18 October 2012
EMA/706651/2012/corr.

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Betmiga

International non-proprietary name: **mirabegron**

Procedure No. **EMEA/H/C/002388**

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse event
APTC/MACE	Antiplatelet Trialists' Collaboration/Major adverse cardiovascular events
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
CL_{cr}	Creatinine clearance
CL_R	Renal clearance
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
E_{max}	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
MDRD	Modification of diet in renal disease
MRHD	Maximum recommended human dose (50 mg mirabegron daily)
NDA	New Drug Application
NSA	National Scientific Advice
OAB	Overactive bladder
OAB-q	Overactive Bladder Questionnaires
OCAS	Oral controlled absorption system
OCAS-M	Oral controlled absorption system with an intermediate dissolution rate
OCT	Organic cation transporters
PD	Pharmacodynamic
PDCO	Pediatric 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
PRO	Patient related outcomes
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
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. Background information on the procedure

1.1. Submission of the dossier

The applicant Astellas Pharma Europe B.V. submitted on 25 August 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Betmiga, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 July 2010.

The applicant applied for the following indication: Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in patients with overactive bladder (OAB) syndrome.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/172/2010 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/172/2010 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance mirabegron contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Betmiga has been granted a Marketing Authorisation in Japan on 01/07/2011 and the United States of America on 28/06/2012.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur:	**Concepcion Prieto Yerro**	Co-Rapporteur:	**Ian Hudson**
Evaluators:	Marta Moreno	Evaluators:	Vikas Jaitely
	Luisa Arreaza		Michelle McDonald
	Fernando Méndez		Olaperi Aghadiuno
	Macarena Rodríguez		Denise Till
	Germán Kreis		Martin Hurst
	Inmaculada Corrales		Geraldine Richter

- The application was received by the EMA on 25 August 2011.
- The procedure started on 21 September 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 December 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 December 2011.
- During the meeting on 19 January 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 January 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 May 2012.
- The finalised report for the inspection carried out at the following site Astellas Pharma Technologies Inc, 3300 Marshall Avenue, Norman, OK 73072, USA between 16-18/04/2012 was issued on 04/06/2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 4 July 2012.
- During the CHMP meeting on 16-19 July 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 August 2012.

  The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of outstanding issues to all CHMP members on 10 September 2012.
- During the meeting on 15-18 October 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Betmiga on 18 October 2012.

2. Scientific discussion

2.1. Introduction

Problem statement

The International Continence Society defines Overactive bladder (OAB) as urgency, with or without urge incontinence associated with increased micturition frequency and nocturia.[1] Its aetiology is not completely clear, but involves detrusor overactivity, a status of increased sensitivity of the bladder to contraction-mediating transmitters and mediators originating from the urothelium[2] Detrusor over-activation involves afferent signalling conveyed as bladder sensations that are felt as urgency in patients with OAB.[3]

The overall prevalence of OAB in Europe has been estimated to be 16.6% on the basis of a population-based survey (15.6% for men and 17.4% for women). There is a female-to-male preponderance in the prevalence of OAB with urge urinary incontinence, while OAB without urge urinary incontinence is more prevalent in men.

The prevalence of OAB symptomatology increased with advancing age in both men and women (41.9% of men and 31.3% of women over the age of 75 years). Obesity relates also with an increase in the prevalence of OAB.

The functional integrity of the lower urinary tract, the kidneys, and the nervous system (predominantly under the control of the parasympathetic nervous system) are the key factors to maintain continence and bladder function. Bladder function involves a bladder filling and urine storage phase, which leads to a bladder emptying phase. A stable bladder wall muscle (detrusor) and a functional sphincter allow bladder filling during the storage phase.

Undesired bladder muscle contraction may occur as the result of a break in the neurological pathway from the brain to the bladder. It can also occur if the bladder is irritated and the normal neurological impulses to inhibit urination are insufficient to keep the bladder relaxed as it fills.

