1.77, -1.31)	(-1.94, -1.36)
		Adjusted Diff. vs Placebo	Mean	–	-0.70	-0.63	--	-0.67	-0.79
			95% 2-sided CI		(-1.01, -0.38)	(-0.99, -0.27)		(-0.99, -0.36)	(-1.16, -0.42)
	Insufficient Effect No	Adjusted Change from Baseline	n	182	171	112	238	224	164
			Mean (SE)	-1.33 (0.154)	-1.69 (0.159)	-1.59 (0.199)	-1.13 (0.162)	-2.06 (0.166)	-1.74 (0.197)
			95% 2-sided CI	(-1.64, -1.03)	(-2.00, -1.38)	(-1.98, -1.20)	(-1.44, -0.81)	(-2.38, -1.73)	(-2.13, -1.36)
		Adjusted Diff. vs Placebo	Mean	–	-0.35	-0.26	--	-0.93	-0.61
			95% 2-sided CI		(-0.79, 0.08)	(-0.75, 0.24)		(-1.38, -0.47)	(-1.12, -0.11)
	Interaction P value:				**0.34**			**0.38**	
	Poor Tolerability Yes	Adjusted Change from Baseline	n	136	138	80	185	173	113
			Mean (SE)	-1.09 (0.179)	-1.59 (0.178)	-1.65 (0.235)	-0.93 (0.183)	-1.81 (0.190)	-2.00 (0.236)
			95% 2-sided CI	(-1.44, -0.74)	(-1.94, -1.24)	(-2.11, -1.19)	(-1.29, -0.57)	(-2.19, -1.44)	(-2.46, -1.53)
		Adjusted Diff. vs Placebo	Mean	–	-0.50	-0.56	--	-0.88	-1.07
			95% 2-sided CI		(-1.00, -0.01)	(-1.14, 0.02)		(-1.40, -0.37)	(-1.66, -0.48)
	Poor Tolerability No	Adjusted Change from Baseline	n	382	368	256	519	515	347
			Mean (SE)	-1.01 (0.107)	-1.61 (0.109)	-1.49 (0.134)	-0.96 (0.110)	-1.67 (0.110)	-1.58 (0.138)
			95% 2-sided CI	(-1.22, -0.80)	(-1.82, -1.39)	(-1.76, -1.23)	(-1.18, -0.75)	(-1.89, -1.46)	(-1.85, -1.31)
		Adjusted Diff. vs Placebo	Mean	–	-0.60	-0.49	--	-0.71	-0.62
			95% 2-sided CI		(-0.90, -0.30)	(-0.82, -0.15)		(-1.01, -0.41)	(-0.97, -0.27)
	Interaction P value:				**0.87**			**0.43**	

Table 61. Change from Baseline to Final Visit for the Coprimary Efficacy Endpoints by Subpopulation, Intrinsic/Extrinsic Factors, Pooled Pivotal Studies

Sub-population and Category				Mean Number of Incontinence Episodes per 24 hours, FAS-I			Mean Number of Micturitions per 24 hours, FAS		
				Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
History of BPH†	Yes	Adjusted	n	60	56	36	147	142	95
		Change from Baseline	Mean (SE)	-0.84 (0.251)	-0.70 (0.260)	-0.81 (0.329)	-0.82 (0.218)	-0.99 (0.223)	-1.69 (0.277)
			95% 2-sided CI	(-1.33, -0.34)	(-1.21, -0.18)	(-1.45, -0.16)	(-1.25, -0.39)	(-1.42, -0.55)	(-2.24, -1.15)
		Adjusted Diff. vs Placebo	Mean	--	0.14	0.03	--	-0.16	-0.87
			95% 2-sided CI		(-0.57, 0.85)	(-0.79, 0.85)		(-0.77, 0.45)	(-1.57, -0.17)
	No	Adjusted	n	94	112	58	215	240	146
		Change from Baseline	Mean (SE)	-1.36 (0.200)	-1.45 (0.183)	-1.33 (0.261)	-1.10 (0.181)	-1.58 (0.171)	-1.60 (0.226)
			95% 2-sided CI	(-1.76, -0.97)	(-1.81, -1.09)	(-1.84, -0.82)	(-1.46, -0.75)	(-1.91, -1.24)	(-2.04, -1.15)
		Adjusted Diff. vs Placebo	Mean	--	-0.09	0.04	--	-0.48	-0.50
			95% 2-sided CI		(-0.62, 0.44)	(-0.62, 0.69)		(-0.97, 0.01)	(-1.07, 0.08)
		Interaction P value:			**0.85**			**0.30**	
History of Diabetes	Yes	Adjusted	n	76	79	59	105	115	75
		Change from Baseline	Mean (SE)	-0.99 (0.227)	-1.54 (0.222)	-1.34 (0.258)	-0.93 (0.250)	-1.71 (0.239)	-1.76 (0.296)
			95% 2-sided CI	(-1.43, -0.54)	(-1.98, -1.11)	(-1.85, -0.83)	(-1.42, -0.44)	(-2.18, -1.24)	(-2.34, -1.18)
		Adjusted Diff. vs Placebo	Mean	--	-0.55	-0.35	--	-0.78	-0.83
			95% 2-sided CI		(-1.18, 0.07)	(-1.03, 0.32)		(-1.45, -0.10)	(-1.59, -0.06)
	No	Adjusted	n	802	783	518	1223	1209	815
		Change from Baseline	Mean (SE)	-1.11 (0.070)	-1.49 (0.071)	-1.52 (0.090)	-1.22 (0.073)	-1.75 (0.074)	-1.74 (0.093)
			95% 2-sided CI	(-1.25, -0.97)	(-1.63, -1.35)	(-1.70, -1.35)	(-1.37, -1.08)	(-1.90, -1.61)	(-1.92, -1.56)
		Adjusted Diff. vs Placebo	Mean	--	-0.38	-0.41	--	-0.53	-0.52
			95% 2-sided CI		(-0.57, -0.19)	(-0.64, -0.19)		(-0.73, -0.33)	(-0.75, -0.28)
		Interaction P value:			**0.78**			**0.69**	
Renal Status (CrCCG), mL/min	≥ 90 Normal	Adjusted	n	471	431	319	728	697	498
		Change from Baseline	Mean (SE)	-1.08 (0.091)	-1.38 (0.095)	-1.47 (0.113)	-1.14 (0.095)	-1.67 (0.097)	-1.66 (0.117)
			95% 2-sided CI	(-1.26, -0.90)	(-1.57, -1.20)	(-1.69, -1.25)	(-1.33, -0.95)	(-1.86, -1.48)	(-1.89, -1.43)
		Adjusted Diff. vs Placebo	Mean	--	-0.30	-0.39	--	-0.53	-0.52
			95% 2-sided CI		(-0.56, -0.04)	(-0.67, -0.10)		(-0.80, -0.27)	(-0.82, -0.22)
	60 to < 90 Mild Impairment	Adjusted	n	310	348	201	469	520	318
		Change from Baseline	Mean (SE)	-1.10 (0.112)	-1.56 (0.106)	-1.45 (0.141)	-1.27 (0.118)	-1.76 (0.112)	-1.82 (0.145)
			95% 2-sided CI	(-1.32, -0.88)	(-1.77, -1.35)	(-1.73, -1.18)	(-1.51, -1.04)	(-1.98, -1.54)	(-2.10, -1.53)
		Adjusted Diff. vs Placebo	Mean	--	-0.46	-0.36	--	-0.48	-0.54
			95% 2-sided CI		(-0.76, -0.16)	(-0.71, 0.00)		(-0.80, -0.17)	(-0.91, -0.17)
	30 to < 60 Moderate Impairment	Adjusted	n	95	82	56	128	105	71
		Change from Baseline	Mean (SE)	-1.11 (0.202)	-1.74 (0.218)	-1.85 (0.265)	-1.26 (0.226)	-2.20 (0.250)	-1.99 (0.305)
			95% 2-sided CI	(-1.51, -0.71)	(-2.17, -1.31)	(-2.37, -1.33)	(-1.70, -0.81)	(-2.69, -1.71)	(-2.59, -1.39)
		Adjusted Diff. vs Placebo	Mean	--	-0.63	-0.74	--	-0.94	-0.73
			95% 2-sided CI		(-1.22, -0.05)	(-1.40, -0.09)		(-1.60, -0.29)	(-1.48, 0.01)
	< 30 Severe Impairment	Adjusted	n	2	0	1	2	1	2
		Change from Baseline	Mean (SE)	--	--	--	-2.23 (1.807)	-3.82 (2.555)	-0.56 (1.806)
			95% 2-sided CI				(-5.77, 1.32)	(-8.83, 1.19)	(-4.10, 2.98)
		Adjusted Diff. vs Placebo	Mean	--	--	--	--	-1.60	1.67
			95% 2-sided CI					(-7.73, 4.54)	(-3.34, 6.68)
		Interaction P value:			**0.69**			**0.75**	

Table 61 continued. Change from Baseline to Final Visit for the Coprimary Efficacy Endpoints by Subpopulation, Intrinsic/Extrinsic Factors, Pooled Pivotal Studies

Sub-population and Category				Mean Number of Incontinence Episodes per 24 hours, FAS-I			Mean Number of Micturitions per 24 hours, FAS		
				Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
Renal Status (GFR MDRD) mL/min/1.73 m^2	≥ 90 Normal	Adjusted Change from Baseline	n	288	280	191	467	462	316
			Mean (SE)	-1.20 (0.116)	-1.22 (0.118)	-1.33 (0.145)	-1.08 (0.118)	-1.72 (0.119)	-1.76 (0.146)
			95% 2-sided CI	(-1.43, -0.98)	(-1.45, -0.99)	(-1.62, -1.05)	(-1.31, -0.85)	(-1.96, -1.49)	(-2.05, -1.48)
		Adjusted Diff. vs Placebo	Mean	--	-0.02	-0.13	--	-0.64	-0.68
			95% 2-sided CI		(-0.34, 0.30)	(-0.49, 0.24)		(-0.97, -0.32)	(-1.05, -0.32)
	60 to < 90 Mild Impairment	Adjusted Change from Baseline	n	525	501	341	768	751	509
			Mean (SE)	-1.06 (0.087)	-1.60 (0.089)	-1.57 (0.109)	-1.27 (0.093)	-1.74 (0.094)	-1.69 (0.116)
			95% 2-sided CI	(-1.23, -0.89)	(-1.78, -1.43)	(-1.79, -1.36)	(-1.46, -1.09)	(-1.92, -1.55)	(-1.92, -1.47)
		Adjusted Diff. vs Placebo	Mean	--	-0.54	-0.51	--	-0.46	-0.42
			95% 2-sided CI		(-0.78, -0.30)	(-0.79, -0.24)		(-0.72, -0.21)	(-0.72, -0.13)
	30 to < 60 Moderate Impairment	Adjusted Change from Baseline	n	65	80	44	93	110	63
			Mean (SE)	-0.94 (0.244)	-1.73 (0.220)	-1.70 (0.298)	-1.21 (0.265)	-1.95 (0.244)	-2.01 (0.323)
			95% 2-sided CI	(-1.42, -0.46)	(-2.17, -1.30)	(-2.29, -1.12)	(-1.73, -0.69)	(-2.43, -1.47)	(-2.65, -1.38)
		Adjusted Diff. vs Placebo	Mean	--	-0.80	-0.76	--	-0.74	-0.80
			95% 2-sided CI		(-1.44, -0.15)	(-1.52, -0.01)		(-1.44, -0.03)	(-1.62, 0.02)
	< 30 Severe Impairment	Adjusted Change from Baseline	n	0	0	1	0	0	2
			Mean (SE)	--	--	--	--	--	--
			95% 2-sided CI						
		Adjusted Diff. vs Placebo	Mean	--	--	--	--	--	--
			95% 2-sided CI						
		Interaction P value:			0.070			0.70	
Beta-blocker Use at Baseline	Yes	Adjusted Change from Baseline	n	154	127	102	206	185	156
			Mean (SE)	-1.11 (0.159)	-1.66 (0.175)	-1.46 (0.197)	-1.08 (0.178)	-1.59 (0.188)	-1.64 (0.206)
			95% 2-sided CI	(-1.42, -0.79)	(-2.00, -1.32)	(-1.84, -1.07)	(-1.43, -0.73)	(-1.96, -1.22)	(-2.05, -1.24)
		Adjusted Diff. vs Placebo	Mean	--	-0.55	-0.35	--	-0.51	-0.56
			95% 2-sided CI		(-1.02, -0.09)	(-0.85, 0.14)		(-1.02, -0.00)	(-1.10, -0.03)
	No	Adjusted Change from Baseline	n	724	735	475	1122	1139	734
			Mean (SE)	-1.10 (0.074)	-1.46 (0.073)	-1.51 (0.093)	-1.22 (0.077)	-1.78 (0.076)	-1.76 (0.098)
			95% 2-sided CI	(-1.24, -0.95)	(-1.61, -1.32)	(-1.70, -1.33)	(-1.37, -1.07)	(-1.93, -1.63)	(-1.95, -1.57)
		Adjusted Diff. vs Placebo	Mean	--	-0.37	-0.42	--	-0.55	-0.54
			95% 2-sided CI		(-0.57, -0.17)	(-0.65, -0.18)		(-0.77, -0.34)	(-0.78, -0.29)
		Interaction P value:			0.64			0.97	
Concomitant Diuretic Use	Yes	Adjusted Change from Baseline	n	151	141	103	211	192	143
			Mean (SE)	-0.81 (0.161)	-1.69 (0.166)	-1.55 (0.196)	-0.91 (0.176)	-1.56 (0.185)	-1.33 (0.215)
			95% 2-sided CI	(-1.13, -0.50)	(-2.02, -1.36)	(-1.93, -1.17)	(-1.25, -0.56)	(-1.92, -1.20)	(-1.76, -0.91)
		Adjusted Diff. vs Placebo	Mean	--	-0.88	-0.74	--	-0.65	-0.43
			95% 2-sided CI		(-1.33, -0.43)	(-1.24, -0.24)		(-1.15, -0.15)	(-0.97, 0.12)
	No	Adjusted Change from Baseline	n	727	721	474	1117	1132	747
			Mean (SE)	-1.16 (0.073)	-1.45 (0.074)	-1.49 (0.093)	-1.26 (0.077)	-1.78 (0.076)	-1.82 (0.097)
			95% 2-sided CI	(-1.30, -1.01)	(-1.60, -1.31)	(-1.68, -1.31)	(-1.41, -1.10)	(-1.93, -1.63)	(-2.01, -1.63)
		Adjusted Diff. vs Placebo	Mean	--	-0.30	-0.34	--	-0.53	-0.56
			95% 2-sided CI		(-0.50, -0.09)	(-0.57, -0.10)		(-0.74, -0.32)	(-0.81, -0.32)
					0.062			0.70	
Concomitant Alpha-1-antagonist Use †	Yes	Adjusted Change from Baseline	n	32	37	23	76	79	59
			Mean (SE)	-1.01 (0.346)	-1.43 (0.324)	-1.17 (0.412)	-0.87 (0.304)	-0.98 (0.298)	-1.92 (0.348)
			95% 2-sided CI	(-1.69, -0.34)	(-2.07, -0.79)	(-1.98, -0.36)	(-1.46, -0.27)	(-1.57, -0.40)	(-2.61, -1.24)
		Adjusted Diff. vs Placebo	Mean	--	-0.42	-0.16	--	-0.12	-1.06
			95% 2-sided CI		(-1.35, 0.51)	(-1.21, 0.90)		(-0.95, 0.72)	(-1.96, -0.15)
	No	Adjusted Change from Baseline	n	122	131	71	286	303	182
			Mean (SE)	-1.20 (0.179)	-1.14 (0.172)	-1.11 (0.239)	-1.02 (0.158)	-1.46 (0.153)	-1.53 (0.204)
			95% 2-sided CI	(-1.55, -0.85)	(-1.48, -0.80)	(-1.58, -0.64)	(-1.33, -0.71)	(-1.76, -1.16)	(-1.93, -1.13)
		Adjusted Diff. vs Placebo	Mean	--	0.06	0.09	--	-0.44	-0.51
			95% 2-sided CI		(-0.42, 0.54)	(-0.51, 0.69)		(-0.87, -0.01)	(-1.03, 0.00)
		Interaction P value:			0.67			0.25	

7.4. Evaluator's conclusions on clinical efficacy

Overall, the submitted efficacy data shows that mirabegron has a minor beneficial effect on the symptoms OAB. The statistical evidence in support of the efficacy of mirabegron 50mg is robust and consistent: all three pivotal studies and the pooled analysis showed a statistically significant

treatment effect for both of the co-primary endpoints, micturition frequency and incontinence frequency. Secondary endpoints were also achieved with statistical significance in most cases, including a number of subjective endpoints, such as the Treatment Satisfaction VAS.

There were no major methodological flaws compromising the statistical interpretation of the major endpoints, but there was a pronounced placebo response for both co-primary endpoints and most secondary endpoints. The placebo-subtracted treatment effect was relatively small compared to this placebo response.

The magnitude of the placebo-subtracted treatment effect was disappointing. In the pooled analysis of the pivotal studies, the number of voluntary micturitions avoided per 24 hours was 0.55 episodes for the proposed 50mg dose, and 0.54 for the 100mg dose, from a baseline of 11 to 12 episodes. This hardly seems worth pursuing. The mean number of incontinence episodes was reduced with mirabegron 50mg by 0.40 episodes, from a baseline of about two and a half episodes across the various treatment groups. The reduction with mirabegron 100mg was 0.41 episodes.

This modest quantitative improvement was associated with a statistically significant improvement in the subjective TS-VAS, which showed a placebo-subtracted improvement of 0.76 for mirabegron 50mg and 1.08 for mirabegron 100mg, in a scale ranging from 0 to 10 and baseline values of about 4. The improvement in the placebo group was 1.89, 0.7, 1.05 across the three studies. A fully effective drug would potentially produce a rating of 10 (complete satisfaction with treatment), giving an overall improvement of 6 points, and a placebo-subtracted improvement of 4-5 points.

Results in the 50mg and 100mg groups were generally similar to each other. The lower dose of 25mg was only assessed in one pivotal study, and although this dose achieved significance for many endpoints, it was inferior to 50mg and did not achieve all of its secondary endpoints.

The efficacy of mirabegron was broadly similar to that seen with the active control, tolterodine.

Thus, overall, mirabegron has modest efficacy, which some patients might find useful, and is comparable to another agent already used for OAB.

8. Clinical safety

8.1. Studies providing evaluable safety data

The studies listed below are the major source of evaluable safety data. The sponsor defined 5 different study populations, as indicated by the last 5 columns of the table below. The most important of these were the global phase 2/3 population and the 12-week (placebo-controlled) global phase 2/3 population; the contribution of each study to these populations is detailed in the subsequent table, on the following page. Patient disposition in the phase 2/3 population is listed in Table 64. Most subjects (85.6%) completed treatment with mirabegron, but some patients withdrew for a variety of reasons, as listed. Adverse events (AEs) caused withdrawals in 5% of the global phase 2/3 population.

Table 62. Overview of Phase 2/3 Study Populations

Study	Phase	Mirabegron Formulation	Population	Duration of Treatment	Global Phase 2/3	Global OAB 12-week Phase 2/3	EU/NA OAB 12-week Phase 3	EU/NA Long-term Controlled	Japan Long-term Uncontrolled
178-CL-044	2	OCAS	OAB	12 weeks	X	X			
178-CL-045	2	OCAS	OAB	12 weeks	X	X			
178-CL-046	3	OCAS	OAB	12 weeks	X	X	X		
178-CL-047	3	OCAS	OAB	12 weeks	X	X	X		
178-CL-074	3	OCAS	OAB	12 weeks	X	X	X		
178-CL-048	3	OCAS	OAB	12 weeks	X	X			
178-CL-049	3	OCAS	OAB	52 weeks (12 months)	X			X	
178-CL-051	3	OCAS	OAB	52 weeks (12 months)	X				X
178-CL-008	2	IR	OAB	4 weeks	X				
178-CL-060	2	OCAS	LUTS/BOO	12 weeks	X				
178-CL-003	2	IR	Type 2 diabetes mellitus	12 weeks	X				
178-CL-004	2	IR	Type 2 diabetes mellitus	12 weeks	X				

BOO: bladder outlet obstruction; IR: immediate release; ISS: integrated summary of safety; LUTS: lower urinary tract symptoms; OAB: overactive bladder; OCAS: oral controlled absorption system.

Table 63. Source and Number of Patients Treated in the Global Phase 2/3 Clinical Population

Study	Treatments							
Global OAB 12-week Phase 2/3 Population								
		Total Daily Dose of Mirabegron						
	Placebo	25 mg	50 mg	100 mg	200 mg		Total Mirabegron	Tolterodine ER 4 mg
178-CL-046	494		493	496			989	495
178-CL-047	453		442	433			875	
178-CL-074	433	432	440				872	
Subtotal of EU/NA OAB 12-week Phase 3 population	*1380*	*432*	*1375*	*929*			*2736*	*495*
178-CL-044	169	169	169	168	167		673	85
178-CL-045	213	210	208	208			626	
178-CL-048	380		379				379	378
Totals	2142	811	2131	1305	167		**4414**	958
Other phase 2 studies included in the Global Phase 2/3 Population								
		Mirabegron mg/day						
	Placebo	25 mg	50 mg	100 mg	200 mg	300 mg	Total Mirabegron	Tolterodine ER 4 mg
178-CL-003 †	19				40		40	
178-CL-004 †‡	20				40		40	
178-CL-008	66				65	65	130	64
178-CL-060	65		70	65			135	
Totals	170		70	65	145	65	**345**	64
EU/NA Long-term Controlled Population								
	Mirabegron mg/day		Mirabegron New Exposure§		Mirabegron Re-exposure¶		Total Mirabegron	Tolterodine ER 4 mg
	50 mg	100 mg						
178-CL-049	812	820	**901**		731		1632	812††
Japan Long-term Uncontrolled Population								
	Mirabegron mg/day							
	50 mg (only)	100 mg (used)					Total Mirabegron	
178-CL-051‡‡	153	50					**203**	
Total Number of Unique Mirabegron Patients in the Global Phase 2/3 Population §§	4414 + 345 + 901 + 203 = **5863**							

All randomized patients who took at least one dose of study drug (Safety Analysis Set).

ER: extended release; OAB: overactive bladder.

† Patients randomized to mirabegron in Studies 178-CL-003 and 178-CL-004 received a daily dose of 60 mg (1 week), 130 mg (1 week), and 200 mg (10 weeks); they are included in the 200 mg column.

‡ Patients in Study 178-CL-004 received either placebo or mirabegron in combination with metformin.

§ Mirabegron new exposure indicates patients on mirabegron in Study 178-CL-049 who did not receive mirabegron in Studies 178-CL-046 or 178-CL-047.

¶ Mirabegron re-exposure indicates patients on mirabegron in Study 178-CL-049 who also took mirabegron in Studies 178-CL-046 or 178-CL-047.

†† Includes 108 tolterodine new exposures and 704 tolterodine re-exposures [Study 178-CL-049, Table 3].

‡‡ Patients in Study 178-CL-051 received a starting dose of 50 mg mirabegron and could potentially increase to 100 mg mirabegron. Patients in the mirabegron 50 mg (only) column only received mirabegron 50 mg; patients in the mirabegron 100 mg (used) column had their dose increased from 50 mg to 100 mg.

§§Total number of patients treated with mirabegron in phase 2/ 3 clinical trials: total mirabegron from placebo-controlled 12-week OAB phase 2/3 population + total mirabegron from other phase 2 studies + mirabegron new exposures from the EU/NA Long-Term Controlled Phase 3 Population + total mirabegron from the Japan Long-Term Uncontrolled Phase 3 Population.

Table 64. Patient Disposition, Global Phase 2/3 Population

n (%) of Patients	Total Mirabegron
Received at least one dose of mirabegron	5863
Completed treatment with mirabegron	5016 (85.6%)
Discontinued from mirabegron	847 (14.4%)
Primary reason for discontinuation	
AE	296 (5.0%)
Withdrawal of consent	256 (4.4%)
Lack of efficacy	96 (1.6%)
Protocol violation	64 (1.1%)
Patient lost to follow up	50 (0.9%)
Not fulfilling inclusion or exclusion criteria	21 (0.4%)
Worsening of disease	1 (< 0.1%)
Other	63 (1.1%)

Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by interviewing patients at each visit and reviewing hospital records for unscheduled visits.
- AEs of particular interest, including urological events and cardiovascular events.
- Laboratory tests, including full blood counts, liver function tests and electrolytes, were performed at regular intervals and the results were compared with normal reference ranges.