Although OAB is not life threatening, symptoms may affect quality of life. Patients consider urinary leakage, frequency and urgency to be bothersome. Complications and comorbidities include urinary tract infection (UTI), skin ulceration in OAB with urge incontinence, and a greater risk of bone fracture from a fall, although some research has found little association. Sleep disturbances, restricted mobility, isolation and depression are described as the psychological and lifestyle related consequences of OAB.

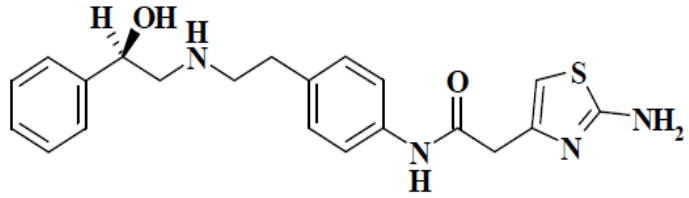
Treatment may be managed using nonpharmacologic and pharmacologic strategies. Nonpharmacologic treatment includes lifestyle changes (controlled fluid intake), behavioural therapies, pelvic floor electrical stimulation, and surgical procedures.

The pharmacotherapeutic treatment options indicated for OAB are aimed at reducing or suppressing the intensity of involuntary detrusor contractions. Anticholinergic agents such as solifenacin, oxybutynin, trospium, darifenacin, tolterodine and fesoterodine are the most commonly used. Non pharmacologic treatment options contain behavioural techniques, neuromodulaton and surgery.

[1] Wein A & Rovner E.Definition and epidemiology of overactive bladder. Urology 60 (supplement 5A), November 2002.
[2] Birder et al. Neural control of the lower urinary tract:peripheral and spinal mechanisms. Neurourology and urodynamics 29: 128-139 (2010)
[3] Gillespie J.I Noradrenaline inhibits autonomous activity in the isolated pig bladder. BJU international 93: 401-409 2004

About the product

Mirabegron is a selective agonist for human beta 3-adrenoceptor (beta 3-AR) which is dominant in the human detrusor muscle. Activation of beta-AR in the bladder trigone facilitates urine storage through flattening and lengthening of the bladder base.[4]



Mirabegron dose-dependently increased cyclic adenosine 3', 5'-monophosphate (cAMP) concentrations in bladder tissues isolated from rats and showed a potent relaxant effect in isolated rat and human bladder strips precontracted with carbachol at low contraction tonus.

The drug product is formulated as prolonged release film coated tablets. The tablets are formulated as a hydrophilic gel-forming matrix tablet formulation, designed for continuous drug release throughout the GI tract.

The claimed and approved indication for Betmiga is for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in patients with overactive bladder (OAB) syndrome.

The proposed posology is 50 mg once daily with or without food. In patients with severe renal impairment or with moderate hepatic impairment, the recommended dose of mirabegron is 25 mg orally once daily with or without food.

Type of application and aspects on development

This application is submitted as a centralised procedure according to Article 8(3) of Directive 2001/83/EC (i.e. a dossier with administrative, quality, pre-clinical and clinical data).

The initial clinical development program examined an indication of type 2 diabetes mellitus and was subsequently discontinued due to the absence of efficacy demonstrated in this population based on proof of concept studies. A total of 29 phase 1 studies and 12 phase 2 and 3 studies (9 in patients with OAB, 1 in patients with LUTS/BOO and 2 in patients with type 2 diabetes mellitus) have been conducted globally in Europe, the US, Canada, Japan, Australia/New Zealand and South Africa.

The primary studies to support efficacy of mirabegron were designed consistent with Committee for Medicinal Products for Human Use (CHMP) guidance for the clinical investigation of medicinal products for urinary incontinence. Further, the company received national scientific advice from the Competent Authorities in the Netherlands, Sweden and Spain during the development programme. In general, the recommendations from the authorities were followed.

A Pediatric Investigation Plan (PIP) for mirabegron was submitted to the EMA Pediatric Committee (PDCO), and a positive opinion was fowarded to the applicant in August 2010; the measures of the agreed PIP were deferred at the time of the submission of the MAA.

[4] Yamanishi T, Chapple C Yasuda K et al. Role of β-Adrenoceptor subtypes in mediating relaxation of the pig bladder trigonal muscle in vitro. Neurourology and urodynamics 22: 338-342 (2003).

2.2. Quality aspects

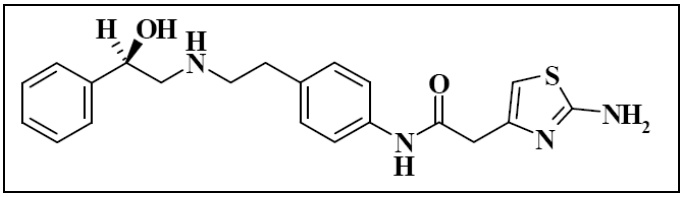
2.2.1. Introduction

The finished product is presented as prolonged released film coated tablet containing 25 and 50 mg of mirabegron as the active substance. The composition is described in section 6.1 of the SmPC.

The product is available in the primary packaging as described in section 6.5 of the SmPC.

2.2.2. Active substance

Mirabegron is a white crystalline powder, not hygroscopic and freely soluble in dimethyl sulfoxide, soluble in methanol and soluble in water between neutral to acidic pH. The chemical name is 2-(2-Amino-1,3-thiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2- phenylethyl]amino}ethyl)phenyl]acetamide. The molecular formula is $C_{21}H_{24}N_4O_2S$ and has the following structural formula:



Mirabegron exhibits stereoisomerism due to the presence of one chiral centre. The R enantiomer has been used in the manufacture of the finished product. The enantiomeric purity is controlled routinely by chiral HPLC-UV. Polymorphism has been observed for the active substance. The polymorphic form α is routinely and consistently produced by the synthetic process and it is used in the manufacture of the finished product.

Full information on the active substance mirabegron is provided in the dossier.

Manufacture

Mirabegron is synthesized in five main steps using commercially available and well defined starting materials. The final active substance is purified by crystallisation. The manufacturing process is well described. The defined critical process parameters (CPPs) and proposed in-process tests are considered suitable. All relevant parameters are controlled within the specified ranges in order to maintain the quality of the active substance.

Two manufacturing sites are involved in the synthesis of this active substance.

The specifications and control methods for intermediate products, starting materials and reagents have been presented

For the manufacturing process development the applicant has applied the Quality by Design (QbD) approach based on the risk-assessment of the synthetic process. The risk-assessment has provided valuable information to understand the synthetic process. In summary, the QbD principles were used

only during the drug development in order to optimise the manufacturing conditions. No design space has been established for manufacturing process of the active substance.

The purified active substance is packed in double low-density polyethylene (LDPE) bags, closed by cable-ties and placed inside sealed fiber drums.

Specification

The active substance specification includes tests for: identification (UV, IR), heavy metals, impurities (HPLC), residual solvents (GC), water content (Ph. Eur.), residue on ignition (Ph. Eur.), microbiology limit test (Eur.), Palladium content (ICP-AES) and assay (HPLC, 98.0– 102.0%).

A detailed description for all analytical methods was provided. Full method validation data was provided for the in-house analytical methods and are in accordance with the relevant ICH Guidelines. In general analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data on eleven commercial batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Six production scale batches of the active substance packed in the intended commercial packaging (LDPE bags) from the proposed manufacturer were put on stability testing as per ICH conditions: under long term (25°C/60%RH) for up 24 months, and accelerated (40°C/75%RH) for up 6 months.

The active substance used in the primary stability studies was manufactured by a process that is representative of the commercial process. The following parameters were tested in the primary stability studies: appearance, identification, X-ray diffraction, thermal analysis, impurities, water content, microbial contamination and assay.
Photostability testing following ICH guidelines Q1B was performed on one batch. The results showed that only the appearance of the active substance slightly changed when exposed to light for two months.

Forced degradation studies were conducted by exposing the active substance to high temperature, high humidity, acid, base, oxidative and high intensity light conditions. Based on the results only minor degradation of mirabegron was noted.