Studies that assessed safety as a primary outcome

Long-term studies 049 and 051 assessed the safety and tolerability of mirabegron over 12 months, and efficacy was a secondary focus. The design of these studies has been described in Sections 7.2.5 and 7.2.6. These studies contributed data to the EU/NA long term population (Study 049) and to the Japanese long-term population (Study 051); the results in these long-term subgroups are included where relevant in the sections below.

Dose-response studies, non-pivotal efficacy and clinical pharmacology studies

The dose-response and non-pivotal efficacy studies provided safety data in the same way as in the pivotal studies, with adverse event monitoring and laboratory surveillance. A couple of clinical pharmacology studies were specifically designed to assess the effect of mirabegron on the QT interval (Thorough QT studies 178-CL-037 and 178-CL-077).

8.2. Patient exposure

Exposure to mirabegron has been fairly extensive, with 10,552 subjects exposed in the clinical study program: this includes 1800 healthy volunteers and 8752 patients. Most patients (8433) have had OAB; the remainder (319) consists of male patients with lower urinary tract symptoms/bladder outlet obstruction (LUTS/BOO) and some patients with type 2 diabetes mellitus.

Not all exposed subjects were in studies that contributed to the integrated safety data set. The safety data set is based on 29 phase 1 studies and 9 phase 2/3 studies in OAB, and 3 studies in other conditions (one study in patients with LUTS/BOO and two studies in patients with type 2 diabetes mellitus). Detailed safety data thus comes from 1462 volunteers in phase 1 studies and 5863 patients (5648 patients with OAB) in the phase 2/3 studies.

The immediate release (IR) formulation was used for most of the phase 1 studies; subsequent studies used the controlled-release (OCAS) formulation. The most relevant safety data comes from the global phase 2/3 studies in OAB, summarised below, which used the proposed formulation for the proposed indication. Exposure in this population is summarised below.

Table 65. Summary of Study Drug Exposure by Total Daily Dose, Global Phase 2/3 Population

	Total Daily Dose of Mirabegron					
Characteristic n (%) of Patients	< 25 mg (n = 0)	≥ 25 mg to < 50 mg (n = 811)	≥ 50 mg to < 100 mg (n = 2831)	≥ 100 mg to < 200 mg (n = 1847)	≥ 200 mg (n = 374)	Total Mirabegron (n = 5863)
Cumulative duration (days)†						
≥ 7	0	800 (98.6%)	2800 (98.9%)	1830 (99.1%)	370 (98.9%)	5800 (98.9%)
≥ 14	0	788 (97.2%)	2766 (97.7%)	1821 (98.6%)	364 (97.3%)	5739 (97.9%)
≥ 28	0	772 (95.2%)	2716 (95.9%)	1783 (96.5%)	354 (94.7%)	5625 (95.9%)
≥ 56	0	752 (92.7%)	2595 (91.7%)	1720 (93.1%)	226 (60.4%)	5293 (90.3%)
≥ 84	0	563 (69.4%)	1951 (68.9%)	1467 (79.4%)	135 (36.1%)	4116 (70.2%)
≥ 182	0	0	827 (29.2%)	741 (40.1%)	0	1568 (26.7%)
≥ 274	0	0	774 (27.3%)	704 (38.1%)	0	1478 (25.2%)
≥ 365	0	0	333 (11.8%)	270 (14.6%)	0	603 (10.3%)
Duration category (days)†						
1 – 6	0	11 (1.4%)	31 (1.1%)	17 (0.9%)	4 (1.1%)	63 (1.1%)
7 – 13	0	12 (1.5%)	34 (1.2%)	9 (0.5%)	6 (1.6%)	61 (1.0%)
14 – 27	0	16 (2.0%)	50 (1.8%)	38 (2.1%)	10 (2.7%)	114 (1.9%)
28 – 55	0	20 (2.5%)	121 (4.3%)	63 (3.4%)	128 (34.2%)	332 (5.7%)
56 – 83	0	189 (23.3%)	644 (22.7%)	253 (13.7%)	91 (24.3%)	1177 (20.1%)
84 – 181	0	563 (69.4%)	1124 (39.7%)	726 (39.3%)	135 (36.1%)	2548 (43.5%)
182 – 273	0	0	53 (1.9%)	37 (2.0%)	0	90 (1.5%)
274– 364	0	0	441 (15.6%)	434 (23.5%)	0	875 (14.9%)
≥ 365	0	0	333 (11.8%)	270 (14.6%)	0	603 (10.3%)
Duration (days)†						
Mean (SD)	0	80.2 (17.87)	158.7 (128.47)	189.3 (137.18)	60.5 (26.24)	151.3 (125.26)
Median	0	84.0	86.0	90.0	71.0	85.0
Min, Max	0	1, 103	1, 391	1, 396	2, 98	1, 396
Patient-years of exposure						
Total	0	178.15	1230.33	957.48	61.98	2427.94

Table 66. Summary of Study Drug Exposure by Total Daily Dose, Global OAB 12-Week Phase 2/3 Population

		Mirabegron					Tolterodine ER 4 mg (n = 958)	Total (n = 7514)
Characteristic n (%) of Patients	Placebo (n = 2142)	25 mg (n = 811)	50 mg (n = 2131)	100 mg (n = 1305)	200 mg (n = 167)	Total Mirabegron (n = 4414)		
Cumulative duration (days)								
≥ 7	2117 (98.8%)	800 (98.6%)	2107 (98.9%)	1289 (98.8%)	165 (98.8%)	4361 (98.8%)	948 (99.0%)	7426 (98.8%)
≥ 14	2099 (98.0%)	788 (97.2%)	2081 (97.7%)	1282 (98.2%)	162 (97.0%)	4313 (97.7%)	941 (98.2%)	7353 (97.9%)
≥ 28	2055 (95.9%)	772 (95.2%)	2043 (95.9%)	1255 (96.2%)	157 (94.0%)	4227 (95.8%)	926 (96.7%)	7208 (95.9%)
≥ 56	1953 (91.2%)	752 (92.7%)	1947 (91.4%)	1216 (93.2%)	152 (91.0%)	4067 (92.1%)	901 (94.1%)	6921 (92.1%)
≥ 84	1245 (58.1%)	563 (69.4%)	1254 (58.8%)	906 (69.4%)	135 (80.8%)	2858 (64.7%)	501 (52.3%)	4604 (61.3%)
Duration category (days)								
n	2142	811	2131	1305	167	4414	958	7514
1 – 6	25 (1.2%)	11 (1.4%)	24 (1.1%)	16 (1.2%)	2 (1.2%)	53 (1.2%)	10 (1.0%)	88 (1.2%)
7 – 13	18 (0.8%)	12 (1.5%)	26 (1.2%)	7 (0.5%)	3 (1.8%)	48 (1.1%)	7 (0.7%)	73 (1.0%)
14 – 27	44 (2.1%)	16 (2.0%)	38 (1.8%)	27 (2.1%)	5 (3.0%)	86 (1.9%)	15 (1.6%)	145 (1.9%)
28 – 55	102 (4.8%)	20 (2.5%)	96 (4.5%)	39 (3.0%)	5 (3.0%)	160 (3.6%)	25 (2.6%)	287 (3.8%)
56 – 83	708 (33.1%)	189 (23.3%)	693 (32.5%)	310 (23.8%)	17 (10.2%)	1209 (27.4%)	400 (41.8%)	2317 (30.8%)
≥ 84	1245 (58.1%)	563 (69.4%)	1254 (58.8%)	906 (69.4%)	135 (80.8%)	2858 (64.7%)	501 (52.3%)	4604 (61.3%)
Duration (days)								
n	2142	811	2131	1305	167	4414	958	7514
Mean (SD)	79.1 (17.84)	80.2 (17.87)	79.4 (17.86)	80.9 (16.96)	79.8 (19.16)	80.0 (17.66)	80.4 (15.78)	79.8 (17.49)
Median	84.0	84.0	84.0	84.0	84.0	84.0	84.0	84.0
Min, Max	1, 104	1, 103	1, 108	1, 111	3, 98	1, 111	1, 124	1, 124
Patient-years of exposure								
Total	463.96	178.15	463.11	288.95	36.48	966.70	210.92	1641.57

Table 67. Summary of Study Drug Exposure, EU/NA Long-term Controlled Population

Characteristic n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Total Mirabegron (n = 1632)	Tolterodine ER 4 mg (n = 812)	Total (n = 2444)
Cumulative duration (days)					
≥ 28	787 (96.9%)	797 (97.2%)	1584 (97.1%)	785 (96.7%)	2369 (96.9%)
≥ 84	743 (91.5%)	739 (90.1%)	1482 (90.8%)	735 (90.5%)	2217 (90.7%)
≥ 182	687 (84.6%)	698 (85.1%)	1385 (84.9%)	675 (83.1%)	2060 (84.3%)
≥ 274	647 (79.7%)	664 (81.0%)	1311 (80.3%)	645 (79.4%)	1956 (80.0%)
≥ 365	294 (36.2%)	270 (32.9%)	564 (34.6%)	274 (33.7%)	838 (34.3%)
Duration category (days)					
n	812	820	1632	812	2444
1 – 27	25 (3.1%)	23 (2.8%)	48 (2.9%)	27 (3.3%)	75 (3.1%)
28 – 83	44 (5.4%)	58 (7.1%)	102 (6.3%)	50 (6.2%)	152 (6.2%)
84 – 181	56 (6.9%)	41 (5.0%)	97 (5.9%)	60 (7.4%)	157 (6.4%)
182 – 273	40 (4.9%)	34 (4.1%)	74 (4.5%)	30 (3.7%)	104 (4.3%)
274 – 364	353 (43.5%)	394 (48.0%)	747 (45.8%)	371 (45.7%)	1118 (45.7%)
≥ 365	294 (36.2%)	270 (32.9%)	564 (34.6%)	274 (33.7%)	838 (34.3%)
Duration (days)					
n	812	820	1632	812	2444
Mean (SD)	311.3 (109.87)	313.6 (108.24)	312.4 (109.03)	308.7 (111.48)	311.2 (109.84)
Median	364.0	364.0	364.0	363.0	364.0
Min, Max	2, 391	1, 396	1, 396	1, 415	1, 415
Patient-years of exposure					
Total	691.96	703.94	1395.90	686.33	2082.23

The demographic characteristics of the main safety population (the global phase 2/3 population) is summarised in the table below. About 36% of this population were ≥ 65 years old, and 9.8% were ≥ 75 years old, so that the population assessed broadly matches the population in which the drug is likely to be used. On the other hand, subjects with significant comorbidities were excluded from the major efficacy studies, so tolerability in a more realistic, less selective population would be expected to be worse than in this carefully monitored and selected trial population.

Table 68. Demographic and Baseline Characteristics, Global Phase 2/3 Population

Parameter	Category/Statistic	Total Mirabegron (n = 5863)
Gender, n (%)	n	5863
	Female	4399 (75.0%)
	Male	1464 (25.0%)
Ethnicity†, n (%)	n	2783
	Not Hispanic or Latino	2655 (95.4%)
	Hispanic or Latino	128 (4.6%)
Race, n (%)	n	5858
	White	4387 (74.9%)
	Asian	1259 (21.5%)
	Black or African American	179 (3.1%)
	Other	33 (0.6%)
Age group 1 (years), n (%)	n	5863
	< 65	3768 (64.3%)
	≥ 65	2095 (35.7%)
Age group 2 (years), n (%)	n	5863
	< 75	5289 (90.2%)
	≥ 75	574 (9.8%)
Age (years)	n	5863
	Mean (SD)	58.6 (12.96)
	Min, Max	18, 91
	Median	60.0
Height (cm)	n	5862
	Mean (SD)	164.4 (9.44)
	Min, Max	130, 199
	Median	164.0
Weight (kg)	n	5862
	Mean (SD)	74.78 (19.114)
	Min, Max	32.9, 190.9
	Median	72.76

Parameter	Category/Statistic	Total Mirabegron (n = 5863)
BMI (kg/m^2)	n	5862
	Mean (SD)	27.5 (6.08)
	Min, Max	15, 63
	Median	26.6
BMI group (kg/m^2), n (%)	n	5862
	< 25	2231 (38.1%)
	25 to < 30	2013 (34.3%)
	≥ 30	1618 (27.6%)
Geographic region ‡, n (%)	n	5863
	Europe	2831 (48.3%)
	North America	1748 (29.8%)
	Japan	1208 (20.6%)
	Southern Hemisphere	76 (1.3%)

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Individual studies (Pivotal studies and major supporting studies)

The incidences of treatment-emergent adverse events (TEAEs) reported in the major studies are listed below for each study and each treatment group. These included any adverse events (AEs) which appeared during the study, as well as AEs that significantly worsened during the treatment phase.

Reviewing the TEAE column for each study shows that, in general, the incidence of TEAEs was comparable in the mirabegron and placebo groups, and was often slightly higher in the placebo group. The incidence of TEAEs varied widely from study to study, but this largely reflects different study durations, with the highest incidence of TEAEs reported in the long-term follow-up studies. In the pivotal studies, the incidence ranged from 40% to 50%, with no consistent

difference between mirabegron dose groups or between mirabegron and placebo treatment. In pivotal Study 046, the incidence of TEAEs was slightly higher in the tolterodine group (46.7%) than the placebo group (43.3%) or the 50mg and 100mg mirabegron dose groups (42.8% and 40.1%, respectively). In pivotal Study 047, the mirabegron 100mg dose group had the lowest incidence of TEAEs (46.9%), followed by the placebo group (50.1%) and the mirabegron 50mg group (51.6%). In pivotal Study 074, the mirabegron 50mg group had the lowest incidence (47.3%), followed by the 25mg group (48.6%%) and the placebo group (50.1%). Overall, this suggests that mirabegron is well tolerated by most subjects. The incidence of specific AEs is considered in the subsequent section.

Table 69. Main Safety Results for Individual Studies

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Adverse Events (SAF)				Vitals (SAF)						
		Any TEAE n/n (%)	Death n/n (%)	Any TESAE n/n (%)	TEAE Leading to DC n/n (%)		Pulse (bpm)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)	
						Statistic†	AM	PM	AM	PM	AM	PM
178-CL-046‡	Placebo 497/453	214/494 (43.3%)	0	8/494 (1.6%)	13/494 (2.6%)	n Adjusted Change from Baseline	481 0.8 (0.28) (0.2, 1.3)	479 0.1 (0.29) (-0.5, 0.7)	481 0.7 (0.40) (-0.1, 1.4)	479 1.2 (0.41) (0.4, 2.0)	481 0.4 (0.26) (-0.1, 0.9)	479 0.3 (0.26) (-0.2, 0.8)
	Mirabegron OCAS 50 mg 497/440	211/493 (42.8%)	0	14/493 (2.8%)	24/493 (4.9%)	n Adjusted Change from Baseline Difference from Placebo	474 1.6 (0.28) (1.0, 2.1) 0.8 (0.39) (0, 1.6)	474 0.8 (0.29) (0.2, 1.4) 0.7 (0.40) (-0.1, 1.5)	474 0.6 (0.40) (-0.2, 1.3) -0.1 (0.56) (-1.2, 1.0)	474 0.3 (0.41) (-0.5, 1.1) -0.9 (0.58) (-2.1, 0.2)	474 0.3 (0.26) (-0.2, 0.8) -0.1 (0.36) (-0.8, 0.6)	474 0.3 (0.26) (-0.2, 0.8) -0.0 (0.37) (-0.8, 0.7)
	Mirabegron OCAS 100 mg 498/453	199/496 (40.1%)	0	12/496 (2.4%)	16/496 (3.2%)	n Adjusted Change from Baseline Difference from Placebo	479 2.4 (0.28) (1.8, 2.9) 1.6 (0.39) (0.8, 2.4)	478 2.1 (0.29) (1.5, 2.6) 2.0 (0.40) (1.2, 2.8)	479 1.0 (0.40) (0.3, 1.8) 0.4 (0.56) (-0.7, 1.5)	478 1.7 (0.41) (0.8, 2.5) 0.5 (0.58) (-0.7, 1.6)	478 0.5 (0.26) (0, 1.0) 0.2 (0.36) (-0.5, 0.9)	478 1.2 (0.26) (0.7, 1.7) 0.9 (0.37) (0.1, 1.6)
	Tolterodine ER 4 mg 495/445	231/495 (46.7%)	1/495 (0.2%)	11/495 (2.2%)	22/495 (4.4%)	n Adjusted Change from Baseline Difference from Placebo	476 1.6 (0.28) (1.0, 2.1) 0.8 (0.39) (0, 1.6)	476 2.0 (0.29) (1.4, 2.5) 1.9 (0.40) (1.1, 2.7)	476 0.1 (0.40) (-0.6, 0.9) -0.5 (0.56) (-1.6, 0.6)	476 0.4 (0.41) (-0.4, 1.2) -0.8 (0.58) (-1.9, 0.4)	476 0.9 (0.26) (0.4, 1.4) 0.5 (0.36) (-0.2, 1.2)	476 1.3 (0.26) (0.8, 1.8) 1.0 (0.37) (0.2, 1.7)
178-CL-047‡	Placebo 454/385	227/453 (50.1%)	0	9/453 (2.0%)	17/453 (3.8%)	n Adjusted Change from Baseline	433 0.3 (0.32) (-0.3, 0.9)	433 -0.9 (0.31) (-1.5, -0.3)	433 0.2 (0.45) (-0.7, 1.0)	433 0.5 (0.45) (-0.4, 1.4)	433 0.1 (0.30) (-0.5, 0.7)	433 0.6 (0.31) (0, 1.2)
	Mirabegron OCAS 50 mg 442/383	228/442 (51.6%)	0	11/442 (2.5%)	18/442 (4.1%)	n Adjusted Change from Baseline Difference from Placebo	426 1.7 (0.32) (1.1, 2.3) 1.4 (0.45) (0.5, 2.3)	426 0.3 (0.32) (-0.3, 1.0) 1.3 (0.45) (0.4, 2.1)	426 0.7 (0.45) (-0.2, 1.6) 0.6 (0.64) (-0.7, 1.8)	426 1.6 (0.46) (0.7, 2.5) 1.1 (0.64) (-0.2, 2.3)	426 0.4 (0.30) (-0.2, 1.0) 0.3 (0.43) (-0.6, 1.1)	426 1.3 (0.31) (0.7, 1.9) 0.7 (0.43) (-0.2, 1.5)
	Mirabegron OCAS 100 mg 433/380	203/433 (46.9%)	1/433 (0.2%)	14/433 (3.2%)	18/433 (4.2%)	n Adjusted Change from Baseline Difference from Placebo	412 2.6 (0.32) (1.9, 3.2) 2.3 (0.45) (1.4, 3.2)	412 1.7 (0.32) (1.0, 2.3) 2.6 (0.45) (1.7, 3.5)	412 0.1 (0.46) (-0.8, 1.0) -0.1 (0.65) (-1.3, 1.2)	412 1.3 (0.46) (0.3, 2.2) 0.8 (0.65) (-0.5, 2.0)	412 -0.0 (0.31) (-0.6, 0.6) -0.2 (0.43) (-1.0, 0.7)	412 0.7 (0.31) (0.1, 1.3) 0 (0.44) (-0.8, 0.9)

Table 69 continued. Main Safety Results for Individual Studies

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Adverse Events (SAF)				Vitals (SAF)						
		Any TEAE n/n (%)	Death n/n (%)	Any TESAE n/n (%)	TEAE Leading to DC n/n (%)		Pulse (bpm)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)	
						Statistic†	AM	PM	AM	PM	AM	PM
178-CL-074‡	Placebo 433/367	217/433 (50.1%)	0	12/433 (2.8%)	16/433 (3.7%)	n Adjusted Change from Baseline	415 0 (0.31) (-0.6, 0.6)	414 -0.7 (0.33) (-1.4, -0.1)	415 -0.5 (0.45) (-1.3, 0.4)	414 -0.1 (0.46) (-1.0, 0.8)	415 -0.6 (0.27) (-1.1, -0.1)	414 0.1 (0.29) (-0.4, 0.7)
	Mirabegron OCAS 25 mg 433/387	210/432 (48.6%)	0	7/432 (1.6%)	17/432 (3.9%)	n Adjusted Change from Baseline Difference from Placebo	410 0.8 (0.31) (0.2, 1.4) 0.8 (0.44) (-0.1, 1.6)	410 -0.1 (0.33) (-0.7, 0.6) 0.6 (0.47) (-0.3, 1.5)	410 -0.5 (0.46) (-1.4, 0.4) -0.1 (0.64) (-1.3, 1.2)	410 -0.6 (0.46) (-1.5, 0.3) -0.5 (0.65) (-1.7, 0.8)	410 -0.4 (0.27) (-0.9, 0.1) 0.2 (0.39) (-0.6, 1.0)	410 -0.1 (0.29) (-0.7, 0.4) -0.2 (0.41) (-1.0, 0.6)
	Mirabegron OCAS 50 mg 440/386	208/440 (47.3%)	0	4/440 (0.9%)	11/440 (2.5%)	n Adjusted Change from Baseline Difference from Placebo	427 0.9 (0.30) (0.3, 1.5) 0.9 (0.43) (0, 1.7)	427 0.4 (0.32) (-0.3, 1.0) 1.1 (0.46) (0.2, 2.0)	427 1.1 (0.45) (0.2, 2.0) 1.5 (0.64) (0.3, 2.8)	427 1.4 (0.45) (0.5, 2.3) 1.5 (0.64) (0.3, 2.8)	427 0.4 (0.27) (-0.1, 1.0) 1.0 (0.38) (0.3, 1.8)	427 0.6 (0.28) (0.1, 1.2) 0.5 (0.40) (-0.3, 1.3)
178-CL-048§	Placebo 381/350	292/379 (77.0%)	0	4/379 (1.1%)	8/379 (2.1%)	n Adjusted Change from Baseline	364 0.97	361 0	364 1.74 (10.68)	361 1.81 (9.90)	364 0.69 (7.91)	361 1.32 (7.65)
	Mirabegron OCAS 50 mg 380/349	281/379 (74.1%)	0	3/379 (0.8%)	12/379 (3.2%)	n Adjusted Change from Baseline Difference from Placebo	366 2.68 1.71 (0.83, 2.59)	367 1.44 1.44 (0.47, 2.40)	366 2.67 (11.12) ND	367 1.79 (10.71) ND	366 1.77 (7.90) ND	367 1.77 (7.69) ND
	Tolterodine ER 4 mg 378/355	305/375 (81.3%)	0	4/375 (1.1%)	12/375 (3.2%)	n Adjusted Change from Baseline Difference from Placebo	367 1.74 0.77 (-0.11, 1.65)	361 2.88 2.87 (1.90, 3.84)	367 1.76 (10.34) ND	361 2.10 (10.02) ND	367 0.95 (7.66) ND	361 2.13 (7.02) ND
178-CL-049¶	Mirabegron OCAS 50 mg 815/629	485/812 (59.7%)	2/812 (0.2%)	42/812 (5.2%)	48/812 (5.9%)	n Adjusted Change from Baseline	791 0.9 (0.23) (0.5, 1.4)	789 0.4 (0.24) (-0.1, 0.8)	791 0.2 (0.33) (-0.4, 0.9)	789 -0.3 (0.33) (-0.9, 0.3)	791 -0.3 (0.21) (-0.7, 0.1)	789 -0.0 (0.21) (-0.4, 0.4)
	Mirabegron OCAS 100 mg 824/645	503/820 (61.3%)	0	51/820 (6.2%)	50/820 (6.1%)	n Adjusted Change from Baseline	802 1.6 (0.22) (1.2, 2.1)	802 1.3 (0.24) (0.8, 1.7)	802 0.4 (0.33) (-0.2, 1.1)	802 0.1 (0.32) (-0.5, 0.8)	802 0.4 (0.20) (-0.0, 0.8)	802 0.1 (0.21) (-0.3, 0.5)
	Tolterodine ER 4 mg 813/621	508/812 (62.6%)	2/812 (0.2%)	44/812 (5.4%)	46/812 (5.7%)	n Adjusted Change from Baseline	792 1.5 (0.22) (1.1, 2.0)	792 1.9 (0.24) (1.4, 2.4)	793 -0.5 (0.33) (-1.1, 0.2)	793 -0.0 (0.33) (-0.7, 0.6)	793 0.1 (0.21) (-0.3, 0.5)	793 0.6 (0.21) (0.2, 1.0)

Table 69 continued. Main Safety Results for Individual Studies

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Adverse Events (SAF)				Vitals (SAF)						
		Any TEAE n/n (%)	Death n/n (%)	Any TESAE n/n (%)	TEAE Leading to DC n/n (%)		Pulse (bpm)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)	
						Statistic†	AM	PM	AM	PM	AM	PM
178-CL-051††	Mirabegron OCAS 50 mg [only]	139/152 (91.4%)	0	4/152 (2.6%)	10/152 (6.6%)	n Change from Baseline	143 1.04 (6.69)	145 -0.37 (6.51)	143 -3.18 (11.40)	145 -0.80 (9.87)	143 -3.20 (8.19)	145 -1.24 (7.06)
	Mirabegron OCAS 100 mg [used]	50/50 (100%)	1/50 (2.0%)	3/50 (6.0%)	5/50 (10.0%)	n Change from Baseline	50 1.40 (7.11)	50 1.52 (6.97)	50 -1.67 (10.06)	50 -2.36 (12.19)	50 -1.38 (9.09)	50 -1.80 (8.17)
178-CL-044‡‡	Placebo 169/157	73/169 (43.2%)	0	1/169 (0.6%)	5/169 (3.0%)	n Adjusted Change from Baseline	166 0.51	166 -0.04	166 0.35	166 0.38	166 0.24	166 0.67
	Mirabegron OCAS 25 mg 169/153	74/169 (43.8%)	0	1/169 (0.6%)	9/169 (5.3%)	n Adjusted Change from Baseline	167 0.34	167 0.44	167 -0.70	167 0.57	167 -0.77	167 0.07
						Difference from Placebo	-0.17 (0.64) (-1.42, 1.08)	0.48 (0.71) (-0.92, 1.87)	-1.05 (0.99) (-3.00, 0.90)	0.20 (0.95) (-1.67, 2.06)	-1.01 (0.58) (-2.15, 0.13)	-0.60 (0.62) (-1.82, 0.61)
	Mirabegron OCAS 50 mg 169/153	74/169 (43.8%)	0	1/169 (0.6%)	4/169 (2.4%)	n Adjusted Change from Baseline	168 1.64	168 1.12	168 -1.14	168 0.39	168 -0.22	168 0.50
						Difference from Placebo	1.13 (0.63) (-0.11, 2.38)	1.15 (0.71) (-0.24, 2.55)	-1.49 (0.99) (-3.44, 0.45)	0.01 (0.95) (-1.85, 1.87)	-0.46 (0.58) (-1.60, 0.68)	-0.17 (0.62) (-1.38, 1.05)
	Mirabegron OCAS 100 mg 169/161	77/168 (45.8%)	0	2/168 (1.2%)	4/168 (2.4%)	n Adjusted Change from Baseline	168 2.15	168 2.71	168 0.79	168 0.65	168 1.06	168 1.32
						Difference from Placebo	1.64 (0.64) (0.39, 2.89)	2.74 (0.71) (1.34, 4.14)	0.43 (1.00) (-1.52, 2.39)	0.28 (0.95) (-1.59, 2.15)	0.82 (0.58) (-0.32, 1.97)	0.65 (0.62) -0.57, 1.87)
	Mirabegron OCAS 200 mg 167/151	80/167 (47.9%)	0	3/167 (1.8%)	7/167 (4.2%)	n Adjusted Change from Baseline	165 4.66	166 4.63	165 0.83	166 2.24	165 0.90	166 0.94
						Difference from Placebo	4.14 (0.64) (2.90, 5.39)	4.67 (0.71) (3.27, 6.06)	0.47 (0.99) (-1.48, 2.43)	1.86 (0.95) (-0.00, 3.73)	0.66 (0.58) (-0.48, 1.80)	0.28 (0.62) (-0.94, 1.49)
	Tolterodine ER 4 mg 85/82	41/85 (48.2%)	0	1/85 (1.2%)	1/85 (1.2%)	Adjusted Change from Baseline	NR	NR	NR	NR	NR	NR
						Difference from Placebo	NR	NR	NR	NR	NR	NR

Table 69 continued. Main Safety Results for Individual Studies

Study No.	Treatment Arm Number of Patients Randomized/ Completed	Adverse Events (SAF)				Vitals (SAF)						
		Any TEAE n/n (%)	Death n/n (%)	Any TESAE n/n (%)	TEAE Leading to DC n/n (%)		Pulse (bpm)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)	
						Statistic†	AM	PM	AM	PM	AM	PM
178-CL-045§	Placebo 214/198	157/212 (74.1%)	0	4/212 (1.9%)	4/212 (1.9%)	n Adjusted Change from Baseline	210 0.21	210 -1.63	210 1.14 (9.96)	209 0.72 (9.34)	210 -0.12 (7.85)	209 0.02 (7.12)
	Mirabegron OCAS 25 mg 211/200	169/210 (80.5%)	0	3/210 (1.4%)	5/210 (2.4%)	n Adjusted Change from Baseline	203 1.08	208 0.48	202 0.65 (10.41)	205 1.16 (10.34)	202 0.20 (7.39)	205 0.14 (7.43)
						Difference from Placebo	0.87 (-0.35, 2.10)	2.11 (0.88, 3.34)	ND	ND	ND	ND
	Mirabegron OCAS 50 mg 208/195	171/208 (82.2%)	0	1/208 (0.5%)	7/208 (3.4%)	n Adjusted Change from Baseline	206 2.63	206 1.45	205 0.82 (10.02)	206 -0.06 (9.10)	205 0.51 (7.10)	206 -0.01 (6.84)
						Difference from Placebo	2.42 (1.20, 3.65)	3.08 (1.86, 4.31)	ND	ND	ND	ND
	Mirabegron OCAS 100 mg 209/196	175/208 (84.1%)	0	1/208 (0.5%)	8/208 (3.8%)	n Adjusted Change from Baseline	203 3.93	207 3.33	200 1.67 (10.10)	206 2.41 (9.94)	200 1.03 (8.00)	206 2.10 (8.22)
						Difference from Placebo	3.72 (2.49, 4.95)	4.96 (3.73, 6.19)	ND	ND	ND	ND
178-CL-008§§	Placebo 66/62	22/66 (33.3%)	0	0	0	n Change from Baseline	62 -0.8 (10.5)		62 1.3 (14.3)		62 1.5 (10.1)	
	Mirabegron IR 100 mg, bid 65/61	25/65 (38.5%)	0	0	2/65 (3.1%)	n Change from Baseline	62 1.1 (11.5)		62 -1.1 (13.4)		62 0.2 (8.3)	
	Mirabegron IR 150 mg, bid 65/60	22/65 (33.8%)	0	0	4/65 (6.2%)	n Change from Baseline	61 4.0 (9.4)		61 2.0 (14.0)		61 1.6 (9.5)	
	Tolterodine ER 4 mg, qd 66/62	27/64 (42.2%)	0	1/64 (1.6%)	1/64 (1.6%)	n Change from Baseline	61 0 (8.1)		61 -1.5 (14.8)		61 -0.3 (8.6)	

8.3.1.2. Pooled phase 2/3 studies

In the pooled 12-week phase 2/3 population (involving subjects followed for 12 weeks, but excluding subjects from the non-placebo-controlled long-term studies), the incidence of TEAEs in the total mirabegron population (53.4%) was similar to that in the placebo group (55.2%), and there was actually a trend to reduced incidence of TEAEs at higher mirabegron doses, as shown in the table below.

Table 70. SAE, TEAE and TEAE leading to Discontinuation of Study Drug, Global OAB 12-Week Phase 2/3 Population

n (%) of Patients	Placebo (n = 2142)	Mirabegron					Tolt ER 4 mg (n = 958)
		25 mg (n = 811)	50 mg (n = 2131)	100 mg (n = 1305)	200 mg (n = 167)	Total Mira (n = 4414)	
SAE	38 (1.8%)	11 (1.4%)	34 (1.6%)	29 (2.2%)	3 (1.8%)	77 (1.7%)	16 (1.7%)
Drug-related SAE†	8 (0.4%)	4 (0.5%)	8 (0.4%)	5 (0.4%)	0	17 (0.4%)	7 (0.7%)
TEAE	1182 (55.2%)	452 (55.7%)	1173 (55.0%)	654 (50.1%)	80 (47.9%)	2359 (53.4%)	577 (60.2%)
Drug-related TEAE†	389 (18.2%)	169 (20.8%)	438 (20.6%)	262 (20.1%)	37 (22.2%)	906 (20.5%)	275 (28.7%)
TEAE leading to permanent d/c of study drug	63 (2.9%)	31 (3.8%)	75 (3.5%)	47 (3.6%)	7 (4.2%)	160 (3.6%)	36 (3.8%)
Drug-related TEAE leading to permanent d/c of study drug†	36 (1.7%)	19 (2.3%)	48 (2.3%)	32 (2.5%)	5 (3.0%)	104 (2.4%)	28 (2.9%)

Considering specific AEs, the most common AEs reported in the mirabegron group were: nasopharyngitis, hypertension, increased blood glucose, headache, UTI, increased gamma GT, and abnormal urinary sediment, with incidences as shown in the table below.

Table 71. TEAE by Preferred Term (Reported by ≥ 3.0% in the Total Mirabegron group), Global Phase 2/3 Population

MedDRA v12.1 PT†, n (%) of Patients	Total Mirabegron (n = 5863)				
	TEAE	Mild	Moderate	Severe‡	Drug-related
Overall	**3473 (59.2%)**	**2165 (36.9%)**	**1053 (18.0%)**	**255 (4.3%)**	**1397 (23.8%)**
Nasopharyngitis	438 (7.5%)	364 (6.2%)	64 (1.1%)	10 (0.2%)	3 (0.1%)
Hypertension	377 (6.4%)	287 (4.9%)	86 (1.5%)	4 (0.1%)	234 (4.0%)
Blood glucose increased	275 (4.7%)	271 (4.6%)	3 (0.1%)	1 (< 0.1%)	17 (0.3%)
Headache	214 (3.7%)	139 (2.4%)	62 (1.1%)	13 (0.2%)	109 (1.9%)
UTI	199 (3.4%)	133 (2.3%)	63 (1.1%)	3 (0.1%)	25 (0.4%)
GGT increased	175 (3.0%)	150 (2.6%)	22 (0.4%)	3 (0.1%)	77 (1.3%)
Urinary sediment abnormal	175 (3.0%)	175 (3.0%)	0	0	11 (0.2%)

Many of these reflect the intercurrent illnesses present in any population studied for a prolonged period. When compared with the incidence of the same AEs in the placebo population, as shown in the table below, there was no substantial difference between active treatment and placebo. The overall incidence of each AE was similar with active treatment and placebo, as was the distribution amongst the mild, moderate and severe categories.

Table 72. TEAE by Preferred Term (Reported by ≥ 3.0% in the Total Mirabegron group), Global OAB 12-Week Phase 2/3 Population

MedDRA v12.1 PT†, n (%) of Patients	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Mirabegron Total (n = 4414)	Tolterodine ER 4 mg (n = 958)
Overall	**1182 (55.2%)**	**452 (55.7%)**	**1173 (55.0%)**	**654 (50.1%)**	**80 (47.9%)**	**2359 (53.4%)**	**577 (60.2%)**
Mild	820 (38.3%)	317 (39.1%)	828 (38.9%)	404 (31.0%)	46 (27.5%)	1595 (36.1%)	428 (44.7%)
Moderate	295 (13.8%)	115 (14.2%)	283 (13.3%)	201 (15.4%)	30 (18.0%)	629 (14.3%)	117 (12.2%)
Severe‡	67 (3.1%)	20 (2.5%)	62 (2.9%)	49 (3.8%)	4 (2.4%)	135 (3.1%)	32 (3.3%)
Drug-related	389 (18.2%)	169 (20.8%)	438 (20.6%)	262 (20.1%)	37 (22.2%)	906 (20.5%)	275 (28.7%)
Nasopharyngitis	**141 (6.6%)**	**61 (7.5%)**	**157 (7.4%)**	**74 (5.7%)**	**4 (2.4%)**	**296 (6.7%)**	**57 (5.9%)**
Mild	125 (5.8%)	55 (6.8%)	136 (6.4%)	58 (4.4%)	2 (1.2%)	251 (5.7%)	50 (5.2%)
Moderate	16 (0.7%)	6 (0.7%)	17 (0.8%)	13 (1.0%)	2 (1.2%)	38 (0.9%)	7 (0.7%)
Severe‡	0	0	4 (0.2%)	3 (0.2%)	0	7 (0.2%)	0
Drug-related	1 (< 0.1%)	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Hypertension	**107 (5.0%)**	**54 (6.7%)**	**110 (5.2%)**	**55 (4.2%)**	**2 (1.2%)**	**221 (5.0%)**	**43 (4.5%)**
Mild	84 (3.9%)	44 (5.4%)	83 (3.9%)	35 (2.7%)	2 (1.2%)	164 (3.7%)	35 (3.7%)
Moderate	23 (1.1%)	9 (1.1%)	26 (1.2%)	20 (1.5%)	0	55 (1.2%)	8 (0.8%)
Severe‡	0	1 (0.1%)	1 (< 0.1%)	0	0	2 (< 0.1%)	0
Drug-related	63 (2.9%)	35 (4.3%)	69 (3.2%)	36 (2.8%)	2 (1.2%)	142 (3.2%)	33 (3.4%)
Blood glucose increased	**115 (5.4%)**	**39 (4.8%)**	**122 (5.7%)**	**46 (3.5%)**	**0**	**207 (4.7%)**	**73 (7.6%)**
Mild	113 (5.3%)	38 (4.7%)	121 (5.7%)	46 (3.5%)	0	205 (4.6%)	73 (7.6%)
Moderate	2 (0.1%)	1 (0.1%)	1 (< 0.1%)	0	0	2 (< 0.1%)	0
Severe‡	0	0	0	0	0	0	0
Drug-related	7 (0.3%)	4 (0.5%)	6 (0.3%)	4 (0.3%)	0	14 (0.3%)	3 (0.3%)
GGT increased	**53 (2.5%)**	**29 (3.6%)**	**63 (3.0%)**	**40 (3.1%)**	**4 (2.4%)**	**136 (3.1%)**	**44 (4.6%)**
Mild	50 (2.3%)	26 (3.2%)	58 (2.7%)	33 (2.5%)	2 (1.2%)	119 (2.7%)	42 (4.4%)
Moderate	2 (0.1%)	2 (0.2%)	4 (0.2%)	7 (0.5%)	2 (1.2%)	15 (0.3%)	2 (0.2%)
Severe‡	1 (< 0.1%)	1 (0.1%)	1 (< 0.1%)	0	0	2 (< 0.1%)	0
Drug-related	19 (0.9%)	14 (1.7%)	30 (1.4%)	18 (1.4%)	2 (1.2%)	64 (1.4%)	11 (1.1%)
Headache	**60 (2.8%)**	**24 (3.0%)**	**66 (3.1%)**	**35 (2.7%)**	**6 (3.6%)**	**131 (3.0%)**	**30 (3.1%)**
Mild	39 (1.8%)	20 (2.5%)	43 (2.0%)	23 (1.8%)	2 (1.2%)	88 (2.0%)	18 (1.9%)
Moderate	16 (0.7%)	3 (0.4%)	20 (0.9%)	9 (0.7%)	4 (2.4%)	36 (0.8%)	10 (1.0%)
Severe‡	5 (0.2%)	1 (0.1%)	3 (0.1%)	3 (0.2%)	0	7 (0.2%)	2 (0.2%)
Drug-related	25 (1.2%)	11 (1.4%)	34 (1.6%)	19 (1.5%)	3 (1.8%)	67 (1.5%)	14 (1.5%)

The sponsor also presented a summary of TEAEs in the long-term population from the European Union and North America (EU/NA) long-term population; note that this data is derived from studies that lacked a placebo control group, so interpretation is difficult.

Table 73. SAE, TEAE and TEAE leading to Discontinuation of Study Drug, EU/NA Long-term Controlled Population

n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total (n = 1632)	Tolterodine ER 4 mg (n = 812)
SAE	42 (5.2%)	51 (6.2%)	93 (5.7%)	44 (5.4%)
Drug-related SAE†	10 (1.2%)	4 (0.5%)	14 (0.9%)	5 (0.6%)
TEAE	485 (59.7%)	503 (61.3%)	988 (60.5%)	508 (62.6%)
Drug-related TEAE†	213 (26.2%)	192 (23.4%)	405 (24.8%)	224 (27.6%)
TEAE leading to permanent d/c of study drug	48 (5.9%)	50 (6.1%)	98 (6.0%)	46 (5.7%)
Drug-related TEAE leading to permanent d/c of study drug†	35 (4.3%)	29 (3.5%)	64 (3.9%)	31 (3.8%)

Table 74. TEAE by Preferred Term (Reported by ≥3.0% in the Total Mirabegron Group), EU/NA Long-term Controlled Population

MedDRA v12.1 PT†, n (%) of Patients	Mirabegron			Tolterodine ER 4 mg (n = 812)
	50 mg (n = 812)	100 mg (n = 820)	Total Mirabegron (n = 1632)	
Overall	**485 (59.7%)**	**503 (61.3%)**	**988 (60.5%)**	**508 (62.6%)**
Mild	222 (27.3%)	240 (29.3%)	462 (28.3%)	251 (30.9%)
Moderate	212 (26.1%)	211 (25.7%)	423 (25.9%)	218 (26.8%)
Severe‡	51 (6.3%)	52 (6.3%)	103 (6.3%)	39 (4.8%)
Drug-related	213 (26.2%)	192 (23.4%)	405 (24.8%)	224 (27.6%)
Hypertension	**75 (9.2%)**	**80 (9.8%)**	**155 (9.5%)**	**78 (9.6%)**
Mild	61 (7.5%)	64 (7.8%)	125 (7.7%)	61 (7.5%)
Moderate	14 (1.7%)	15 (1.8%)	29 (1.8%)	17 (2.1%)
Severe‡	0	1 (0.1%)	1 (0.1%)	0
Drug-related	43 (5.3%)	50 (6.1%)	93 (5.7%)	42 (5.2%)
UTI	**48 (5.9%)**	**45 (5.5%)**	**93 (5.7%)**	**52 (6.4%)**
Mild	31 (3.8%)	27 (3.3%)	58 (3.6%)	44 (5.4%)
Moderate	16 (2.0%)	16 (2.0%)	32 (2.0%)	8 (1.0%)
Severe‡	1 (0.1%)	2 (0.2%)	3 (0.2%)	0
Drug-related	5 (0.6%)	7 (0.9%)	12 (0.7%)	9 (1.1%)
Nasopharyngitis	**32 (3.9%)**	**35 (4.3%)**	**67 (4.1%)**	**25 (3.1%)**
Mild	20 (2.5%)	22 (2.7%)	42 (2.6%)	17 (2.1%)
Moderate	11 (1.4%)	10 (1.2%)	21 (1.3%)	7 (0.9%)
Severe‡	1 (0.1%)	3 (0.4%)	4 (0.2%)	1 (0.1%)
Drug-related	1 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
Headache	**33 (4.1%)**	**26 (3.2%)**	**59 (3.6%)**	**20 (2.5%)**
Mild	19 (2.3%)	13 (1.6%)	32 (2.0%)	9 (1.1%)
Moderate	9 (1.1%)	12 (1.5%)	21 (1.3%)	10 (1.2%)
Severe‡	5 (0.6%)	1 (0.1%)	6 (0.4%)	1 (0.1%)
Drug-related	18 (2.2%)	14 (1.7%)	32 (2.0%)	14 (1.7%)
Back pain	**23 (2.8%)**	**29 (3.5%)**	**52 (3.2%)**	**13 (1.6%)**
Mild	10 (1.2%)	13 (1.6%)	23 (1.4%)	9 (1.1%)
Moderate	11 (1.4%)	15 (1.8%)	26 (1.6%)	4 (0.5%)
Severe ‡	2 (0.2%)	1 (0.1%)	3 (0.2%)	0
Drug-related	0	1 (0.1%)	1 (0.1%)	0

8.3.2. Treatment-related adverse events (adverse drug reactions)

As is typical for placebo-controlled studies, AEs reported in the phase 2/3 study program were classified according to whether the reporting investigator thought that study drug was likely to have played a significant causal role. The attribution of causation in such circumstances is inherently unreliable, and may merely reflect the investigators preconceived notions about the likely side effects of active treatment. Investigators may be particularly unlikely to attribute a causal role to the study drug when side effects are novel or unexpected.

The tables above include data about which AEs were considered 'drug-related' by the reporting investigator. Note that investigators often thought that AEs were drug related even when subjects were receiving placebo, and the overall incidence of drug-related AEs was similar in the active and placebo groups. The main table of interest in this regard is Table 70 above, which considers drug-related TEAEs in the global 12-week phase 2/3 population. About 1 in 5 subjects had a drug-related TEAE, with a slight excess in the active groups (20.5% overall in the pooled mirabegron population) compared to the placebo group (18.2%). As shown in the table, there was also a slight excess of discontinuations that were thought to be drug-related: this occurred in 2.4% of mirabegron recipients, compared to 1.7% of placebo recipients, an excess of 0.7% or 7 in 1000 patients.

8.3.3. Deaths and other serious adverse events

Deaths in the major study populations and in individual studies are listed in the tables below. In the global phase 2/3 population, one death occurred in a placebo recipient, and 5 in mirabegron recipients, but this difference reflects the unequal patient number assigned to active treatment

vs placebo. When expressed in deaths per 1000 patient-years of exposure (PYE), the highest mortality in the global phase 2/3 population was seen with tolterodine (3.3 deaths per 1000 PYE), followed by placebo (2.0 deaths per 1000 PYE) and then mirabegron (1.9 deaths per 1000 PYE).

Table 75. Mortality by Treatment Group

Treatment Group	Total Number of Patients †	Total Number of Deaths ‡	Patient-years of Exposure §	Mortality per 1000 PYE ¶
Global Phase 2/3 Population				
Placebo	2292	1	488.38	2.0
Total mirabegron	5863	5	2603.55	1.9
Tolterodine	1726	3††	902.54	3.3
Metformin	20	0	4.59	0.0
Global OAB Phase 2/3 Population				
Placebo	2208	1	469.36	2.1
Total mirabegron	5648	5	2555.57	2.0
Tolterodine	1726	3††	902.54	3.3
EU/NA Long-term Controlled Population				
Tolterodine/mirabegron	237	0	211.90	0.0
Mirabegron only	1395	3	1183.99	2.5
Mirabegron/tolterodine	368	2	310.30	6.4
Tolterodine only	444	0	376.03	0.0

A review of the individual causes of death, as shown in the table below, shows no concerning trends, with multiple different causes appearing. In general, investigators did not feel that study drug had played a role in the deaths, but 'possible' causation was indicated for one case of pneumonia in a mirabegron 50mg recipient, one of suicide in a mirabegron 50mg recipient, and one of a ruptured cerebral aneurysm in a tolterodine recipient.

[Information redacted]: Table 76 below has been modified from the original to remove patient numbers and age.