Pharmaceutical development

Mirabegron prolonged released film coated tablets have been developed to control the drug release from the tablet, leading to a slower absorption rate in the gastrointestinal (GI) tract compared to immediate release formulations, even in fasted conditions.
During the development several modified released formulations were evaluated. Based on the results of the experimental studies the OCAS was selected as a modified release platform that could achieve the quality target product profile.

The OCAS is a hydrophilic gel-forming matrix tablet formulation, composed of active substance and Macrogols. This matrix tablet formulation designed for continuous drug release in the human GI tract.

The solubility of the selected gel forming agent and gel-enhancing agent are pH-independent. Therefore, drug release from prolonged released film coated tablets is relatively unaffected by different pH dissolution media.

Mirabegron prolonged released film coated tablets were developed using QbD principles. The CQAs identified were dissolution, appearance, assay, uniformity of dosage units, impurities, stability Prior knowledge, risk assessment, design of experiments and mathematical models were applied to identify the and CPPs. The CPPs have been adequately established. The QbD approach was also used to optimise the manufacturing conditions.

It can be concluded that the QbD principles were used for optimisation of the final formulation as well as for the development of the manufacturing process, but no Design Space is claimed for the manufacturing of the finished product.

The primary packaging proposed is described as stated in section 6.5 of the SmPC. The material complies with Ph. Eur. requirements and it is adequate to support the stability and use of the medicinal product.

Adventitious agents

No excipients derived from animal or human origin have been used

Manufacture of the product

The manufacturing process consists of eight main steps: mixing, granulation, pulverization, blending, compression, dispersing, coating and packaging. The process is considered to be a standard manufacturing process.

The manufacturing process has been validated at commercial scale for both strengths and has been demonstrated to be capable to reproducibly produce a finished product of the intended quality. The in-process controls are adequate.

Product specification

The finished product release specification includes appropriate tests for appearance (visual), identification (UV, HPLC), impurities (HPLC), uniformity of dosage units (Ph. Eur), dissolution, water content (Ph. Eur), microbial limit test (Ph. Eur) and assay (95.0%-105.0%).

Batch analysis results in three commercial batches of 25 mg and four commercial batches of 50 mg batches confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability of the product

Stability data of three batches of each strength have been provided. The batches were stored under long term conditions at 25ºC/60%RH for up to 36 months and under accelerated conditions at 40ºC/75%RH for up to 6 months according to ICH guidelines. These batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The stability samples were tested for appearance, impurities, dissolution, assay, water content, hardness, BHT content and microbiological quality. The analytical procedures used were stability indicating.

Forced degradation tests were performed under high temperatures, high humidity and high temperature/high humidity. These tests demonstrated no major changes in the parameters specified of the finished product. Only the increase of the dissolution rate was observed.

In addition, the photostability of one batch of each strength was evaluated in accordance with ICH guideline Q1B (Photostability Testing of New Drug Substances and Products). Based on the results there is no need to protect the finished product from light.

Based on available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.3. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The Applicant used the Quality by Design principles in this application during the pharmaceutical development but a design space was not claimed for the manufacturing process of the active substance neither for the finished product. Risk assessment was done to optimise the manufacturing conditions of the active substance. For the finished product, the Quality by Design approach was used for optimisation of the formulation as well as for the development of the manufacturing process. The control strategy and process validation follow the traditional approach. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.4. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.5. Recommendation(s) for future quality development

None

2.3. Non-clinical aspects

2.3.1. Introduction

A comprehensive non-clinical programme has been performed covering studies to investigate pharmacology including safety pharmacology, pharmacokinetics as well as toxicology including single and repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and

development. The studies have been performed in rats, mice, rabbits, dogs and cynomolgus monkeys. Drug administration was performed IV. or *per os*, mimicking the human route of administration.

No scientific advice was received from the European Medicines Agency on non-clinical development.