Table 76. Listing of Deaths

Study No. Patient No. Age/Gender	MedDRA (v12.1) Preferred Term (Investigator Verbatim Description)	Onset/ Stop Day (Last Dose Day)	Day of Death	Relationship to Study Drug	Adjudicated Term
Mirabegron					
[ ] Female Mirabegron 100 mg	Bladder cancer (bladder cancer)	38/99 (49)	99	Not related	Non-CV event
	Colon cancer metastatic (metastatic colon cancer)	38/99 (49)	99	Not related	Non-CV event
[Female Mirabegron 50 mg	Pneumonia (pneumonia)	104/108 (86 E)	108	Possible	Non-CV event
	Acute respiratory failure (acute respiratory failure)	107/108 (86 E)	108	Not related	
	Multi-organ failure (multiple organ failure)	107/108 (86 E)	108	Not related	
	Renal vein thrombosis (renal vein thrombosis)	107/108 (86 E)	108	Not related	
	Staphylococcal sepsis (staphylococcal sepsis)	107/108 (86 E)	108	Not related	
[Female Mirabegron 50 mg	Cardiac failure (cardiac failure)	190/190 (190)	190	Not related	CV death
[† Female Mirabegron 50 mg	Completed suicide (suicide patient)	359/359 (267 E)	359	Possible	Non-CV event
[] Female Mirabegron 50 mg/100 mg	Aortic dissection (aortic dissection)	237/237 (224)	237	Not related‡	CV death
Placebo					
[ ] /Female	Cardiac arrest (Cardiac arrest)	142/142 (86)	142	Not related	CV death
Tolterodine ER 4 mg					
[] /Male	Ruptured cerebral aneurysm (rupture of brain aneurysm / cerebral aneurysm)	68/70 (60)	70	Possible	CV death
[] /Female (Prior exposure to mirabegron 50 mg mirabegron for 12-weeks in Study 178-CL-047)	Coronary artery disease (probably CAD)	208/208 (208)	208	Not related	CV death
[] /Male (Prior exposure to mirabegron 100 mg for 12-weeks in Study 178-CL-047)	Cerebrovascular accident (stroke)	62/72 (62)	72	Not related	CV death
	Pneumonia aspiration (aspiration pneumonia)	62/72 (62)	72	Not related	CV death
Prior to Randomization					
(ongoing study) Female Treatment Group Blinded	Chemical poisoning (Chemical ingestion toxicity, nonaccidental)	8 days (onset from first dose of placebo)/ day 10 (event stop day) day 2 (last dose day)	17 Jun 2010	Not related	Non-CV event
(ongoing study) /Male	Sudden death (sudden death)	45 days (onset from first dose)/ day 45 (event stop day) day 44 (last dose day)	14 Jul 2010	Not related	CV death

Relationship to study drug is assessed by investigator. CAD: coronary artery disease; CV: cardiovascular; E: estimated value; ER: extended release; SAP: Statistical Analysis Plan. † Last dose day for this patient was unknown. Based on the estimated last dose day (per SAP imputation rules), the death was non-treatment-emergent. ‡ Investigator's causality determination: there was insufficient information at the time of the event because the subject was dead on arrival at the hospital, and the Sponsor concluded that the event (aortic dissection), which occurred during study treatment, was not completely unrelated to the study drug.

The incidence of serious AEs (SAEs) in the global 12-week phase 2/3 population were listed in Table 70 above. There was no notable overall difference between the incidence of SAEs in the placebo group (1.8%) versus the pooled mirabegron group (1.7%). At the proposed dose of 50mg, the incidence of SAEs was mildly lower (1.6%) than in the placebo group, and at 25mg the incidence was even lower (1.4%), whereas at 100mg the incidence was slightly higher (2.2%) than in the placebo group. Considering the subgroup of SAEs that were considered potentially 'drug-related', the incidence was similar across the placebo group (0.4%), the pooled mirabegron group (0.4%) and the individual dose groups (0.5%, 0.4%, 0.4% and 0% across the 25mg, 50mg, 100mg and 200mg dose groups, respectively).

The individual SAEs reported by two or more patients in the pooled mirabegron group of the 12-week phase 2/3 population are summarised below, under organ/system headings and individual AE designations. There was no overall pattern in the distribution of SAEs. Cardiac SAEs were reported in 10 mirabegron recipients (0.2%), which was a slightly lower proportion than that observed in the placebo group (0.3%). Neoplasms were observed in a slightly higher proportion of mirabegron recipients (0.2%) than placebo recipients (0.1%), but the comparison is based on few individual cases. Given the long lead time required to produce a tumour after exposure to a carcinogenic agent, it seems very unlikely that a 12-week study would be able to detect such a risk. In the long-term study, the incidence of neoplasms was 0.7%, and the most common neoplasms were breast, lung and prostate cancer, which occurred in two patients each. These are common cancers in the general aged population.

Table 77. SAE (Reported by ≥ 2 Patients in the Total Mirabegron Group), Global OAB 12-Week Phase 2/3 Population

MedDRA v12.1 SOC PT†, n (%) of Patients	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Mirabegron Total Mirabegron (n = 4414)	Tolt ER 4 mg (n = 958)
Overall	38 (1.8%)	11 (1.4%)	34 (1.6%)	29 (2.2%)	3 (1.8%)	77 (1.7%)	16 (1.7%)
Cardiac disorders	6 (0.3%)	1 (0.1%)	5 (0.2%)	4 (0.3%)	0	10 (0.2%)	1 (0.1%)
Atrial fibrillation	1 (< 0.1%)	0	3 (0.1%)	2 (0.2%)	0	5 (0.1%)	0
Cardiac failure	0	1 (0.1%)	0	1 (0.1%)	0	2 (< 0.1%)	0
General disorders and administration site conditions	3 (0.1%)	1 (0.1%)	0	3 (0.2%)	0	4 (0.1%)	0
Chest pain	2 (0.1%)	1 (0.1%)	0	3 (0.2%)	0	4 (0.1%)	0
Infections and infestations	6 (0.3%)	2 (0.2%)	9 (0.4%)	3 (0.2%)	2 (1.2%)	16 (0.4%)	2 (0.2%)
Pneumonia	1 (< 0.1%)	0	2 (0.1%)	0	2 (1.2%)	4 (0.1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.1%)	1 (0.1%)	4 (0.2%)	3 (0.2%)	0	8 (0.2%)	1 (0.1%)
Prostate cancer	0	0	2 (0.1%)	0	0	2 (< 0.1%)	0
Surgical and medical procedures	3 (0.1%)	0	2 (0.1%)	2 (0.2%)	0	4 (0.1%)	1 (0.1%)
Bunion operation	0	0	0	2 (0.2%)	0	2 (< 0.1%)	0

Table 78. SAE (Reported by ≥ 2 Patients in the Total Mirabegron Group), EU/NA Long-Term Controlled Population

MedDRA v12.1 SOC PT+, n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Total Mirabegron (n = 1632)	Tolterodine ER 4 mg (n = 812)
Overall	42 (5.2%)	51 (6.2%)	93 (5.7%)	44 (5.4%)
Cardiac disorders	8 (1.0%)	2 (0.2%)	10 (0.6%)	8 (1.0%)
Atrial fibrillation	2 (0.2%)	0	2 (0.1%)	3 (0.4%)
Gastrointestinal disorders	3 (0.4%)	7 (0.9%)	10 (0.6%)	2 (0.2%)
Gastritis	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Upper gastrointestinal haemorrhage	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Infections and infestations	5 (0.6%)	3 (0.4%)	8 (0.5%)	3 (0.4%)
Abscess intestinal	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Investigations	1 (0.1%)	3 (0.4%)	4 (0.2%)	0
Liver function test abnormal	0	2 (0.2%)	2 (0.1%)	0
Musculoskeletal and connective tissue disorders	3 (0.4%)	5 (0.6%)	8 (0.5%)	2 (0.2%)
Osteoarthritis	2 (0.2%)	1 (0.1%)	3 (0.2%)	1 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.1%)	11 (1.3%)	12 (0.7%)	4 (0.5%)
Breast cancer	0	2 (0.2%)	2 (0.1%)	2 (0.2%)
Lung neoplasm malignant	0	2 (0.2%)	2 (0.1%)	0
Prostate cancer	0	2 (0.2%)	2 (0.1%)	0
Nervous system disorders	5 (0.6%)	2 (0.2%)	7 (0.4%)	5 (0.6%)
Cerebrovascular accident	3 (0.4%)	0	3 (0.2%)	1 (0.1%)
Renal and urinary disorders	1 (0.1%)	5 (0.6%)	6 (0.4%)	3 (0.4%)
Uterine polyp	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Surgical and medical procedures	2 (0.2%)	7 (0.9%)	9 (0.6%)	3 (0.4%)
Hysterectomy	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Vascular disorders	4 (0.5%)	1 (0.1%)	5 (0.3%)	2 (0.2%)
Hypertension	1 (0.1%)	1 (0.1%)	2 (0.1%)	0

8.3.4. Discontinuation due to adverse events

Discontinuations due to adverse events were shown in Table 70, seen earlier. In the 12-week phase 2/3 population, there was a slight excess of discontinuations in the pooled mirabegron group (3.6%) than the placebo group (2.9%), amounting to 0.7% or 7 patients per 1000. When longer studies are included, as in Table 81 below, the incidence of discontinuations due to AEs was slightly higher (4.9% in the pooled mirabegron group). The types of AEs leading to discontinuation are shown in Table 79 (global phase 2/3 population) and Table 80 (12-week phase 2/3 population). As shown in Table 79, most individual types of AE leading to discontinuations occurred with an incidence ≤ 0.1%, with the exception of constipation (0.3%), nausea (0.2%), dizziness (0.2%), headache (0.3%) and hypertension (0.3%). The results in the 12-week phase 2/3 population (Table 80) were similar; the inclusion of a placebo comparator in this group shows that gastrointestinal intolerance, including nausea, was more common with placebo than with mirabegron.

Table 79. TEAE Leading to Permanent Discontinuation of Study Drug (Reported by ≥ 0.1% in the Total Mirabegron Group), Global Phase 2/3 Population

MedDRA v12.1 SOC PT†, n (%) of Patients	Total Mirabegron (n = 5863)
Overall	285 (4.9%)
Cardiac disorders	27 (0.5%)
Atrial fibrillation	3 (0.1%)
Palpitations	8 (0.1%)
Tachycardia	5 (0.1%)
Ear and labyrinth disorders	5 (0.1%)
Vertigo	3 (0.1%)
Eye disorders	13 (0.2%)
Dry eye	3 (0.1%)
Vision blurred	5 (0.1%)
Gastrointestinal disorders	64 (1.1%)
Abdominal pain	4 (0.1%)
Abdominal pain upper	6 (0.1%)
Constipation	17 (0.3%)
Diarrhoea	6 (0.1%)
Dry mouth	8 (0.1%)
Dyspepsia	4 (0.1%)
Gastritis	4 (0.1%)
Nausea	14 (0.2%)
Vomiting	7 (0.1%)
General disorders and administration site conditions	30 (0.5%)
Chest pain	3 (0.1%)
Fatigue	6 (0.1%)
Malaise	4 (0.1%)
Oedema peripheral	4 (0.1%)
Immune system disorders	4 (0.1%)
Hypersensitivity	3 (0.1%)
Infections and infestations	16 (0.3%)
Pneumonia	3 (0.1%)
UTI	3 (0.1%)
Investigations	24 (0.4%)
ALT increased	6 (0.1%)
AST increased	5 (0.1%)
Blood pressure increased	4 (0.1%)
GGT increased	4 (0.1%)
Liver function test abnormal	4 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (0.2%)
Prostate cancer	3 (0.1%)
Nervous system disorders	42 (0.7%)
Dizziness	13 (0.2%)
Headache	20 (0.3%)
Psychiatric disorders	9 (0.2%)
Depression	4 (0.1%)
Skin and subcutaneous tissue disorders	32 (0.5%)
Dermatitis allergic	4 (0.1%)
Pruritus	3 (0.1%)
Rash	8 (0.1%)
Urticaria	5 (0.1%)
Vascular disorders	22 (0.4%)
Hypertension	16 (0.3%)

Table 80. TEAE Leading to Permanent Discontinuation of Study Drug (Reported by ≥0.1% in the Total Mirabegron Group), Global OAB 12-Week Phase 2/3 Population

MedDRA v12.1 SOC PT†, n (%) of Patients	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Total Mira (n = 4414)	Tolt ER 4 mg (n = 958)
Overall	63 (2.9%)	31 (3.8%)	75 (3.5%)	47 (3.6%)	7 (4.2%)	160 (3.6%)	36 (3.8%)
Cardiac disorders	4 (0.2%)	2 (0.2%)	8 (0.4%)	7 (0.5%)	0	17 (0.4%)	3 (0.3%)
Atrial fibrillation	1 (< 0.1%)	0	2 (0.1%)	1 (0.1%)	0	3 (0.1%)	0
Palpitations	2 (0.1%)	1 (0.1%)	1 (< 0.1%)	3 (0.2%)	0	5 (0.1%)	1 (0.1%)
Tachycardia	0	1 (0.1%)	3 (0.1%)	1 (0.1%)	0	5 (0.1%)	0
Gastrointestinal disorders	18 (0.8%)	7 (0.9%)	18 (0.8%)	6 (0.5%)	2 (1.2%)	33 (0.7%)	12 (1.3%)
Abdominal pain upper	0	2 (0.2%)	1 (< 0.1%)	0	1 (0.6%)	4 (0.1%)	1 (0.1%)
Constipation	3 (0.1%)	1 (0.1%)	3 (0.1%)	3 (0.2%)	0	7 (0.2%)	2 (0.2%)
Diarrhoea	1 (< 0.1%)	0	4 (0.2%)	0	0	4 (0.1%)	2 (0.2%)
Dyspepsia	1 (< 0.1%)	1 (0.1%)	2 (0.1%)	0	0	3 (0.1%)	0
Nausea	10 (0.5%)	1 (0.1%)	4 (0.2%)	1 (0.1%)	0	6 (0.1%)	0
Vomiting	3 (0.1%)	2 (0.2%)	3 (0.1%)	0	0	5 (0.1%)	1 (0.1%)
General disorders and administration site conditions	6 (0.3%)	3 (0.4%)	10 (0.5%)	6 (0.5%)	1 (0.6%)	20 (0.5%)	5 (0.5%)
Chest pain	3 (0.1%)	1 (0.1%)	1 (< 0.1%)	0	1 (0.6%)	3 (0.1%)	0
Malaise	1 (< 0.1%)	0	2 (0.1%)	2 (0.2%)	0	4 (0.1%)	2 (0.2%)
Oedema peripheral	1 (< 0.1%)	0	2 (0.1%)	1 (0.1%)	0	3 (0.1%)	0
Investigations	3 (0.1%)	5 (0.6%)	7 (0.3%)	5 (0.4%)	0	17 (0.4%)	0
ALT increased	1 (< 0.1%)	1 (0.1%)	2 (0.1%)	2 (0.2%)	0	5 (0.1%)	0
AST increased	0	0	2 (0.1%)	2 (0.2%)	0	4 (0.1%)	0
Blood pressure increased	1 (< 0.1%)	0	1 (< 0.1%)	2 (0.2%)	0	3 (0.1%)	0
GGT increased	2 (0.1%)	0	2 (0.1%)	2 (0.2%)	0	4 (0.1%)	0
Nervous system disorders	12 (0.6%)	5 (0.6%)	10 (0.5%)	7 (0.5%)	0	22 (0.5%)	5 (0.5%)
Dizziness	3 (0.1%)	2 (0.2%)	3 (0.1%)	1 (0.1%)	0	6 (0.1%)	1 (0.1%)
Headache	5 (0.2%)	1 (0.1%)	6 (0.3%)	4 (0.3%)	0	11 (0.2%)	2 (0.2%)
Skin and subcutaneous tissue disorders	3 (0.1%)	2 (0.2%)	8 (0.4%)	8 (0.6%)	2 (1.2%)	20 (0.5%)	2 (0.2%)
Rash	0	1 (0.1%)	2 (0.1%)	1 (0.1%)	0	4 (0.1%)	0
Vascular disorders	3 (0.1%)	4 (0.5%)	6 (0.3%)	3 (0.2%)	0	13 (0.3%)	2 (0.2%)
Hypertension	2 (0.1%)	3 (0.4%)	4 (0.2%)	3 (0.2%)	0	10 (0.2%)	1 (0.1%)

Table 81 lists discontinuations in the long-term EU/NA population for both mirabegron and tolterodine. Overall, discontinuations occurred with similar frequency in the total mirabegron group (6.0%) and the tolterodine group (5.7%). Of the more common types of AE leading to discontinuation, most occurred with similar frequency in the mirabegron and tolterodine groups, including headache and hypertension, but not dizziness, which was only seen in the mirabegron and placebo groups.

Table 81. TEAE Leading to Permanent Discontinuation of Study Drug (Reported by ≥ 2 Patients in the Total Mirabegron Group), EU/NA Long-Term Controlled Population

MedDRA v12.1 SOC PT†, n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total Mirabegron (n = 1632)	Tolterodine ER 4 mg (n = 812)
Overall	48 (5.9%)	50 (6.1%)	98 (6.0%)	46 (5.7%)
Cardiac disorders	4 (0.5%)	4 (0.5%)	8 (0.5%)	7 (0.9%)
Palpitations	0	2 (0.2%)	2 (0.1%)	0
Ear and labyrinth disorders	0	2 (0.2%)	2 (0.1%)	2 (0.2%)
Vertigo	0	2 (0.2%)	2 (0.1%)	1 (0.1%)
Eye disorders	5 (0.6%)	3 (0.4%)	8 (0.5%)	3 (0.4%)
Dry eye	3 (0.4%)	0	3 (0.2%)	1 (0.1%)
Vision blurred	3 (0.4%)	1 (0.1%)	4 (0.2%)	1 (0.1%)
Gastrointestinal disorders	14 (1.7%)	9 (1.1%)	23 (1.4%)	11 (1.4%)
Abdominal pain	1 (0.1%)	2 (0.2%)	3 (0.2%)	0
Abdominal pain upper	1 (0.1%)	1 (0.1%)	2 (0.1%)	3 (0.4%)
Constipation	7 (0.9%)	2 (0.2%)	9 (0.6%)	0
Dry mouth	3 (0.4%)	1 (0.1%)	4 (0.2%)	4 (0.5%)
Gastritis	2 (0.2%)	0	2 (0.1%)	1 (0.1%)
Nausea	3 (0.4%)	2 (0.2%)	5 (0.3%)	1 (0.1%)
General disorders and administration site conditions	4 (0.5%)	5 (0.6%)	9 (0.6%)	2 (0.2%)
Fatigue	1 (0.1%)	3 (0.4%)	4 (0.2%)	1 (0.1%)
Pain	2 (0.2%)	0	2 (0.1%)	0
Infections and infestations	6 (0.7%)	2 (0.2%)	8 (0.5%)	3 (0.4%)
UTI	3 (0.4%)	0	3 (0.2%)	1 (0.1%)
Investigations	1 (0.1%)	3 (0.4%)	4 (0.2%)	4 (0.5%)
Liver function test abnormal	0	2 (0.2%)	2 (0.1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	7 (0.9%)	7 (0.4%)	1 (0.1%)
Lung neoplasm malignant	0	2 (0.2%)	2 (0.1%)	0
Prostate cancer	0	2 (0.2%)	2 (0.1%)	0
Nervous system disorders	10 (1.2%)	8 (1.0%)	18 (1.1%)	10 (1.2%)
Dizziness	4 (0.5%)	2 (0.2%)	6 (0.4%)	0
Headache	5 (0.6%)	4 (0.5%)	9 (0.6%)	3 (0.4%)
Renal and urinary disorders	2 (0.2%)	4 (0.5%)	6 (0.4%)	4 (0.5%)
Dysuria	0	2 (0.2%)	2 (0.1%)	0
Skin and subcutaneous tissue disorders	2 (0.2%)	5 (0.6%)	7 (0.4%)	1 (0.1%)
Pruritus	0	2 (0.2%)	2 (0.1%)	0
Rash	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Urticaria	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Vascular disorders	4 (0.5%)	3 (0.4%)	7 (0.4%)	4 (0.5%)
Hypertension	4 (0.5%)	2 (0.2%)	6 (0.4%)	3 (0.4%)

8.3.5. Adverse events of particular interest

8.3.5.1. Postural hypotension and falls

The incidence of postural hypotension and falls was infrequent with both active treatment and placebo, as shown in the table below.

Table 82. Syncope, Postural Hypotension and Falls TEAE, Global OAB 12-Week Phase 2/3 Population

MedDRA v12.1 CATEGORY, n (%) of Patients	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Mirabegron Total Mirabegron (n = 4414)	Tolterodine ER 4 mg (n = 958)
Overall	35 (1.6%)	20 (2.5%)	47 (2.2%)	20 (1.5%)	3 (1.8%)	90 (2.0%)	14 (1.5%)
SYNCOPE	2 (0.1%)	2 (0.2%)	2 (0.1%)	0	0	4 (0.1%)	0
POSTURAL HYPOTENSION	1 (< 0.1%)	1 (0.1%)	0	0	0	1 (< 0.1%)	0
FALLS	32 (1.5%)	17 (2.1%)	46 (2.2%)	20 (1.5%)	3 (1.8%)	86 (1.9%)	14 (1.5%)

Table 83. Syncope, Postural Hypotension and Falls TEAE, EU/NA Long-Term Controlled Population

MedDRA v12.1 CATEGORY, n (%) of Patients	Mirabegron			Tolterodine ER 4 mg (n = 812)
	50 mg (n = 812)	100 mg (n = 820)	Total Mirabegron (n = 1632)	
Overall	40 (4.9%)	30 (3.7%)	70 (4.3%)	41 (5.0%)
SYNCOPE	2 (0.2%)	0	2 (0.1%)	2 (0.2%)
POSTURAL HYPOTENSION	1 (0.1%)	0	1 (0.1%)	0
FALLS	38 (4.7%)	30 (3.7%)	68 (4.2%)	40 (4.9%)

8.3.5.2. Urinary AEs

Urinary AEs, including urinary retention, occurred with a low incidence in all treatment groups, with no substantial differences between active treatment and placebo, as shown below.

Table 84. Urinary Tract Infection TEAE, Global OAB 12-Week Phase 2/3 Population

MedDRA v12.1 SOC HLT PT†, n (%) of Patients	Placebo (n = 2142)	Mirabegron					Tolt ER 4 mg (n = 958)
		25 mg (n = 811)	50 mg (n = 2131)	100 mg (n = 1305)	200 mg (n = 167)	Total Mira (n = 4414)	
Overall	65 (3.0%)	48 (5.9%)	85 (4.0%)	48 (3.7%)	10 (6.0%)	191 (4.3%)	42 (4.4%)
Infections and infestations	55 (2.6%)	42 (5.2%)	78 (3.7%)	39 (3.0%)	7 (4.2%)	166 (3.8%)	36 (3.8%)
Bacterial infections NEC	1 (< 0.1%)	4 (0.5%)	3 (0.1%)	2 (0.2%)	0	9 (0.2%)	1 (0.1%)
Bacteriuria	1 (< 0.1%)	3 (0.4%)	2 (0.1%)	2 (0.2%)	0	7 (0.2%)	1 (0.1%)
UTI bacterial	0	1 (0.1%)	1 (< 0.1%)	0	0	2 (< 0.1%)	0
UTIs	52 (2.4%)	38 (4.7%)	75 (3.5%)	37 (2.8%)	7 (4.2%)	157 (3.6%)	35 (3.7%)
Cystitis	21 (1.0%)	10 (1.2%)	32 (1.5%)	11 (0.8%)	2 (1.2%)	55 (1.2%)	21 (2.2%)
Pyelonephritis acute	0	1 (0.1%)	0	0	0	1 (< 0.1%)	1 (0.1%)
Urethritis	0	0	0	0	1 (0.6%)	1 (< 0.1%)	0
UTI	30 (1.4%)	29 (3.6%)	43 (2.0%)	27 (2.1%)	4 (2.4%)	103 (2.3%)	13 (1.4%)
Investigations	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Urinalysis NEC	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Nitrite urine present	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Musculoskeletal and connective tissue disorders	3 (0.1%)	1 (0.1%)	3 (0.1%)	1 (0.1%)	0	5 (0.1%)	0
Musculoskeletal and connective tissue pain and discomfort	3 (0.1%)	1 (0.1%)	3 (0.1%)	1 (0.1%)	0	5 (0.1%)	0
Flank pain	3 (0.1%)	1 (0.1%)	3 (0.1%)	1 (0.1%)	0	5 (0.1%)	0
Renal and urinary disorders	8 (0.4%)	5 (0.6%)	6 (0.3%)	10 (0.8%)	3 (1.8%)	24 (0.5%)	8 (0.8%)
Bladder and urethral symptoms	7 (0.3%)	4 (0.5%)	6 (0.3%)	10 (0.8%)	0	20 (0.5%)	7 (0.7%)
Bladder pain	1 (< 0.1%)	2 (0.2%)	0	1 (0.1%)	0	3 (0.1%)	1 (0.1%)
Dysuria	5 (0.2%)	2 (0.2%)	6 (0.3%)	9 (0.7%)	0	17 (0.4%)	6 (0.6%)
Urethral pain	1 (< 0.1%)	1 (0.1%)	0	0	0	1 (< 0.1%)	0
Genitourinary tract infections and inflammations NEC	0	0	0	0	2 (1.2%)	2 (< 0.1%)	0
Urinary tract inflammation	0	0	0	0	2 (1.2%)	2 (< 0.1%)	0
Urinary abnormalities	1 (< 0.1%)	1 (0.1%)	0	0	1 (0.6%)	2 (< 0.1%)	1 (0.1%)
Leukocyturia	1 (< 0.1%)	1 (0.1%)	0	0	1 (0.6%)	2 (< 0.1%)	1 (0.1%)

Table 85. Urinary Tract Infection TEAE, EU/NA Long-Term Controlled Population

MedDRA v12.1 SOC HLT PT†, n (%) of Patients	Mirabegron			Tolterodine ER 4 mg (n = 812)
	50 mg (n = 812)	100 mg (n = 820)	Total Mirabegron (n = 1632)	
Overall	74 (9.1%)	69 (8.4%)	143 (8.8%)	81 (10.0%)
Infections and infestations	65 (8.0%)	56 (6.8%)	121 (7.4%)	76 (9.4%)
Bacterial infections NEC	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
Bacteriuria	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
Escherichia infections	1 (0.1%)	1 (0.1%)	2 (0.1%)	2 (0.2%)
Escherichia UTI	1 (0.1%)	1 (0.1%)	2 (0.1%)	2 (0.2%)
UTIs	64 (7.9%)	55 (6.7%)	119 (7.3%)	73 (9.0%)
Cystitis	17 (2.1%)	11 (1.3%)	28 (1.7%)	19 (2.3%)
Kidney infection	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
Pyelonephritis acute	0	1 (0.1%)	1 (0.1%)	0
UTI	48 (5.9%)	45 (5.5%)	93 (5.7%)	52 (6.4%)
Investigations	1 (0.1%)	0	1 (0.1%)	0
Urinalysis NEC	1 (0.1%)	0	1 (0.1%)	0
White blood cells urine positive	1 (0.1%)	0	1 (0.1%)	0
Musculoskeletal and connective tissue disorders	0	1 (0.1%)	1 (0.1%)	2 (0.2%)
Musculoskeletal and connective tissue pain and discomfort	0	1 (0.1%)	1 (0.1%)	2 (0.2%)
Flank pain	0	1 (0.1%)	1 (0.1%)	2 (0.2%)
Renal and urinary disorders	11 (1.4%)	15 (1.8%)	26 (1.6%)	4 (0.5%)
Bladder and urethral symptoms	7 (0.9%)	7 (0.9%)	14 (0.9%)	4 (0.5%)
Dysuria	7 (0.9%)	6 (0.7%)	13 (0.8%)	4(0.5%)
Urethral pain	0	1 (0.1%)	1 (0.1%)	0
Urinary abnormalities	4 (0.5%)	9 (1.1%)	13 (0.8%)	0
Leukocyturia	3 (0.4%)	9 (1.1%)	12 (0.7%)	0
Pyuria	1 (0.1%)	0	1 (0.1%)	0

Table 86. Urinary Retention TEAE, Global OAB 12-Week Phase 2/3 Population

MedDRA v12.1 SOC HLT PT, n (%) of Patients LLT†	Placebo (n = 2142)	Mirabegron					Tolterodine ER 4 mg (n = 958)
		25 mg (n = 811)	50 mg (n = 2131)	100 mg (n = 1305)	200 mg (n = 167)	Total Mirabegron (n = 4414)	
Overall	7 (0.3%)	0	1 (< 0.1%)	0	1 (0.6%)	2 (< 0.1%)	3 (0.3%)
Investigations	1 (< 0.1%)	0	0	0	0	0	0
Urinary tract function analyses NEC	1 (< 0.1%)	0	0	0	0	0	0
Residual urine volume increased	1 (< 0.1%)	0	0	0	0	0	0
Residual urine volume increased	1 (< 0.1%)	0	0	0	0	0	0
Renal and urinary disorders	6 (0.3%)	0	1 (< 0.1%)	0	1 (0.6%)	2 (< 0.1%)	3 (0.3%)
Bladder and urethral symptoms	6 (0.3%)	0	1 (< 0.1%)	0	1 (0.6%)	2 (< 0.1%)	3 (0.3%)
Urinary retention	6 (0.3%)	0	1 (< 0.1%)	0	1 (0.6%)	2 (< 0.1%)	3 (0.3%)
Acute retention of urine	3 (0.1%)	0	1 (< 0.1%)	0	0	1 (< 0.1%)	3 (0.3%)
Urinary retention	3 (0.1%)	0	0	0	1 (0.6%)	1 (< 0.1%)	0

Table 87. Urinary Retention, EU/NA Long-Term Controlled Population

MedDRA v12.1 SOC HLT PT, n (%) of Patients LLT†	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total Mirabegron (n = 1632)	Tolterodine ER 4 mg (n = 812)
Overall	1 (0.1%)	1 (0.1%)	2 (0.1%)	3 (0.4%)
Renal and urinary disorders	1 (0.1%)	1 (0.1%)	2 (0.1%)	3 (0.4%)
Bladder and urethral symptoms	1 (0.1%)	1 (0.1%)	2 (0.1%)	3 (0.4%)
Urinary retention	1 (0.1%)	1 (0.1%)	2 (0.1%)	3 (0.4%)
Acute retention of urine	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
Bladder inability to empty	0	0	0	1 (0.1%)
Urinary retention	1 (0.1%)	0	1 (0.1%)	1 (0.1%)

Table 88. Combined Summary of Urinary Retention, Based on TEAE and Post-Void Residual Volume Measured During Baseline and Postbaseline, Global OAB 12-Week Phase 2/3 Population

Type of Event Event, n (%) of Patients	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Mirabegron Total Mira (n = 4414)	Tolt ER 4 mg (n = 958)
Any urinary retention	15 (0.7%)	0	6 (0.3%)	4 (0.3%)	1 (0.6%)	11 (0.2%)	6 (0.6%)
Urinary retention as TEAE	7 (0.3%)	0	1 (< 0.1%)	0	1 (0.6%)	2 (< 0.1%)	3 (0.3%)
Residual urine volume increased	1 (< 0.1%)	0	0	0	0	0	0
Urinary retention	6 (0.3%)	0	1 (< 0.1%)	0	1 (0.6%)	2 (< 0.1%)	3 (0.3%)
Urinary retention as TEAE and any PVR change from baseline ≥ 150 mL	**2 (0.1%)**	**0**	**0**	**0**	**0**	**0**	**1 (0.1%)**
Urinary retention as TEAE and all PVR change from baseline < 150 mL	4 (0.2%)	0	0	0	1 (0.6%)	1 (< 0.1%)	1 (0.1%)
Urinary retention as TEAE and unknown PVR change from baseline	1 (< 0.1%)	0	1 (< 0.1%)	0	0	1 (< 0.1%)	1 (0.1%)
PVR change from baseline ≥ 150 mL	10 (0.5%)	0	5 (0.2%)	4 (0.3%)	0	9 (0.2%)	4 (0.4%)

Table 89. Urolithiasis TEAE, Global OAB 12-Week Phase 2/3 Population

MedDRA v12.1 SOC HLT PT†, n (%) of Patients	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Mirabegron Total Mira (n = 4414)	Tolt ER 4 mg (n = 958)
Overall	1 (< 0.1%)	3 (0.4%)	3 (0.1%)	2 (0.2%)	0	8 (0.2%)	0
Renal and urinary disorders	1 (< 0.1%)	3 (0.4%)	3 (0.1%)	2 (0.2%)	0	8 (0.2%)	0
Renal lithiasis	1 (< 0.1%)	3 (0.4%)	2 (0.1%)	1 (0.1%)	0	6 (0.1%)	0
Nephrolithiasis	1 (< 0.1%)	3 (0.4%)	2 (0.1%)	1 (0.1%)	0	6 (0.1%)	0
Urinary tract lithiasis (excl renal)	0	0	1 (< 0.1%)	2 (0.2%)	0	3 (0.1%)	0
Calculus ureteric	0	0	1 (< 0.1%)	1 (0.1%)	0	2 (< 0.1%)	0
Calculus urinary	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Urinary tract signs and symptoms NEC	0	0	1 (< 0.1%)	1 (0.1%)	0	2 (< 0.1%)	0
Renal colic	0	0	1 (< 0.1%)	1 (0.1%)	0	2 (< 0.1%)	0

Table 90. Urolithiasis TEAE, EU/NA Long-Term Controlled Population

MedDRA v12.1 SOC HLT PT†, n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total Mirabegron (n = 1632)	Tolterodine ER 4 mg (n = 812)
Overall	2 (0.2%)	3 (0.4%)	5 (0.3%)	4 (0.5%)
Renal and urinary disorders	2 (0.2%)	3 (0.4%)	5 (0.3%)	4 (0.5%)
Renal lithiasis	1 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
Nephrolithiasis	1 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
Renal obstructive disorders	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
Hydronephrosis	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
Urinary tract lithiasis (excl renal)	0	0	0	2 (0.2%)
Calculus ureteric	0	0	0	2 (0.2%)
Urinary tract signs and symptoms NEC	1 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
Renal colic	1 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)

8.4. Laboratory tests

8.4.1. Liver function

Liver function tests in the phase 2/3 studies did not suggest that mirabegron is prone to causing hepatotoxicity. In mirabegron recipients, mean shifts from baseline in ALT, AST, and ALP were generally minor and similar to those observed in placebo recipients. Table 91 shows the mean shifts observed with each treatment in the pooled 12-week global OAB phase 2/3 population, and Table 92 shows the mean shifts in the long-term EU/NA population.

Table 91. Hepatic Laboratory Test Results, Global OAB 12-Week Phase 2/3 Population

Laboratory Parameter (Units)	Placebo (n = 2142)	Mirabegron				Tolterodine ER 4 mg (n = 958)
		25 mg (n = 811)	50 mg (n = 2131)	100 mg (n = 1305)	200 mg (n = 167)	
ALT (U/L)						
Baseline						
n	2142	811	2130	1305	167	958
Mean (SD)	20.4 (10.38)	20.7 (9.17)	20.8 (10.27)	21.3 (11.43)	19.9 (8.82)	20.5 (10.55)
Change from baseline to Final Visit						
n	2087	792	2078	1273	166	939
Mean (SD)	0.3 (8.89)	1.2 (15.09)	0.5 (8.34)	1.3 (11.52)	0.8 (6.70)	0.9 (17.46)
95% CI	(-0.0, 0.7)	(0.2, 2.3)	(0.1, 0.8)	(0.6, 1.9)	(-0.2, 1.8)	(-0.2, 2.0)
AST (U/L)						
Baseline						
n	2142	811	2130	1305	167	958
Mean (SD)	21.6 (6.99)	21.4 (6.78)	21.9 (7.01)	21.9 (7.50)	19.6 (4.94)	21.9 (6.45)
Change from baseline to Final Visit						
N	2087	792	2078	1273	166	939
Mean (SD)	0.3 (6.57)	1.0 (10.09)	0.3 (6.19)	0.8 (8.78)	1.1 (5.73)	0.3 (6.04)
95% CI	(0.0, 0.6)	(0.3, 1.7)	(0.0, 0.6)	(0.4, 1.3)	(0.2, 1.9)	(-0.1, 0.7)
ALP (U/L)						
Baseline						
n	2142	811	2130	1305	167	958
Mean (SD)	112.9 (75.67)	110.5 (75.59)	113.1 (78.37)	97.6 (64.29)	77.3 (20.89)	128.3 (85.54)
Change from baseline to Final Visit						
n	2087	792	2078	1273	166	939
Mean (SD)	2.9 (24.83)	1.5 (19.16)	2.7 (20.02)	0.7 (24.62)	-2.1 (9.99)	0.5 (22.72)
95% CI	(1.9, 4.0)	(0.2, 2.8)	(1.8, 3.5)	(-0.7, 2.0)	(-3.6, -0.6)	(-1.0, 1.9)
Bilirubin (mcmol/L)						
Baseline						
n	2142	811	2130	1305	167	958
Mean (SD)	8.17 (4.608)	8.17 (3.977)	8.54 (4.853)	7.87 (4.514)	7.27 (3.322)	9.04 (4.571)
Change from baseline to Final Visit						
n	2087	792	2078	1273	166	939
Mean (SD)	-0.12 (3.126)	-0.29 (2.863)	-0.42 (3.324)	-0.16 (3.346)	-0.38 (2.598)	-0.02 (3.796)
95% CI	(-0.26, 0.01)	(-0.49, -0.09)	(-0.56, -0.28)	(-0.35, 0.02)	(-0.78, 0.02)	(-0.26, 0.22)
GGT (U/L)						
Baseline						
n	2142	811	2130	1305	167	958
Mean (SD)	24.6 (20.15)	25.7 (21.68)	24.9 (21.09)	26.2 (23.47)	23.3 (17.08)	25.8 (23.29)
Change from baseline to Final Visit						
n	2087	792	2078	1273	166	939
Mean (SD)	0.3 (14.16)	0.3 (12.32)	0.3 (14.35)	0.3 (18.54)	-0.7 (9.67)	1.9 (28.72)
95% CI	(-0.3, 0.9)	(-0.5, 1.2)	(-0.3, 0.9)	(-0.7, 1.3)	(-2.1, 0.8	(0.1, 3.7)

Table 92. Hepatic Laboratory Test Results, EU/NA Long-Term Controlled Population

Laboratory Parameter (Units)	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Tolterodine ER 4 mg (n = 812)
ALT (U/L)			
Baseline			
n	810	820	812
Mean (SD)	22.9 (10.94)	22.1 (12.20)	21.8 (10.45)
Change from baseline to Final Visit			
n	790	803	791
Mean (SD)	-0.2 (10.58)	-0.6 (12.42)	0.1 (9.65)
95% CI	(-1.0, 0.5)	(-1.4, 0.3)	(-0.6, 0.8)
AST (U/L)			
Baseline			
n	810	820	812
Mean (SD)	22.5 (7.55)	22.0 (9.06)	21.8 (7.18)
Change from baseline to Final Visit			
n	790	803	791
Mean (SD)	-0.2 (8.07)	-0.4 (9.06)	-0.4 (6.45)
95% CI	(-0.8, 0.4)	(-1.0, 0.2)	(-0.8, 0.1)
ALP (U/L)			
Baseline			
n	810	820	812
Mean (SD)	72.6 (20.93)	73.4 (20.99)	73.0 (21.70)
Change from baseline to Final Visit			
n	789	803	791
Mean (SD)	-0.5 (12.22)	-0.4 (13.23)	-0.8 (18.25)
95% CI	(-1.3, 0.4)	(-1.3, 0.5)	(-2.0, 0.5)
Bilirubin (mcmol/L)			
Baseline			
n	810	820	812
Mean (SD)	7.62 (3.955)	7.72 (4.164)	7.92 (4.130)
Change from baseline to Final Visit			
n	790	803	791
Mean (SD)	0.10 (3.057)	-0.15 (3.190)	-0.23 (3.344)
95% CI	(-0.11, 0.31)	(-0.37, 0.07)	(-0.47, 0.00)

Laboratory Parameter (Units)	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Tolterodine ER 4 mg (n = 812)
GGT			
Baseline			
n	810	820	812
Mean (SD)	26.4 (22.63)	25.9 (25.89)	25.4 (22.15)
Change from baseline to Final Visit			
n	790	803	791
Mean (SD)	0.7 (17.64)	-0.0 (21.68)	2.3 (29.41)
95% CI	(-0.6, 1.9)	(-1.5, 1.5)	(0.2, 4.3)

When considering the incidence of shifts to levels of concern, mirabegron appeared no more likely than placebo to be associated with levels at various multiples of the upper limit of normal (ULN), as shown in the table below. Hy's law, which indicates a poor prognosis for drug-induced hepatic injury in the presence of ALT elevation>3xULN and serum bilirubin >2xULN, was not explicitly mentioned by name in the Integrated Summary of Safety, but the number of cases with this combination of abnormalities was assessed: in the global Phase 2/3 population, just one patient (1/5860, < 0.1%) receiving mirabegron experienced ALT and/or AST > 3 x ULN and total bilirubin > 2 x ULN and ALP < 2 x ULN on the same date. This patient had viral hepatitis as an alternative aetiology. One other mirabegron patent had concurrent ALT and bilirubin abnormalities satisfying this definition in the local laboratory, but not in the centralised laboratory. Given that similar elevations of ALT and bilirubin were also seen in the placebo group, there does not appear to be significantly increased risk of hepatic injury with active treatment.

Table 93. Potentially Clinically Significant Hepatic Laboratory Abnormalities, Global OAB 12-Week Phase 2/3 Population

Laboratory Parameter (Units), n/n (%) of Patients	Criteria	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Tolt ER 4 mg (n = 958)
ALT or AST (U/L)	> 3 x ULN	11/2087 (0.5%)	10/792 (1.3%)	7/2079 (0.3%)	16/1273 (1.3%)	2/166 (1.2%)	6/939 (0.6%)
	> 5 x ULN	3/2087 (0.1%)	5/792 (0.6%)	2/2079 (0.1%)	2/1273 (0.2%)	0/166	3/939 (0.3%)
	> 10 x ULN	1/2087 (< 0.1%)	2/792 (0.3%)	0/2079	0/1273	0/166	1/939 (0.1%)
	> 20 x ULN	1/2087 (< 0.1%)	0/792	0/2079	0/1273	0/166	0/939
ALT (U/L)	> 3 x ULN	9/2087 (0.4%)	10/792 (1.3%)	7/2079 (0.3%)	12/1273 (0.9%)	1/166 (0.6%)	5/939 (0.5%)
	> 5 x ULN	2/2087 (0.1%)	4/792 (0.5%)	2/2079 (0.1%)	2/1273 (0.2%)	0/166	3/939 (0.3%)
	> 10 x ULN	0/2087	2/792 (0.3%)	0/2079	0/1273	0/166	1/939 (0.1%)
	> 20 x ULN	0/2087	0/ 792	0/2079	0/1273	0/166	0/939
AST (U/L)	> 3 x ULN	3/2087 (0.1%)	2/792 (0.3%)	1/2079 (< 0.1%)	9/1273 (0.7%)	1/166 (0.6%)	2/939 (0.2%)
	> 5 x ULN	2/2087 (0.1%)	2/792 (0.3%)	0/2079	0/1273	0/166	0/939
	> 10 x ULN	1/2087 (< 0.1%)	0/792	0/2079	0/1273	0/166	0/939
	> 20 x ULN	1/2087 (< 0.1%)	0/792	0/2079	0/1273	0/166	0/939
ALP (U/L)	> 1.5 x ULN	9/2087 (0.4%)	4/792 (0.5%)	9/2079 (0.4%)	9/1273 (0.7%)	0/166	4/939 (0.4%)
Bilirubin (mcmol/L)	> 1.5 x ULN	12/2087 (0.6%)	4/792 (0.5%)	15/2079 (0.7%)	6/1273 (0.5%)	1/166 (0.6%)	8/939 (0.9%)
	> 2 x ULN	3/2087 (0.1%)	0/792	5/2079 (0.2%)	0/1273	0/166	2/939 (0.2%)
GGT (U/L)	> 100 U/L	47/2087 (2.3%)	27/792 (3.4%)	37/2079 (1.8%)	45/1273 (3.5%)	6/166 (3.6%)	28/939 (3.0%)

Table 94. Potentially Clinically Significant Hepatic Laboratory Abnormalities, EU/NA Long-Term Controlled Population

Laboratory Parameter (Units), n/n (%) of Patients	Criteria	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Tolterodine ER 4 mg (n = 812)
ALT or AST (U/L)	> 3 x ULN	10/792 (1.3%)	9/803 (1.1%)	7/791 (0.9%)
	> 5 x ULN	2/792 (0.3%)	3/803 (0.4%)	1/791 (0.1%)
	> 10 x ULN	2/792 (0.3%)	0/803	0/791
	> 20 x ULN	1/792 (0.1%)	0/803	0/791
ALT (U/L)	> 3 x ULN	8/792 (1.0%)	8/803 (1.0%)	6/791 (0.8%)
	> 5 x ULN	1/792 (0.1%)	3/803 (0.4%)	1/791 (0.1%)
	> 10 x ULN	1/792 (0.1%)	0/803	0/791
	> 20 x ULN	1/792 (0.1%)	0/803	0/791
AST (U/L)	> 3 x ULN	6/792 (0.8%)	5/803 (0.6%)	3/791 (0.4%)
	> 5 x ULN	2/792 (0.3%)	2/803 (0.2%)	0/791
	> 10 x ULN	2/792 (0.3%)	0/803	0/791
	> 20 x ULN	0/792	0/803	0/791
ALP (U/L)	> 1.5 x ULN	3/791 (0.4%)	3/803 (0.4%)	6/791 (0.8%)
Bilirubin (mcmol/L)	> 1.5 x ULN	5/792 (0.6%)	9/803 (1.1%)	3/791 (0.4%)
	> 2 x ULN	1/792 (0.1%)	3/803 (0.4%)	0/791

TEAEs related to the liver are summarised in the table below. Overall, in the 12-week phase 2/3 population, liver-related AEs occurred in 5.5% of mirabegron recipients, and 5.6% of placebo recipients, with no consistent dose trend observed across the mirabegron dose 25mg, 50mg and 100mg. In the tolterodine group, liver-related AEs were reported in 8.1% of recipients, which is a slightly higher incidence than seen with placebo or mirabegron.

Table 95. Hepatotoxicity TEAE, Global OAB 12-Week Phase 2/3 Population

MedDRA v12.1 SOC HLT PT†, n (%) of Patients	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Mirabegron Total Mira (n = 4414)	Tolt ER 4 mg (n = 958)
Overall	121 (5.6%)	52 (6.4%)	119 (5.6%)	64 (4.9%)	7 (4.2%)	242 (5.5%)	78 (8.1%)
Hepatobiliary disorders	4 (0.2%)	3 (0.4%)	2 (0.1%)	1 (0.1%)	0	6 (0.1%)	2 (0.2%)
Cholestasis and jaundice	1 (< 0.1%)	1 (0.1%)	1 (< 0.1%)	1 (0.1%)	0	3 (0.1%)	1 (0.1%)
Cholestasis	0	1 (0.1%)	0	1 (0.1%)	0	2 (< 0.1%)	0
Hyperbilirubinaemia	1 (< 0.1%)	0	1 (< 0.1%)	0	0	1 (< 0.1%)	1 (0.1%)
Hepatic and hepatobiliary disorders NEC	3 (0.1%)	2 (0.2%)	0	0	0	2 (< 0.1%)	0
Liver disorder	3 (0.1%)	2 (0.2%)	0	0	0	2 (< 0.1%)	0
Hepatocellular damage and hepatitis NEC	0	0	1 (< 0.1%)	0	0	1 (< 0.1%)	1 (0.1%)
Hepatic steatosis	0	0	1 (< 0.1%)	0	0	1 (< 0.1%)	0
Hepatitis	0	0	0	0	0	0	1 (0.1%)
Investigations	117 (5.5%)	49 (6.0%)	118 (5.5%)	63 (4.8%)	7 (4.2%)	237 (5.4%)	76 (7.9%)
Liver function analyses	94 (4.4%)	45 (5.5%)	97 (4.6%)	57 (4.4%)	7 (4.2%)	206 (4.7%)	69 (7.2%)
ALT increased	22 (1.0%)	9 (1.1%)	32 (1.5%)	21 (1.6%)	2 (1.2%)	64 (1.4%)	17 (1.8%)
AST increased	22 (1.0%)	12 (1.5%)	19 (0.9%)	14 (1.1%)	1 (0.6%)	46 (1.0%)	16 (1.7%)
Blood bilirubin abnormal	0	0	1 (< 0.1%)	0	0	1 (< 0.1%)	0
Blood bilirubin increased	19 (0.9%)	5 (0.6%)	16 (0.8%)	5 (0.4%)	1 (0.6%)	27 (0.6%)	11 (1.1%)
GGT increased	53 (2.5%)	29 (3.6%)	63 (3.0%)	40 (3.1%)	4 (2.4%)	136 (3.1%)	44 (4.6%)
Hepatic enzyme increased	1 (< 0.1%)	2 (0.2%)	1 (< 0.1%)	3 (0.2%)	1 (0.6%)	7 (0.2%)	1 (0.1%)
Liver function test abnormal	1 (< 0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)	1 (0.6%)	5 (0.1%)	1 (0.1%)
Transaminases increased	0	0	1 (< 0.1%)	0	0	1 (< 0.1%)	0
Tissue enzyme analyses NEC	32 (1.5%)	10 (1.2%)	33 (1.5%)	12 (0.9%)	0	55 (1.2%)	14 (1.5%)
Blood ALP increased	32 (1.5%)	10 (1.2%)	33 (1.5%)	12 (0.9%)	0	55 (1.2%)	14 (1.5%)

The long-term population lacked a placebo control group, making it more difficult to interpret the incidence of hepatic TEAEs in this population, but the results were generally reassuring. TEAEs potentially consistent with hepatotoxicity were reported in 3.3% of mirabegron recipients overall, compared to 2.7% of tolterodine recipients, as shown in the table below.

Table 96. Combined Summary of Hepatotoxicity Events Based on TEAE and Laboratory Data, EU/NA Long-Term Controlled Population

Type of Event, n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total Mirabegron (n = 1632)	Tolterodine ER 4 mg (n = 812)
Any event of hepatotoxicity	24 (3.0%)	30 (3.7%)	54 (3.3%)	22 (2.7%)
Hepatotoxicity as TEAE	17 (2.1%)	19 (2.3%)	36 (2.2%)	15 (1.8%)
Hepatoxicity from laboratory data†	17 (2.1%)	20 (2.4%)	37 (2.3%)	14 (1.7%)
Hepatotoxicity both as TEAE and from laboratory data†	10 (1.2%)	9 (1.1%)	19 (1.2%)	7 (0.9%)

8.4.2. Kidney function

Mean changes from baseline in serum creatinine and urea (BUN) were generally minor in all treatment groups of the 12-week phase 2/3 study population, as shown in the table below. Results in the long-term EU/NA population were similar, with only minor changes observed that were similar in the mirabegron and tolterodine groups.

Table 97. Chemistry Laboratory Test Results, Global OAB 12-Week Phase 2/3 Population

Laboratory Parameter (Units)	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Tolterodine ER 4 mg (n = 958)
Creatinine (mcmol/L)						
Baseline						
n	2142	811	2130	1305	167	958
Mean (SD)	69.4 (16.97)	70.8 (18.16)	69.7 (17.22)	71.2 (18.04)	72.2 (15.42)	65.9 (15.69)
Change from baseline to Final Visit						
n	2087	792	2078	1273	166	939
Mean (SD)	0.5 (8.55)	1.3 (22.19)	0.6 (8.41)	1.2 (8.98)	-0.1 (10.62)	0.2 (8.01)
95% CI	(0.2, 0.9)	(-0.2, 2.9)	(0.3, 1.0)	(0.7, 1.7)	(-1.8, 1.5)	(-0.3, 0.7)
BUN (mmol/L)						
Baseline						
n	1973	642	1961	1137	NA	873
Mean (SD)	5.71 (1.705)	5.64 (1.637)	5.72 (1.680)	5.85 (1.795)	NA	5.73 (1.658)
Change from baseline to Final Visit						
n	1921	626	1910	1105		854
Mean (SD)	0.04 (1.285)	0.12 (1.217)	0.05 (1.255)	-0.02 (1.283)	NA	0.03 (1.228)
95% CI	(-0.02, 0.10)	(0.02, 0.21)	(-0.00, 0.11)	(-0.09, 0.06)	NA	(-0.05, 0.11)

Table 98. Chemistry Laboratory Test Results, EU/NA Long-Term Controlled Population

Laboratory Parameter (Units)	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Tolterodine ER 4 mg (n = 812)
Creatinine (mcmol/L)			
Baseline			
n	810	820	812
Mean (SD)	74.1 (15.80)	74.2 (14.79)	75.2 (16.53)
Change from baseline			
Final visit			
n	790	803	791
Mean (SD)	1.2 (9.18)	2.3 (10.15)	1.4 (10.56)
BUN (mmol/L)			
Baseline			
n	810	820	812
Mean (SD)	5.91 (1.628)	5.98 (1.816)	6.04 (1.806)
Change from baseline			
Final visit			
n	790	803	791
Mean (SD)	-0.01 (1.378)	0.04 (1.510)	-0.01 (1.814)

Mean changes in creatinine may not reflect the actual risk of renal toxicity, because concerning changes in a small proportion of patients are diluted by the overall group. To address this, the sponsor also assessed the number of patients in each group that exhibited a rise of at least 15% in serum creatinine (and more concerning rises of ≥ 30%, ≥ 50% ≥ 100%). As shown in the table below, about 10% of each group in the 12-week phase 2/3 population showed a creatinine rise of at least 15% at the final visit. The differences between groups were minor; the incidence of such a rise with proposed dose of mirabegron 50mg (10.1%) and placebo (10%) were almost identical. Considering other visits or other degrees of change did not show any substantial between-group differences. In the long-term population, rises of at least 15% at the final visit were slightly more common (12.4% of the mirabegron 25mg group, and 16.9% of the mirabegron 50mg group) but the incidence was similar in the tolterodine group (13.4%).

Table 99. Serum Creatinine: Patients with Increases of at Least 15% from Baseline, Global OAB 12-Week Phase 2/3 Population

Visit/Category n/n (%) of Patients	Placebo (n = 2142)	Mirabegron				Tolterodine ER 4 mg (n = 958)
		25 mg (n = 811)	50 mg (n = 2131)	100 mg (n = 1305)	200 mg (n = 167)	
Final Visit						
≥15%	208/2087 (10.0%)	82/792 (10.4%)	210/2078 (10.1%)	156/1273 (12.3%)	12/166 (7.2%)	92/939 (9.8%)
≥30%	42/2087 (2.0%)	17/792 (2.1%)	44/2078 (2.1%)	28/1273 (2.2%)	3/166 (1.8%)	9/939 (1.0%)
≥50%	11/2087 (0.5%)	7/792 (0.9%)	10/2078 (0.5%)	7/1273 (0.5%)	1/166 (0.6%)	2/939 (0.2%)
≥100%	0/2087	1/792 (0.1%)	1/2078 (< 0.1%)	0/1273	0/166	0/939
Any Visit						
≥15%	390/2087 (18.7%)	161/792 (20.3%)	417/2078 (20.1%)	285/1273 (22.4%)	29/166 (17.5%)	166/939 (17.7%)
≥30%	83/2087 (4.0%)	38/792 (4.8%)	76/2078 (3.7%)	66/1273 (5.2%)	7/166 (4.2%)	22/939 (2.3%)
≥50%	24/2087 (1.1%)	13/792 (1.6%)	14/2078 (0.7%)	12/1273 (0.9%)	1/166 (0.6%)	5/939 (0.5%)
≥100%	1/2087 (<0.1%)	2/792 (0.3%)	1/2078 (0.1%)	0/1273	0/166	0/939

Table 100. Serum Creatinine: Patients with Increases of at Least 15% from Baseline, EU/NA Long-Term Controlled Population

Visit/Category n/n (%) of Patients	Mirabegron		Tolterodine ER 4 mg (n = 812)
	50 mg (n = 812)	100 mg (n = 820)	
Final Visit			
≥ 15%	98/790 (12.4%)	136/803 (16.9%)	106/791 (13.4%)
≥ 30%	23/790 (2.9%)	28/803 (3.5%)	30/791 (3.8%)
≥ 50%	2/790 (0.3%)	6/803 (0.7%)	8/791 (1.0%)
≥ 100%	0/790	1/803 (0.1%)	0/791
Any Visit			
≥ 15%	187/790 (23.7%)	223/803 (27.8%)	191/791 (24.1%)
≥ 30%	48/790 (6.1%)	53/803 (6.6%)	49/791 (6.2%)
≥ 50%	9/790 (1.1%)	10/803 (1.2%)	11/791 (1.4%)
≥ 100%	0/790	2/803 (0.2%)	1/791 (0.1%)

8.4.3. Other clinical chemistry

Laboratory results for other clinical chemistry tests in the 12-week phase 2/3 population are summarised in the table below. Shifts to concerning levels of sodium, potassium, chloride, calcium, urate, albumin and total protein were relatively rare, and occurred with similar frequency in the placebo and active groups. LDH levels >250 U/L were more common and appeared to show a dose trend in incidence, being slightly more common with increasing dose (placebo 4.0%, mirabegron 25mg 4.3%, mirabegron 50mg 5.5%, mirabegron 100mg 5.6%, mirabegron 200mg 6.0%). Changes were also observed in 4.6% of tolterodine recipients and, overall, these changes do not appear to be of clinical concern. The long-term population showed an incidence of LDH >250 U/L that was less than or equal to the placebo incidence in the 12-week studies, suggesting that there is no lasting effect on this laboratory parameter.

Table 101. Potentially Clinically Significant Abnormalities in Biochemistry, Global OAB 12-Week Phase 2/3 Population

Laboratory Parameter (Units), n/n (%) of Patients	Criteria	Placebo (n = 2142)	Mirabegron				Tolterodine ER 4 mg (n = 958)
			25 mg (n = 811)	50 mg (n = 2131)	100 mg (n = 1305)	200 mg (n = 167)	
Creatinine (mcmol/L)	> 177 mcmol/L	0/2087	3/792 (0.4%)	0/2079	0/1273	1/166 (0.6%)	0/939
BUN (mmol/L)	> 12.5 mmol/L	12/1921 (0.6%)	3/626 (0.5%)	7/1911 (0.4%)	11/1105 (1.0%)	0/0	3/854 (0.4%)
Sodium (mmol/L)	< 125 mmol/L	1/2087 (< 0.1%)	0/792	0/2079	0/1273	0/166	0/939
	> 150 mmol/L	17/2087 (0.8%)	5/792 (0.6%)	13/2079 (0.6%)	14/1273 (1.1%)	3/166 (1.8%)	14/939 (1.5%)
Potassium (mmol/L)	< 3.1 mmol/L	4/2087 (0.2%)	3/792 (0.4%)	2/2079 (0.1%)	0/1273	0/166	2/938 (0.2%)
	> 5.6 mmol/L	14/2087 (0.7%)	7/792 (0.9%)	12/2079 (0.6%)	15/1273 (1.2%)	1/166 (0.6%)	5/938 (0.5%)
Chloride (mmol/L)	< 85 mmol/L	1/2087 (< 0.1%)	0/792	0/2079	0/1273	0/ 166	0/939
	> 120 mmol/L	0/2087	0/792	0/2079	1/1273 (0.1%)	0/166	0/939
Calcium (mmol/L)	< 1.75 mmol/L	6/1501 (0.4%)	1/584 (0.2%)	2/1496 (0.1%)	4/1066 (0.4%)	0/166	4/565 (0.7%)
	> 3.00 mmol/L	0/1501	0/584	0/1496	0/1066	0/166	0/565
Urate (mcmol/L)	> 535 mcmol/L	17/2087 (0.8%)	9/792 (1.1%)	15/2079 (0.7%)	9/1273 (0.7%)	0/166	7/939 (0.7%)
LDH (U/L)	> 250 U/L	60/1501 (4.0%)	25/ 584 (4.3%)	83/1496 (5.5%)	60/1066 (5.6%)	10/166 (6.0%)	26/565 (4.6%)
Albumin (g/L)	< 26 g/L	0/2087	0/792	1/2079 (< 0.1%)	0/1273	0/166	0/939
	> 60 g/L	0/2087	0/792	0/2079	0/1273	0/ 166	0/939
Protein (g/L)	< 50 g/L	0/2087	0/792	0/2079	0/1273	0/166	0/939
	> 100 g/L	0/2087	1/792 (0.1%)	0/2079	0/1273	0/166	0/939

Table 102. Potentially Clinically Significant Abnormalities in Biochemistry, EU/NA Long-Term Controlled Population

Laboratory Parameter (Units), n/n (%) of Patients	PCS Criterion	Mirabegron		Tolterodine ER 4 mg (n = 812)
		50 mg (n = 812)	100 mg (n = 820)	
Renal Function				
Creatinine (mcmol/L)	> 177 mcmol/L	0/792	0/803	1/791 (0.1%)
BUN (mmol/L)	> 12.5 mmol/L	3/792 (0.4%)	7/803 (0.9%)	8/791 (1.0%)
Electrolytes				
Sodium (mmol/L)	> 150 mmol/L	2/792 (0.3%)	1/803 (0.1%)	5/791 (0.6%)
Potassium (mmol/L)	< 3.1 mmol/L	1/791 (0.1%)	3/803 (0.4%)	1/791 (0.1%)
	> 5.6 mmol/L	14/791 (1.8%)	5/803 (0.6%)	4/791 (0.5%)
Other				
Calcium (mmol/L)	< 1.75 mmol/L	0/791	0/803	1/791 (0.1%)
	> 3.00 mmol/L	0/791	0/803	1/791 (0.1%)
Urate (mcmol/L)	> 535 mcmol/L	4/792 (0.5%)	9/803 (1.1%)	7/791 (0.9%)
LDH (U/L)	> 250 U/L	32/792 (4.0%)	25/803 (3.1%)	28/791 (3.5%)
Albumin (g/L)	< 26 g/L	0/792	0/803	1/791 (0.1%)
	> 60 g/L	0/792	0/803	0/791
Protein (g/L)	< 50 g/L	0/792	0/803	1/791 (0.1%)
	> 100 g/L	0/792	0/803	1/791 (0.1%)

8.4.4. Haematology

The results of haematology monitoring are summarised in the tables below. Mean shifts in haematology parameters were relatively minor, and were generally similar between treatment groups in the 12-week phase 2/3 population, as shown in the Table below. Mean leukocyte counts shifted downwards with mirabegron therapy, and although the shifts were small in magnitude, there appeared to be a dose trend, with greater mean shifts in the 100mg and 200mg dose groups than the 25mg and 50mg dose groups. At the proposed 50mg dose, the mean shift was only -0.07 from a baseline value of 6.4 x 10^9/L.

Table 103. Haematology Laboratory Test Results, Global OAB 12-Week Phase 2/3Population

Laboratory Parameter (Units)	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Tolterodine ER 4 mg (n = 958)
Hemoglobin (g/L)						
Baseline						
n	2140	811	2129	1301	167	956
Mean (SD)	135.3 (12.39)	136.5 (12.71)	135.2 (12.71)	135.6 (12.08)	136.3 (10.19)	134.7 (12.90)
Change from baseline to Final Visit						
n	2084	791	2078	1269	166	937
Mean (SD)	0.5 (6.65)	-0.1 (6.32)	-0.1 (6.31)	-0.2 (6.72)	-2.0 (6.28)	0.6 (6.25)
95% CI	(0.2, 0.8)	(-0.5, 0.3)	(-0.3, 0.2)	(-0.5, 0.2)	(-3.0, -1.1)	(0.2, 1.0)
Hematocrit (%)						
Baseline						
n	2140	811	2129	1301	167	956
Mean (SD)	40.3 (3.79)	41.0 (3.94)	40.4 (3.86)	40.4 (3.61)	40.9 (2.90)	40.1 (3.83)
Change from baseline to Final Visit						
n	2084	791	2078	1269	166	937
Mean (SD)	-0.1 (2.12)	-0.4 (2.11)	-0.3 (2.05)	-0.3 (2.17)	-0.9 (2.08)	-0.3 (1.97)
95% CI	(-0.2, -0.0)	(-0.6, -0.3)	(-0.4, -0.2)	(-0.4, -0.2)	(-1.3, -0.6)	(-0.4, -0.2)
Platelets (10^9/L)						
Baseline						
n	2124	809	2117	1287	167	955
Mean (SD)	249.5 (60.30)	249.7 (61.12)	248.5 (58.99)	255.0 (61.15)	285.4 (69.03)	248.0 (61.53)
Change from baseline to Final Visit						
n	2067	789	2066	1256	166	936
Mean (SD)	-0.5 (31.57)	-5.1 (29.81)	-0.2 (32.61)	-2.7 (38.89)	-7.1 (37.99)	-1.1 (39.24)
95% CI	(-1.8, 0.9)	(-7.2, -3.0)	(-1.6, 1.2)	(-4.8, -0.5)	(-12.9, -1.3)	(-3.7, 1.4)
Leukocytes (10^9/L)						
Baseline						
n	2138	811	2129	1301	167	956
Mean (SD)	6.44 (1.783)	6.47 (1.777)	6.38 (1.804)	6.72 (2.270)	7.10 (1.834)	6.41 (1.961)
Change from baseline to Final Visit						
n	2082	791	2078	1269	166	937
Mean (SD)	0.02 (1.488)	-0.07 (1.376)	-0.07 (1.323)	-0.28 (1.584)	-0.59 (1.517)	0.02 (1.451)
95% CI	(-0.04, 0.09)	(-0.17, 0.02)	(-0.13, -0.01)	(-0.37, -0.20)	(-0.82, -0.36)	(-0.07, 0.12)
Neutrophils (10^9/L)						
Baseline						
n	1368	432	1364	915	NA	490
Mean (SD)	4176.6 (1426.23)	4214.0 (1371.99)	4158.5 (1405.49)	4258.8 (1579.05)	NA	4343.4 (1563.87)
Change from baseline to Final Visit						
n	1323	418	1317	883	NA	474
Mean (SD)	15.0 (1357.19)	-7.8 (1253.89)	-3.5 (1241.90)	-89.2 (1394.82)	NA	119.2 (1427.69)
95% CI	(-58.2, 88.2)	(-128.4, 112.7)	(-70.7, 63.6)	(-181.3, 3.0)	NA	(-9.7, 248.0)
Lymphocytes (10^9/L)						
Baseline						
n	1368	432	1364	915	NA	490
Mean (SD)	1998.8 (742.23)	1925.7 (636.84)	1943.5 (605.54)	1988.9 (1515.82)	NA	2098.0 (806.50)
Change from baseline to Final Visit						
n	1323	418	1317	883	NA	474
Mean (SD)	-2.7 (771.05)	40.0 (449.51)	-23.4 (441.96)	-95.1 (495.27)	NA	-17.8 (506.02)
95% CI	(-44.3, 38.8)	(-3.2, 83.2)	(-47.3, 0.5)	(-127.8, -62.4)	NA	(-63.5, 27.9)
Eosinophils (10^9/L)						
Baseline						
n	1368	432	1364	915	NA	490
Mean (SD)	139.5 (110.47)	144.6 (115.13)	141.4 (116.55)	146.8 (121.93)	NA	134.0 (106.66)
Change from baseline to Final Visit						
n	1323	418	1317	883	NA	474
Mean (SD)	14.5 (109.49)	11.6 (91.86)	21.0 (109.42)	15.9 (165.18)	NA	33.1 (118.34)
95% CI	(8.6, 20.5)	(2.8, 20.4)	(15.0, 26.9)	(5.0, 26.8)	NA	(22.4, 43.8)

Studies included: 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048 and 178-CL-074.

ER: extended release; NA: not applicable; OAB: overactive bladder.

Table 104 lists the incidence of abnormal haematology results that were in potentially concerning ranges (too high or too low) in the 12-week phase 2/3 studies. Clinically significant changes in red cell and platelet indices were rare. Low leukocyte counts (<2.5 x 10^9/L) were observed in some mirabegron recipients (the incidence was 0.2% to 0.6% across the dose groups) and in tolterodine recipients (0.4%), but in relatively few placebo recipients (0.1%). These counts did not appear to be associated with clinical sequelae.

Table 104. Potentially Clinically Significant Haematology Abnormalities, Global OAB 12-Week Phase 2/3 Population

Laboratory Parameter (Units), n/n (%) of Patients	Criteria	Placebo (n = 2142)	Mirabegron 25 mg (n = 811)	Mirabegron 50 mg (n = 2131)	Mirabegron 100 mg (n = 1305)	Mirabegron 200 mg (n = 167)	Tolterodine ER 4 mg (n = 958)
Erythrocytes (10^{12}/L)	< 2.5 x 10^{12}/L	0/2086	0/791	0/2080	0/1273	0/166	0/939
	> 7.0 x 10^{12}/L	0/2086	0/791	0/2080	1/1273 (0.1%)	0/166	1/939 (0.1%)
Hemoglobin (g/L)	< 80 g/L	0/2086	1/791 (0.1%)	1/2080 (< 0.1%)	1/1273 (0.1%)	0/166	0/939
	> 180 g/L	3/2086 (0.1%)	0/791	2/2080 (0.1%)	0/1273	0/166	1/939 (0.1%)
Hematocrit (%)	< 25%	0/2086	0/791	1/2080 (< 0.1%)	1/1273 (0.1%)	0/166	0/939
	> 55%	2/2086 (0.1%)	0/791	1/2080 (< 0.1%)	0/1273	0/166	1/939 (0.1%)
Platelet count (10^9/L)	< 120 x 10^9/L	11/2081 (0.5%)	4/791 (0.5%)	13/2077 (0.6%)	14/1272 (1.1%)	0/166	9/939 (1.0%)
	> 500 x 10^9/L	8/2081 (0.4%)	6/791 (0.8%)	7/2077 (0.3%)	7/1272 (0.6%)	1/166 (0.6%)	3/939 (0.3%)
Leukocytes (10^9/L)	< 2.5 x 10^9/L	3/2086 (0.1%)	3/791 (0.4%)	8/2080 (0.4%)	2/1273 (0.2%)	1/166 (0.6%)	4/939 (0.4%)
	> 18 x 10^9/L	2/2086 (0.1%)	1/791 (0.1%)	1/2080 (< 0.1%)	1/1273 (0.1%)	0/166	1/939 (0.1%)

In the long-term EU/NA population, mean shifts in haematology parameters were minor and the magnitude and direction of shifts were similar in the two mirabegron dose groups (50mg and 100mg) and the tolterodine group.

Table 105. Haematology Test Results, EU/NA Long-Term Controlled Population

Laboratory Parameter (Units)	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Tolterodine ER 4 mg (n = 812)
Hemoglobin (g/L)			
Baseline			
n	807	819	808
Mean (SD)	137.4 (12.08)	137.6 (11.67)	137.9 (11.69)
Change from baseline to Final Visit			
N	787	802	788
Mean (SD)	0.3 (7.29)	-0.1 (7.85)	0.2 (7.52)
95% CI	(-0.2, 0.8)	(-0.6, 0.5)	(-0.4, 0.7)
Hematocrit (%)			
Baseline			
n	807	819	808
Mean (SD)	40.8 (3.45)	40.8 (3.37)	40.9 (3.37)
Change from baseline to Final Visit			
n	787	802	788
Mean (SD)	0.4 (2.30)	0.3 (2.34)	0.4 (2.32)
95% CI	(0.2, 0.5)	(0.2, 0.5)	(0.2, 0.5)
Platelets (10^9/L)			
Baseline			
n	804	814	804
Mean (SD)	249.2 (61.70)	251.2 (59.60)	251.7 (60.25)
Change from baseline to Final Visit			
n	784	796	783
Mean (SD)	-14.1 (38.79)	-13.6 (38.20)	-14.5 (37.26)
95% CI	(-16.8, -11.4)	(-16.2, -10.9)	(-17.1, -11.9)
Leukocytes (10^9/L)			
Baseline			
n	807	819	808
Mean (SD)	6.87 (1.965)	6.79 (1.791)	6.66 (1.817)
Change from baseline to Final Visit			
n	787	802	788
Mean (SD)	-0.23 (1.631)	-0.23 (1.586)	-0.13 (1.507)
95% CI	(-0.35, -0.12)	(-0.34, -0.12)	(-0.24, -0.03)

Table 105 continued. Haematology Test Results, EU/NA Long-Term Controlled Population

Laboratory Parameter (Units)	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Tolterodine ER 4 mg (n = 812)
Neutrophils (10^6/L)			
Baseline			
n	799	815	802
Mean (SD)	4278.3 (1557.20)	4201.1 (1479.21)	4105.8 (1423.94)
Change from baseline to Final Visit			
n	779	795	781
Mean (SD)	-138.5 (1463.13)	-102.6 (1449.14)	-57.1 (1306.25)
95% CI	(-241.4, -35.6)	(-203.5, -1.8)	(-148.8, 34.7)
Lymphocytes (10^6/L)			
Baseline			
n	799	815	802
Mean (SD)	1969.5 (754.36)	1952.2 (659.54)	1919.1 (610.21)
Change from baseline to Final Visit			
n	779	795	781
Mean (SD)	-67.5 (470.00)	-100.5 (471.54)	-53.0 (462.68)
95% CI	(-100.6, -34.5)	(-133.3, -67.7)	(-85.5, -20.5)
Eosinophils (10^6/L)			
Baseline			
n	799	815	802
Mean (SD)	159.9 (115.77)	158.1 (129.89)	159.4 (116.08)
Change from baseline to Final Visit			
n	779	795	781
Mean (SD)	1.3 (105.66)	-1.8 (126.08)	2.8 (157.40)
95% CI	(-6.1, 8.7)	(-10.5, 7.0)	(-8.3, 13.8)

Table 106. Potentially Clinically Significant Haematology Abnormalities, EU/NA Long-Term Controlled Population

Laboratory Parameter (Units), n/n (%) of Patients	PCS Criterion	Mirabegron 50 mg (n=812)	Mirabegron 100 mg (n=820)	Tolterodine ER 4 mg (n=812)
Erythrocytes (10^{12}/L)	< 2.5 x10^{12}/L	0/792	0/803	0/791
	> 7.0 x10^{12}/L	0/792	0/803	0/791
Hemoglobin (g/L)	< 80 g/L	1/792 (0.1%)	1/803 (0.1%)	0/791
	> 180 g/L	0/792	0/803	0/791
Hematocrit (%)	< 25%	0/792	0/803	0/791
	> 55%	1/792 (0.1%)	0/803	0/791
Platelet count (10^9/L)	< 120 x10^9/L	11/790 (1.4%)	13/799 (1.6%)	11/790 (1.4%)
	> 500 x10^9/L	5/790 (0.6%)	3/799 (0.4%)	5/790 (0.6%)
Leukocytes (10^9/L)	< 2.5 x10^9/L	1/792 (0.1%)	3/803 (0.4%)	1/791 (0.1%)
	> 18 x10^9/L	1/792 (0.1%)	0/803	0/791

8.4.5. Electrocardiograph

8.4.5.1. Phase 2/3 efficacy studies

Regarding electrocardiograph (ECG) abnormalities observed in the 12-week phase 2/3 population. No consistent differences were observed between mirabegron and placebo.

8.4.5.2. Other studies

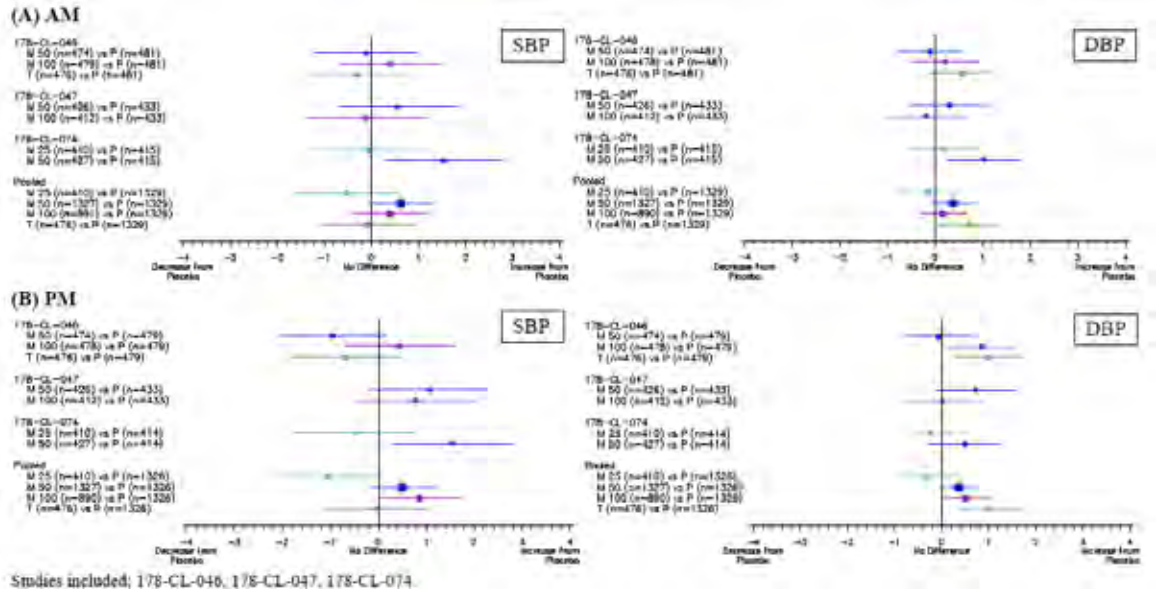
The sponsor performed two thorough QT studies. These studies suggested that supra-therapeutic doses of mirabegron may mildly prolong the QT interval, especially in women, who experience greater exposure than men for the same dose. The upper bounds of the 90%CI for the QT prolongation exceeded 10ms at a number of time points (depending on the dose, gender and study considered).

8.4.6. Vital signs

In the 12-week phase 2/3 studies, mirabegron at the proposed dose of 50mg once daily was associated with an increase in pulse rate of approximately 1 bpm (adjusted mean change from baseline pulse rate compared with placebo).

For blood pressure changes, the adjusted mean difference vs placebo was generally < 1mmHg, as shown in the figure below. For systolic blood pressure (SBP), the placebo-subtracted change from baseline SBP in the 12-week Phase 3 population for mirabegron 25, 50 and 100mg and tolterodine was -0.5, 0.6, 0.4 and -0.1 mm Hg for AM measurements, respectively, and -1.0, 0.5, 0.9 and 0.0 mm Hg for PM measurements, respectively. For diastolic blood pressure (DBP), the placebo-subtracted change from baseline for mirabegron 25, 50 and 100mg and tolterodine was -0.1, 0.4, 0.2 and 0.7 mm Hg for AM measurements, respectively, and -0.3, 0.4, 0.5 and 1.0 mm Hg for PM measurements, respectively.

Figure 29. Adjusted Mean Differences vs Placebo in Change from Baseline, SBP and DBP Measured by Patient Diary, ANCOVA Model, EU/NA OAB 12-Week Phase 3 Population



Adverse events associated with vital signs were relatively rare apart from hypertension, which was reasonably common in all treatment groups: it occurred in 5.0% of mirabegron recipients, 5.0% of placebo recipients, and 4.5% of tolterodine recipients, as shown in Table 72 earlier.

8.5. Post-marketing experience

According to the sponsor's Summary of Clinical Safety, *"There are no postmarketing data available for mirabegron at this time."*

8.6. Safety issues with the potential for major regulatory impact

8.6.1. Liver toxicity

As discussed in Section 8.4.1, there is no evidence in the current submission that mirabegron produces significant liver toxicity.

8.6.2. Haematological toxicity

As discussed in Section 8.4.4, mirabegron was associated with a minor reduction in mean leukocyte counts, but there was no evidence of clinically significant haematological toxicity.

8.6.3. Serious skin reactions and unwanted immunological events

Considering all AEs grouped under "Skin and subcutaneous tissue disorders", there was a slight increase in skin reactions in the active groups compared to placebo, and this increased with increasing doses. The incidence of skin-related AEs leading to discontinuation in the 12-week phase 2/3 population was for each treatment group: placebo 0.1%, mirabegron 25mg 0.2%, mirabegron 50mg 0.4%, mirabegron 100mg 0.6%, mirabegron 200mg 1.2%, total mirabegron 0.5% and tolterodine 0.2%.

Over the whole clinical program, two events were suggestive of moderate skin reactions, reported as Stevens-Johnson syndrome and leukocytoclastic vasculitis. In one event, a 74-year-old woman treated with mirabegron 100mg developed urticaria, a rash and an elevated white cell count, which was reported as Stevens-Johnson syndrome by the treating clinican but the Expert Committee's blinded review of the event classified it as urticaria and not as Stevens-Johnson syndrome. Mirabegron was ceased and she recovered without major sequelae. Subsequently, 72 days after stopping study drug, she developed urticaria again, which resolved without treatment, suggesting an underlying aetiology unrelated to mirabegron.

In another event, a 19-year-old woman treated with mirabegron 30mg IV and 100mg orally had a SAE reported by the investigator as probable drug hypersensitivity vasculitis. She developed symptoms 4 days after the oral dose, and she presented to the emergency room with a skin rash that was described as pruritic and painful. She was treated with methylprednisolone and diphenhydramine, making an uneventful recovery.

These two cases prompted a search for other potential hypersensitivity reactions, and one additional case of urticaria was identified. All cases were reviewed by an Expert Committee of hypersensitivity specialists. The main conclusions of the panel are listed in Appendix 2 of this report (copied from the sponsor's Summary of Clinical Safety). It should be noted that some reactions were reported in placebo recipients, and differences between treatment groups were minor.

Overall, there appears to be a risk of serious skin reactions and hypersensitivity in some susceptible individuals, but the incidence is low, and patients recovered when study drug was ceased.

8.6.4. Cardiovascular safety

Treatment with mirabegron was associated with mild changes in mean pulse rate and blood pressure, as discussed in Section 8.4.6. Despite this, mirabegron treatment was not associated with an increased risk of clinically significant hypertension, as reflected in the incidence of 'hypertension' AEs in the 12-week phase 2/3 population, which was similar in the placebo and mirabegron groups (see Section 8.3.1).

The sponsor submitted a specific assessment of the cardiovascular risk of mirabegron which included a detailed review of all cardiovascular events. Hypertensive events identified in that report are summarised below, and do not suggest a clinically significant impact on the risk of hypertension.

Table 107. TEAE, SAE and TEAE Leading to Permanent Discontinuation of Study Drug for Hypertension, EU/NA OAB 12-Week Phase 3 Population.

Category PT, n (%) of Patients	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Mirabegron Total (n = 2736)	Tolterodine ER 4 mg (n = 495)
Patients with any hypertension TEAE	117 (8.5%)	52 (12.0%)	120 (8.7%)	58 (6.2%)	230 (8.4%)	48 (9.7%)
RR (95% CI) †		1.25 (0.86, 1.80)	1.02 (0.79, 1.32)	0.78 (0.56, 1.08)	0.98 (0.79, 1.23)	
Hypertension	105 (7.6%)	49 (11.3%)	103 (7.5%)	48 (5.2%)	200 (7.3%)	40 (8.1%)
Blood pressure increased	6 (0.4%)	1 (0.2%)	9 (0.7%)	8 (0.9%)	18 (0.7%)	4 (0.8%)
Blood pressure systolic increased	2 (0.1%)	1 (0.2%)	3 (0.2%)	2 (0.2%)	6 (0.2%)	0
Patients with hypertension SAE	0	0	1 (0.1%)	0	1 (< 0.1%)	1 (0.2%)
Hypertensive crisis	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Hypertension	0	0	0	0	0	1 (0.2%)
Patients discontinued study drug due to hypertension TEAE	3 (0.2%)	2 (0.5%)	5 (0.4%)	4 (0.4%)	11 (0.4%)	1 (0.2%)
Hypertension	2 (0.1%)	2 (0.5%)	2 (0.1%)	2 (0.2%)	6 (0.2%)	1 (0.2%)
Blood pressure increased	1 (0.1%)	0	0	2 (0.2%)	2 (0.1%)	0
Hypertensive crisis	0	0	2 (0.1%)	0	2 (0.1%)	0
Blood pressure diastolic increased	0	0	1 (0.1%)	0	1 (< 0.1%)	0

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.

PTs presented in the table include those ≥ 0.2% for any hypertension TEAE in the total mirabegron group and all PTs for hypertension SAE or TEAE leading to discontinuation of study drug.

ER: extended release; OAB: overactive bladder; PT: preferred term; RR: relative risk; TEAE: treatment-emergent adverse event(s); SAE: serious adverse event(s); SMQ: Standardized MedDRA Query.

† RR = relative risk vs placebo.

Postural hypotension and falls also occurred with a similar incidence in the mirabegron and placebo groups (see Section 8.3.5.1).

In the 12-week phase 2/3 population, SAEs listed under 'Cardiac disorders' occurred with similar incidence in the pooled mirabegron (0.2%) and placebo (0.3%) groups (see Section 8.3.3).

The sponsor performed two QT studies, which suggested that mirabegron may mildly prolong the QT interval, especially at higher doses and in women, who experience greater exposure than men for the same dose.

Despite the mildly concerning results in the QT studies, clinically relevant arrhythmias were not observed at a higher frequency with mirabegron. As shown in the table below, arrhythmias occurred with similar frequency in the mirabegron and placebo groups in the 12-week phase 2/3 population.

Table 108. TEAE, SAE and TEAE Leading to Permanent Discontinuation of Study Drug for Cardiac Arrhythmias, Global OAB 12-Week Phase 2/3 Population

Category PT, n (%) of Patients	Placebo (n = 2142)	Mirabegron					Tolterodine ER 4 mg (n = 958)
		25 mg (n = 811)	50 mg (n = 2131)	100 mg (n = 1305)	200 mg (n = 167)	Total (n = 4414)	
Patients with any cardiac arrhythmia TEAE	39 (1.8%)	25 (3.1%)	55 (2.6%)	31 (2.4%)	11 (6.6%)	122 (2.8%)	30 (3.1%)
Tachycardia	8 (0.4%)	10 (1.2%)	23 (1.1%)	7 (0.5%)	6 (3.6%)	46 (1.0%)	1 (0.1%)
Palpitations	4 (0.2%)	7 (0.9%)	12 (0.6%)	5 (0.4%)	2 (1.2%)	26 (0.6%)	4 (0.4%)
Supraventricular extrasystoles	6 (0.3%)	2 (0.2%)	5 (0.2%)	5 (0.4%)	0	12 (0.3%)	7 (0.7%)
Atrial fibrillation	2 (0.1%)	0	5 (0.2%)	4 (0.3%)	1 (0.6%)	10 (0.2%)	2 (0.2%)
Patients with cardiac arrhythmia SAE	3 (0.1%)	0	3 (0.1%)	3 (0.2%)	0	6 (0.1%)	1 (0.1%)
Atrial fibrillation	1 (< 0.1%)	0	3 (0.1%)	2 (0.2%)	0	5 (0.1%)	0
Supraventricular tachycardia	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Arrhythmia	0	0	0	0	0	0	1 (0.1%)
Atrioventricular block first degree	1 (< 0.1%)	0	0	0	0	0	0
Loss of consciousness	1 (< 0.1%)	0	0	0	0	0	0
Patients discontinued study drug due to cardiac arrhythmia TEAE	3 (0.1%)	2 (0.2%)	6 (0.3%)	8 (0.6%)	0	16 (0.4%)	3 (0.3%)
Palpitations	2 (0.1%)	1 (0.1%)	1 (< 0.1%)	3 (0.2%)	0	5 (0.1%)	1 (0.1%)
Tachycardia	0	1 (0.1%)	3 (0.1%)	1 (0.1%)	0	5 (0.1%)	0
Atrial fibrillation	1 (< 0.1%)	0	2 (0.1%)	1 (0.1%)	0	3 (0.1%)	0
Atrioventricular block first degree	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Conduction disorder	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
ECG abnormal	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Supraventricular tachycardia	0	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Arrhythmia	0	0	0	0	0	0	1 (0.1%)
Sinus tachycardia	0	0	0	0	0	0	1 (0.1%)

Studies included: 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048 and 178-CL-074.

PTs presented in the table include those ≥ 0.2% for any cardiac arrhythmia TEAE in the total mirabegron group and all PTs for cardiac arrhythmia SAE or TEAE leading to discontinuation of study drug.

SMQ: Standardized MedDRA Query; ER: extended release; OAB: overactive bladder; PT: preferred term; TEAE: treatment-emergent adverse event(s); SAE: serious adverse event(s); ECG: electrocardiogram.

In the long-term EU/NA population, there was no placebo comparator, but the incidence of arrhythmias with mirabegron compared favourably with the incidence of arrhythmias observed with tolterodine treatment, as shown in the table below.

Table 109. TEAE, SAE and TEAE Leading to Permanent Discontinuation of Study Drug for Cardiac Arrhythmias, EU/NA Long-Term Controlled Population

Category PT, n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total (n = 1632)	Tolterodine ER 4 mg (n = 812)
Patients with any cardiac arrhythmia TEAE	32 (3.9%)	34 (4.1%)	66 (4.0%)	49 (6.0%)
Tachycardia	8 (1.0%)	19 (2.3%)	27 (1.7%)	25 (3.1%)
Palpitations	5 (0.6%)	4 (0.5%)	9 (0.6%)	4 (0.5%)
Atrioventricular block first degree	4 (0.5%)	1 (0.1%)	5 (0.3%)	2 (0.2%)
Atrial fibrillation	3 (0.4%)	1 (0.1%)	4 (0.2%)	4 (0.5%)
Heart rate increased	2 (0.2%)	2 (0.2%)	4 (0.2%)	2 (0.2%)
Arrhythmia	2 (0.2%)	1 (0.1%)	3 (0.2%)	2 (0.2%)
Bundle branch block right	1 (0.1%)	2 (0.2%)	3 (0.2%)	0
ECG QT prolonged	1 (0.1%)	2 (0.2%)	3 (0.2%)	1 (0.1%)
Patients with cardiac arrhythmia SAE	6 (0.7%)	1 (0.1%)	7 (0.4%)	4 (0.5%)
Atrial fibrillation	2 (0.2%)	0	2 (0.1%)	3 (0.4%)
Arrhythmia	0	1 (0.1%)	1 (0.1%)	0
Atrial flutter	1 (0.1%)	0	1 (0.1%)	0
Atrioventricular block first degree	1 (0.1%)	0	1 (0.1%)	0
Cardiac arrest	1 (0.1%)	0	1 (0.1%)	1 (0.1%)
Sick sinus syndrome	1 (0.1%)	0	1 (0.1%)	0
Ventricular fibrillation	1 (0.1%)	0	1 (0.1%)	0
Ventricular tachycardia	1 (0.1%)	0	1 (0.1%)	0
Patients discontinued study drug due to cardiac arrhythmia TEAE	3 (0.4%)	4 (0.5%)	7 (0.4%)	2 (0.2%)
Palpitations	0	2 (0.2%)	2 (0.1%)	0
Arrhythmia	0	1 (0.1%)	1 (0.1%)	0
Atrial flutter	1 (0.1%)	0	1 (0.1%)	0
Cardiac arrest	1 (0.1%)	0	1 (0.1%)	0
ECG QT prolonged	0	1 (0.1%)	1 (0.1%)	0
Supraventricular extrasystoles	1 (0.1%)	0	1 (0.1%)	0
Ventricular extrasystoles	1 (0.1%)	0	1 (0.1%)	0
Ventricular fibrillation	1 (0.1%)	0	1 (0.1%)	0
Ventricular tachycardia	1 (0.1%)	0	1 (0.1%)	0
Atrial fibrillation	0	0	0	2 (0.2%)

Study included: 178-CL-049.

PTs presented in the table include those ≥ 0.2% for any cardiac arrhythmia TEAE in the total mirabegron group and all PTs for cardiac arrhythmia SAE or TEAE leading to discontinuation of study drug.

ECG: electrocardiogram; ER: extended release; PT: preferred term; TEAE: treatment-emergent adverse event(s); SMQ: Standardized MedDRA Query; SAE: serious adverse event(s).

Overall, mirabegron appears to pose a minimal cardiovascular risk. Given the results of the QT studies, which showed mild QT prolongation at supra-therapeutic doses, mirabegron should be avoided in patients with long QT syndrome, and in combinations involving other QT-prolonging drugs.

8.7. Other safety issues

8.7.1. Safety in special populations

Exposure to mirabegron and its metabolites is higher in women than in men, and this was reflected in slightly greater changes in QT interval and pulse rate in females, as discussed in Section 8.4.5.2 and Section 8.4.6. AEs were also reported more frequently in women than in men, but this difference was noted in all treatment groups, including placebo, as shown in the tables below. Dose adjustment is therefore not recommended on the basis of gender.

Table 110. TEAE by Gender (Reported by ≥ 3.0% in the Total Mirabegron Group), Global OAB 12-Week Phase 2/3 Population

GENDER MedDRA (v12.1) PT†, n (%) of Patients	Placebo	Mirabegron					Tolt ER 4 mg
		25 mg	50 mg	100 mg	200 mg	Total Mirabegron	
FEMALE	**n = 1647**	**n = 610**	**n = 1630**	**n = 999**	**n = 155**	**n =3394**	**n = 744**
MALE	**n = 495**	**n = 201**	**n = 501**	**n = 306**	**n = 12**	**n = 1020**	**n = 214**
Overall	**1182 (55.2%)**	**452 (55.7%)**	**1173 (55.0%)**	**654 (50.1%)**	**80 (47.9%)**	**2359 (53.4%)**	**577 (60.2%)**
Female	933 (56.6%)	349 (57.2%)	919 (56.4%)	515 (51.6%)	75 (48.4%)	1858 (54.7%)	461 (62.0%)
Male	249 (50.3%)	103 (51.2%)	254 (50.7%)	139 (45.4%)	5 (41.7%)	501 (49.1%)	116 (54.2%)
Nasopharyn-gitis	**141 (6.6%)**	**61 (7.5%)**	**157 (7.4%)**	**74 (5.7%)**	**4 (2.4%)**	**296 (6.7%)**	**57 (5.9%)**
Female	115 (7.0%)	50 (8.2%)	124 (7.6%)	67 (6.7%)	4 (2.6%)	245 (7.2%)	49 (6.6%)
Male	26 (5.3%)	11 (5.5%)	33 (6.6%)	7 (2.3%)	0	51 (5.0%)	8 (3.7%)
Hypertension	**107 (5.0%)**	**54 (6.7%)**	**110 (5.2%)**	**55 (4.2%)**	**2 (1.2%)**	**221 (5.0%)**	**43 (4.5%)**
Female	71 (4.3%)	32 (5.2%)	67 (4.1%)	39 (3.9%)	2 (1.3%)	140 (4.1%)	24 (3.2%)
Male	36 (7.3%)	22 (10.9%)	43 (8.6%)	16 (5.2%)	0	81 (7.9%)	19 (8.9%)
Blood glucose increased	**115 (5.4%)**	**39 (4.8%)**	**122 (5.7%)**	**46 (3.5%)**	**0**	**207 (4.7%)**	**73 (7.6%)**
Female	92 (5.6%)	25 (4.1%)	98 (6.0%)	30 (3.0%)	0	153 (4.5%)	56 (7.5%)
Male	23 (4.6%)	14 (7.0%)	24 (4.8%)	16 (5.2%)	0	54 (5.3%)	17 (7.9%)
GGT increased	**53 (2.5%)**	**29 (3.6%)**	**63 (3.0%)**	**40 (3.1%)**	**4 (2.4%)**	**136 (3.1%)**	**44 (4.6%)**
Female	46 (2.8%)	26 (4.3%)	60 (3.7%)	34 (3.4%)	4 (2.6%)	124 (3.7%)	39 (5.2%)
Male	7 (1.4%)	3 (1.5%)	3 (0.6%)	6 (2.0%)	0	12 (1.2%)	5 (2.3%)
Headache	**60 (2.8%)**	**24 (3.0%)**	**66 (3.1%)**	**35 (2.7%)**	**6 (3.6%)**	**131 (3.0%)**	**30 (3.1%)**
Female	54 (3.3%)	21 (3.4%)	55 (3.4%)	30 (3.0%)	6 (3.9%)	112 (3.3%)	25 (3.4%)
Male	6 (1.2%)	3 (1.5%)	11 (2.2%)	5 (1.6%)	0	19 (1.9%)	5 (2.3%)

Studies included: 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048 and 178-CL-074.

ER: extended release; GGT: gamma-glutamyltransferase; OAB: overactive bladder; PT: preferred term; TEAE: treatment-emergent adverse event(s); tolt: tolterodine.

† Sorting order: PT, by decreasing frequency in total mirabegron group.

Table 111. TEAE by Gender (Reported by ≥ 3.0% in the Total Mirabegron Group), EU/NA Long-Term Controlled Population

GENDER MedDRA (v12.1) PT†, n (%) of Patients	Mirabegron			Tolterodine ER 4 mg
	50 mg	100 mg	Total Mirabegron	
FEMALE	**n = 602**	**n = 608**	**n = 1210**	**n = 600**
MALE	**n = 210**	**n = 212**	**n = 422**	**n = 212**
Overall	**485 (59.7%)**	**503 (61.3%)**	**988 (60.5%)**	**508 (62.6%)**
Female	359 (59.6%)	382 (62.8%)	741 (61.2%)	376 (62.7%)
Male	126 (60.0%)	121 (57.1%)	247 (58.5%)	132 (62.3%)
Hypertension	**75 (9.2%)**	**80 (9.8%)**	**155 (9.5%)**	**78 (9.6%)**
Female	49 (8.1%)	57 (9.4%)	106 (8.8%)	53 (8.8%)
Male	26 (12.4%)	23 (10.8%)	49 (11.6%)	25 (11.8%)
UTI	**48 (5.9%)**	**45 (5.5%)**	**93 (5.7%)**	**52 (6.4%)**
Female	44 (7.3%)	41 (6.7%)	85 (7.0%)	47 (7.8%)
Male	4 (1.9%)	4 (1.9%)	8 (1.9%)	5 (2.4%)
Nasopharyngitis	**32 (3.9%)**	**35 (4.3%)**	**67 (4.1%)**	**25 (3.1%)**
Female	25 (4.2%)	26 (4.3%)	51 (4.2%)	18 (3.0%)
Male	7 (3.3%)	9 (4.2%)	16 (3.8%)	7 (3.3%)
Headache	**33 (4.1%)**	**26 (3.2%)**	**59 (3.6%)**	**20 (2.5%)**
Female	28 (4.7%)	22 (3.6%)	50 (4.1%)	13 (2.2%)
Male	5 (2.4%)	4 (1.9%)	9 (2.1%)	7 (3.3%)
Back pain	**23 (2.8%)**	**29 (3.5%)**	**52 (3.2%)**	**13 (1.6%)**
Female	14 (2.3%)	21 (3.5%)	35 (2.9%)	11 (1.8%)
Male	9 (4.3%)	8 (3.8%)	17 (4.0%)	2 (0.9%)

Study included: 178-CL-049.

ER: extended release; PT: preferred term; TEAE: treatment-emergent adverse event(s); UTI: urinary tract infection.

† Sorting order: PT, by decreasing frequency in total mirabegron group.

Older subjects (≥ 65 years) were slightly more likely to report AEs than younger subjects (<65 years), as shown in the table below. This difference was observed in the placebo group and the mirabegron group, however, with no overall evidence that the safety of mirabegron is significantly worse in older patients.

Table 112. TEAE by Age (Reported by ≥ 3.0% in the Total Mirabegron Group), Global OAB 12-Week Phase 2/3 Population

AGE MedDRA (v12.1) PT †, n (%) of Patients	Placebo	Mirabegron					Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	200 mg	Total Mira	
< 65 YEARS	n = 1360	n = 536	n = 1359	n = 820	n = 108	n = 2823	n = 594
≥ 65 YEARS	n = 782	n = 275	n = 772	n = 485	n = 59	n = 1591	n = 364
Overall	**1182 (55.2%)**	**452 (55.7%)**	**1173 (55.0%)**	**654 (50.1%)**	**80 (47.9%)**	**2359 (53.4%)**	**577 (60.2%)**
< 65 years	744 (54.7%)	283 (52.8%)	729 (53.6%)	413 (50.4%)	50 (46.3%)	1475 (52.2%)	347 (58.4%)
≥ 65 years	438 (56.0%)	169 (61.5%)	444 (57.5%)	241 (49.7%)	30 (50.8%)	884 (55.6%)	230 (63.2%)
Nasopharyngitis	**141 (6.6%)**	**61 (7.5%)**	**157 (7.4%)**	**74 (5.7%)**	**4 (2.4%)**	**296 (6.7%)**	**57 (5.9%)**
< 65 years	94 (6.9%)	37 (6.9%)	116 (8.5%)	53 (6.5%)	4 (3.7%)	210 (7.4%)	36 (6.1%)
≥ 65 years	47 (6.0%)	24 (8.7%)	41 (5.3%)	21 (4.3%)	0	86 (5.4%)	21 (5.8%)
Hypertension	**107 (5.0%)**	**54 (6.7%)**	**110 (5.2%)**	**55 (4.2%)**	**2 (1.2%)**	**221 (5.0%)**	**43 (4.5%)**
< 65 years	62 (4.6%)	30 (5.6%)	55 (4.0%)	24 (2.9%)	2 (1.9%)	111 (3.9%)	19 (3.2%)
≥ 65 years	45 (5.8%)	24 (8.7%)	55 (7.1%)	31 (6.4%)	0	110 (6.9%)	24 (6.6%)
Blood glucose increased	**115 (5.4%)**	**39 (4.8%)**	**122 (5.7%)**	**46 (3.5%)**	**0**	**207 (4.7%)**	**73 (7.6%)**
< 65 years	71 (5.2%)	23 (4.3%)	77 (5.7%)	26 (3.2%)	0	126 (4.5%)	39 (6.6%)
≥ 65 years	44 (5.6%)	16 (5.8%)	45 (5.8%)	20 (4.1%)	0	81 (5.1%)	34 (9.3%)
GGT increased	**53 (2.5%)**	**29 (3.6%)**	**63 (3.0%)**	**40 (3.1%)**	**4 (2.4%)**	**136 (3.1%)**	**44 (4.6%)**
< 65 years	38 (2.8%)	19 (3.5%)	40 (2.9%)	26 (3.2%)	2 (1.9%)	87 (3.1%)	32 (5.4%)
≥ 65 years	15 (1.9%)	10 (3.6%)	23 (3.0%)	14 (2.9%)	2 (3.4%)	49 (3.1%)	12 (3.3%)
Headache	**60 (2.8%)**	**24 (3.0%)**	**66 (3.1%)**	**35 (2.7%)**	**6 (3.6%)**	**131 (3.0%)**	**30 (3.1%)**
< 65 years	48 (3.5%)	17 (3.2%)	46 (3.4%)	25 (3.0%)	4 (3.7%)	92 (3.3%)	18 (3.0%)
≥ 65 years	12 (1.5%)	7 (2.5%)	20 (2.6%)	10 (2.1%)	2 (3.4%)	39 (2.5%)	12 (3.3%)

Studies included: 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048 and 178-CL-074.

ER: extended release; GGT: gamma-glutamyltransferase; mira: mirabegron; OAB: overactive bladder; PT: preferred term; TEAE: treatment-emergent adverse event(s).

† Sorting order: PT, by decreasing frequency in total mirabegron group.

Table 113. TEAE by Age Group (Reported by ≥ 3.0% in the Total Mirabegron Group), EU/NA Long-Term Controlled Population

AGE MedDRA (v12.1) PT †, n (%) of Patients	Mirabegron			Tolterodine ER 4 mg
	50 mg	100 mg	Total Mirabegron	
< 65 YEARS	n = 523	n = 504	n = 1027	n = 509
≥ 65 YEARS	n = 289	n = 316	n = 605	n = 303
Overall	**485 (59.7%)**	**503 (61.3%)**	**988 (60.5%)**	**508 (62.6%)**
< 65 years	297 (56.8%)	303 (60.1%)	600 (58.4%)	313 (61.5%)
≥ 65 years	188 (65.1%)	200 (63.3%)	388 (64.1%)	195 (64.4%)
Hypertension	**75 (9.2%)**	**80 (9.8%)**	**155 (9.5%)**	**78 (9.6%)**
< 65 years	45 (8.6%)	33 (6.5%)	78 (7.6%)	39 (7.7%)
≥ 65 years	30 (10.4%)	47 (14.9%)	77 (12.7%)	39 (12.9%)
UTI	**48 (5.9%)**	**45 (5.5%)**	**93 (5.7%)**	**52 (6.4%)**
< 65 years	25 (4.8%)	24 (4.8%)	49 (4.8%)	27 (5.3%)
≥ 65 years	23 (8.0%)	21 (6.6%)	44 (7.3%)	25 (8.3%)
Nasopharyngitis	**32 (3.9%)**	**35 (4.3%)**	**67 (4.1%)**	**25 (3.1%)**
< 65 years	23 (4.4%)	21 (4.2%)	44 (4.3%)	19 (3.7%)
≥ 65 years	9 (3.1%)	14 (4.4%)	23 (3.8%)	6 (2.0%)
Headache	**33 (4.1%)**	**26 (3.2%)**	**59 (3.6%)**	**20 (2.5%)**
< 65 years	29 (5.5%)	18 (3.6%)	47 (4.6%)	11 (2.2%)
≥ 65 years	4 (1.4%)	8 (2.5%)	12 (2.0%)	9 (3.0%)
Back pain	**23 (2.8%)**	**29 (3.5%)**	**52 (3.2%)**	**13 (1.6%)**
< 65 years	13 (2.5%)	23 (4.6%)	36 (3.5%)	8 (1.6%)
≥ 65 years	10 (3.5%)	6 (1.9%)	16 (2.6%)	5 (1.7%)

Study included: 178-CL-049.

ER: extended release; PT: preferred term; TEAE: treatment-emergent adverse event(s); UTI: urinary tract infection.

† Sorting order: PT, by decreasing frequency in total mirabegron group.

Subjects with significant comorbidities were excluded from the clinical program, so the safety of mirabegron in subjects with severe hypertension, cardiac disease or other major illnesses has not been tested. Given the mild QT-prolonging effects observed in the QT studies, it would be prudent to avoid mirabegron in subjects with a significant history of cardiac arrhythmia.

The PI recommends caution, as follows:

'Consider observations from the QT study (see PHARMACOLOGY: Pharmacodynamic Effects: Effect on QT Interval) in clinical decisions to prescribe BETENIQ to patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong QT interval.'

Subjects with moderate hepatic impairment or severe renal impairment should halve the dose of mirabegron to 25mg, as discussed in sections 4.2.4.1 and 4.2.4.2. At this reduced dose, such subjects would be expected to have similar exposure to subjects with normal hepatic or renal function. Subjects with severe hepatic impairment or End-Stage Renal Failure should avoid the drug completely; the proposed PI lists these conditions as 'Precautions', with the following comments:

'[BETENIQ] has not been studied in patients with End Stage Renal Disease (eGFR <15 mL/min/1.73 m2 or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population.'

'[BETENIQ] has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population.'

8.7.2. Safety related to drug-drug interactions and other interactions

The sponsor performed a number of safety-related subgroup analyses based on concomitant or prior use of other medications, and no consistent patterns or concerning trends emerged. The results for one such analysis, an assessment of AEs by baseline use of alpha-1 antagonists, is shown below. The sponsor also assessed prior medications for treatment of OAB, and baseline use of beta-blockers, which did not significantly modify the incidence of AEs comparing active and placebo groups (data not shown).

Table 114. TEAE by Baseline Use of Alpha 1-AR Antagonists (Reported by ≥ 3.0% in the Total Mirabegron Group), EU/NA OAB 12-Week Phase 3 Population

Baseline use of Alpha 1-AR Antagonists MedDRA (v12.1) PT †, n (%) of Patients	Placebo	Mirabegron				Tolterodine ER 4 mg
		25 mg	50mg	100mg	Total Mira	
YES	**n = 82**	**n = 32**	**n = 92**	**n = 68**	**n = 192**	**n = 34**
NO	**n = 1298**	**n = 400**	**n = 1283**	**n = 861**	**n = 2544**	**n = 461**
Overall	**658 (47.7%)**	**210 (48.6%)**	**647 (47.1%)**	**402 (43.3%)**	**1259 (46.0%)**	**231 (46.7%)**
Yes	36 (43.9%)	15 (46.9%)	43 (46.7%)	29 (42.6%)	87 (45.3%)	17 (50.0%)
No	622 (47.9%)	195 (48.8%)	604 (47.1%)	373 (43.3%)	1172 (46.1%)	214 (46.4%)
Hypertension	**105 (7.6%)**	**49 (11.3%)**	**103 (7.5%)**	**48 (5.2%)**	**200 (7.3%)**	**40 (8.1%)**
Yes	4 (4.9%)	6 (18.8%)	11 (12.0%)	5 (7.4%)	22 (11.5%)	5 (14.7%)
No	101 (7.8%)	43 (10.8%)	92 (7.2%)	43 (5.0%)	178 (7.0%)	35 (7.6%)
Nasopharyngitis	**35 (2.5%)**	**15 (3.5%)**	**54 (3.9%)**	**25 (2.7%)**	**94 (3.4%)**	**14 (2.8%)**
Yes	2 (2.4%)	0	7 (7.6%)	1 (1.5%)	8 (4.2%)	1 (2.9%)
No	33 (2.5%)	15 (3.8%)	47 (3.7%)	24 (2.8%)	86 (3.4%)	13 (2.8%)
UTI	**25 (1.8%)**	**18 (4.2%)**	**40 (2.9%)**	**25 (2.7%)**	**83 (3.0%)**	**10 (2.0%)**
Yes	1 (1.2%)	0	1 (1.1%)	2 (2.9%)	3 (1.6%)	0
No	24 (1.8%)	18 (4.5%)	39 (3.0%)	23 (2.7%)	80 (3.1%)	10 (2.2%)

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.

AR: adrenoceptor; ER: extended release; mira: mirabegron; OAB: overactive bladder; PT: preferred term; TEAE: treatment-emergent adverse event(s); UTI: urinary tract infection.

† Sorting order: PT, by decreasing frequency in total mirabegron group.

The clinical pharmacology program indicated that mirabegron may be involved in pharmacokinetic interactions with other medications, but the magnitude of the interactions was

generally small (see Section 4.2.5). A mild pharmacodynamic interaction was observed with tamsulosin, as discussed above, but this is unlikely to be clinically relevant.

The QT studies showed that mirabegron is associated with a minor QT-prolonging effect. Although there was no evidence of a clinically significant risk of arrhythmias in the phase 2/3 study population, it would be prudent to avoid combining mirabegron with other QT-prolonging drugs.

8.8. Evaluator's overall conclusions on clinical safety

The safety and tolerability of mirabegron was acceptable in the pooled phase 2/3 population, with an incidence of adverse events only slightly in excess of placebo, as summarised in Table 70, seen earlier. The distribution of individual AE types, including cardiovascular and urological AEs, did not raise specific concerns.

Potential safety issues with mirabegron arise from the mild QT-prolonging effect observed at the supratherapeutic dose of 200mg, a low incidence of skin reactions, and the possibility of drug interactions. Although mirabegron does not require dose adjustment when combined with other drugs, it may modify the pharmacokinetics of drugs metabolised CYP2D6, increasing their levels, which could be relevant for drugs with narrow therapeutic indices. Mirabegron also increases exposure to digoxin when the two are co-administered, so digoxin should be introduced at a low dose and titrated according to blood levels.

The systemic beta agonist effects of mirabegron are minimal, but minor increases in pulse rate and blood pressure have been observed. The incidence of clinically relevant hypertension was not increased with mirabegron. Falls, syncope and hypotension did not occur with increased incidence in mirabegron recipients.

The proposed PI contains appropriate warnings about these few safety issues.

Exposure to mirabegron is increased (approximately doubled) in the setting of severe renal impairment, as discussed in Section 4.2.4.2. The PI therefore recommends halving the dose to 25mg once daily in patients with severe renal impairment, but no adjustment in patients with mild to moderate renal impairment. Given that the proposed dose (50mg) is half the maximum dose tested in the pivotal studies (100mg), patients with severe renal impairment would experience an exposure that has been shown to have an acceptable safety profile. Similarly, a reduction of the dose to 25mg once daily in patients with moderate hepatic impairment is recommended in the PI, and would be expected to produce an exposure similar to that experienced by normal subjects receiving a standard dose.

Mirabegron has not been studied at all in patients with severe hepatic impairment (Child-Pugh Class C), nor in patients with End-Stage Renal Failure (ESRF). The Proposed Product Information sheet (PI) contains appropriate warnings against use in these two populations, under 'Precautions'.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of mirabegron in the proposed usage are:

- A slightly lower micturition frequency (one less void every two days)
- A slightly lower rate of incontinence (~0.4 episodes prevented per day)
- Marginally improved quality of life

9.2. First round assessment of risks

The risks of mirabegron in the proposed usage are:

- A slight risk of QT prolongation in the event of accidental supratherapeuic exposure
- A slight risk of hypersensitivity reactions that would be expected to resolve with discontinuation
- Minor increases in blood pressure in susceptible subjects

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of mirabegron, given the proposed usage, is favourable. It is expected that many patients will find the efficacy of mirabegron unacceptably low, but those who fail to show an adequate response could discontinue the drug, and a therapeutic trial of mirabegron is likely to be a worthwhile exercise in patients distressed by OAB symptoms.

10. First round recommendation regarding authorisation

Mirabegron should be approved for use in patients with overactive bladder.

11. Clinical questions

11.1. Efficacy

Could the sponsor please confirm that Study 074 produced identical placebo-subtracted differences and 95%CIs (-0.42; 95%CI -0.76 to -0.08) for the two coprimary endpoints in the 50mg group. (The results are plausible, but the co-incidence raises the possibility of a transcription error.)

12. Second round evaluation of clinical data submitted in response to questions

The sponsor has confirmed that the results as shown in Table 30 (in this report) are correct. The identical values of the placebo-subtracted differences and of the corresponding 95% confidence intervals, viz -0.42, 95% CI [-0.76, -0.08] for each of the two co-primary endpoints for the mirabegron 50mg dosage group in Study 074, happened by chance. In the s31 response the sponsor also included copies of the source tables from the Study Report [178-CL-074] to verify this fact. Also one can observe that the information in the two relevant cells of Table 30 is not identical in all respects, there being differences in the 3rd decimal place in the standard deviations of the point estimates (0.173 in one cell and 0.174 in the other).

13. Second round benefit-risk assessment

Assessment remains unchanged from that in section 9 of this report.

14. Second round recommendation regarding authorisation

As in section 10 of this report, it is recommended that mirabegron should be approved for use in patients with overactive bladder.

15. References

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Sussman D, Garely A. Treatment of overactive bladder with once-daily extended release of tolterodine and oxybutynin: the antimuscarinic clinical effectiveness trial (ACET). Current Medical Research and Opinion 2002, 18(4): 177-184.

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16. Appendix 1. ICIQ-OAB and ICIQ-OAB qol Questionnaire

Overactive bladder

Many people experience urinary symptoms some of the time. We are trying to find out how many people experience urinary symptoms, and how much they bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

1. Please write in your date of birth:

DAY MONTH YEAR

2. Are you *(tick one)***:** Female Male

3a. How often do you pass urine during the day?

hourly 3

every two hours 2

every three hours 1

every four hours or more 0

3b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

4a. During the night, how many times do you have to get up to urinate, on average?

none 0

one 1

two 2

three 3

four or more 4

4b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

5a. Do you have to rush to the toilet to urinate?

never 0

occasionally 1

sometimes 2

most of the time 3

all of the time 4

5b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

6a. Does urine leak before you can get to the toilet?

never 0

about once a week or less often 1

two or three times a week 2

about once a day 3

several times a day 4

all the time 5

6b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

Thank you very much for answering these questions.

Quality of life

For the following questions, please think about your overall urinary symptoms in the past four weeks and how these symptoms have affected your life. Please answer each question about how often you have felt this way to the best of your ability. Please tick the box that best answers each question.

1. Please write in your date of birth:

DAY MONTH YEAR

2. Are you *(tick one)***:** Female Male

DURING THE PAST FOUR WEEKS, HOW OFTEN HAVE YOUR BLADDER SYMPTOMS…

3. Made you carefully plan your journey?

4. Caused you to feel drowsy or sleepy during the day?

5. Caused you to plan "escape routes" to toilets in public places?

6. Caused you distress?

7. Frustrated you?

8. Made you feel like there is something wrong with you?

9. Interfered with your ability to get a good night's rest?

10. Caused you to decrease your physical activities (exercising, sports, etc.)?

11. Prevented you from feeling rested upon waking in the morning?

12. Frustrated your family and friends?

13. Caused you anxiety or worry?

14. Caused you to stay home more often than you would prefer?

15. Caused you to adjust your travel plans so that you are always near a toilet?

16. Made you avoid activities away from toilets (i.e., walks, running, hiking)?

17. Made you frustrated or annoyed about the amount of time you spend in the toilet?

18. Awakened you during sleep?

19. Made you worry about odour or hygiene?

20. Made you uncomfortable while travelling with others because of needing to stop for a toilet?

21. Affected your relationships with family and friends?

22. Caused you to decrease participating in social gatherings, such as parties or visits with family or friends?

23. Caused you embarrassment?

24. Interfered with getting the amount of sleep you needed?

25. Caused you to have problems with your partner or spouse?

26. Caused you to plan activities more carefully?

27. Caused you to locate the closest toilet as soon as you arrive at a place you have never been?

For questions 3 to 27 one of the following answers can be given:

none of the time 1

a little of the time 2

some of the time 3

a good bit of the time 4

most of the time 5

all of the time 6

28. Overall, how much do your urinary symptoms interfere with your everyday life?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

Thank you very much for answering these questions.

17. Appendix 2. Conclusions from the Expert Committee on Hypersensitivity

The following text is derived from the sponsor's Integrated Summary of Safety:

Across all populations, the Expert Committee identified 2 plausible hypersensitivity reaction cases of immediate type. Both occurred in patients from Global 12-week Phase 2/3 Population (defined as the Global OAB 12-week Phase 2/3 Population with the addition of studies 178-CL-003, 178-CL-004 and 178-CL-049). The events occurred in 1/2292 (< 0.1%) placebo, 0/3012 mirabegron < 100mg-, 1/1667 (0.1%) mirabegron ≥ 100mg-treated patients and 0/1022 tolterodine-treated patients and included pruritus generalized in a mirabegron-treated patient and urticaria in a placebo-treated patient.

Across all populations, the Expert Committee identified 38 subjects who experienced plausible hypersensitivity reactions of nonimmediate type, including 33 subjects with hypersensitivity reactions assessed as primarily cutaneous and 6 subjects with hypersensitivity reactions assessed as primarily noncutaneous. One subject experienced 2 nonimmediate hypersensitivity reactions – one categorized as primarily cutaneous (urticaria) and the other categorized as primarily noncutaneous (leukopenia).

Across all populations, there were 32 mirabegron-treated subjects with plausible hypersensitivity reactions categorized as nonimmediate type, including 29 subjects with primarily cutaneous reactions and 4 subjects with primarily noncutaneous reactions (one mirabegron-treated subject experienced nonimmediate hypersensitivity reactions of both types).

Across all populations, the Expert Committee identified 5 patients who experienced plausible hypersensitivity reaction of undetermined type: 3 patients from Global 12-week Phase 2/3 Population (1/2292 [< 0.1%] placebo, 0/3012 for mirabegron < 100 mg, 2/1667 [0.1%] for mirabegron ≥ 100mg and 0/1022 for tolterodine patients) and 2 patients from EU/NA Long-term Controlled Population (0/812 mirabegron 50mg, 1/820 [0.1%] mirabegron 100mg and1/812 [0.1%] tolterodine patients) [Module 5.3.5.3 Hypersensitivity Research Report Tables 6.1.1.1 and 6.1.1.2]. None of these cases were identified as definite hypersensitivity reactions.

Overall, the available clinical data do not support an association of mirabegron exposure with immediate-type hypersensitivity reactions.

Hypersensitivity reactions of hemolytic anemia and thrombocytopenia (1 patient) and neutropenia (1 patient) occurred in mirabegron-treated patients, but there was not a consistent pattern to establish an association of mirabegron with nonimmediate, primarily noncutaneous hypersensitivity reactions.

Nonimmediate, primarily cutaneous hypersensitivity reactions of urticaria, leukocytoclastic vasculitis, rash, pruritus, purpura, and lip and eyelid edema, occurred in mirabegron-treated patients during the clinical development program including SAE of cutaneous vasculitis (1 patient) and urticaria (2 patients). An association of mirabegron, particularly at doses > 100mg, with nonimmediate, primarily cutaneous reactions cannot be ruled out.

These cutaneous reactions were generally reversible with discontinuation of mirabegron and symptomatic treatment as clinically indicated.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au