Toxicology and some of the definitive safety pharmacology studies conducted by the applicant were reported to be GLP-compliant. The safety studies that were not conducted to GLP were conducted to appropriate scientific standards prevailing at that time.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro, mirabegron has substantially higher (150-and 33-fold) affinity for the β_3 adrenoceptor, when compared to the β_1 and β_2 adrenoceptors, respectively. Intrinsic activities relative to the maximum response induced by the full agonist isoproterenol, for mirabegron were 0.1, 0.2, and 0.8, for human β_1-, β_2- and β_3- ARs respectively. Functional studies to demonstrate agonism at the β-adrenoreceptors demonstrate that mirabegron is a selective β_3 adrenoceptor agonist with EC_{50} values in the nanomolar range. It has been established that mirabegron has weak agonistic activity at the β_1 and β_2 receptors in most of the species studied. However, it was observed that *in vitro* no functional agonism at the β_1 or β_2 receptors occurred at concentrations that were at least 21-fold higher than that observed clinically.

The effect on bladder smooth muscle was assessed *in vitro* in bladder tissues isolated from rats and humans. The results suggest a relaxant effect mediated by β_3-ARs in bladder strips precontracted with the muscarinic receptor agonist, carbachol with a maximum relaxant effect similar to isoproterenol.

In vivo studies in anesthetized rats revealed that mirabegron decreased the resting intravesical pressure and also decreased the frequency of rhythmic bladder contractions without affecting the contraction force. Mirabegron increased cAMP concentrations in the isolated bladder (rat) at ≥1 μM and relaxed pre-contracted bladder smooth muscle (rat and human) with EC_{50} values of 5.1 to 11 μM and 0.78 μM, respectively. The intracellular mechanisms for bladder relaxation in bladder strips pre-contracted with carbachol and KCl is likely to be via an increase in cAMP and activation of Ca^{2+}-activated K^+ (BKCa) channels, respectively and it is noted that not all of the mechanistic aspects have been demonstrated experimentally. It is evident that the three β-adrenoceptor subtypes (i.e. β_1, β_2 and β_3) are expressed in human detrusor muscle and with the aid of selective antagonists for the β_1 and β_2 adrenoceptors, the Applicant has demonstrated that the bladder relaxant effect of mirabegron in the rat may be mediated by the β_3-receptor.

In vivo data from conscious water loaded cynomolgus monkeys reveal that mirabegron increased the micturition mean voided volume and decreased voiding frequency. Intravenously administered mirabegron reduced resting and elevated intravesical pressure in the rat (at ≥0.03 mg/kg) and dog (at ≥0.0003 mg/kg), respectively. In a rat model of hyperactive bladder (cerebral infarction model), mirabegron increased the mean voided volume per micturition. In rats with partial urethral obstruction, mirabegron decreased the frequency of non-voiding contractions without affecting the voided volume per micturition, voiding pressure, or residual urine volume. It was noted that mirabegron at 3 mg/kg had no effect on the voided volume in a rat model of partial urethral obstruction, while this dose was previously shown to be effective in the rat and monkey. The differences in the underlying pathology of and experimental methods for the animal models may be responsible for the observed differences in the effects on voided volume in the rat.

Secondary pharmacodynamic studies

The secondary pharmacology of mirabegron was studied. Mirabegron and the human metabolites M5 and M16 inhibited the binding of specific ligands to the α_{1A}-receptor (rat), muscarinic M_2 receptor (human), sodium channel site 2 (rat), dopamine transporter (human), and/or norepinephrine transporter (human) at 10 µM. The Applicant has suggested that any secondary pharmacological effects would be attributed to mirabegron as opposed to the M5 or M16 metabolite. The K_i values for the secondary targets listed above were at least ~22-fold higher than the clinical C_{max}. Given the magnitude of the observed margin and the adverse event profile observed clinically, the observed interactions at the secondary targets do not appear to be clinically relevant.

In vitro studies have demonstrated that mirabegron possesses lipolytic activity at nanomolar concentrations. *In vivo*, mirabegron caused an increase in energy expenditure and body temperature and improved glucose intolerance in genetically obese rodents at doses known to have effects on bladder function. The effects of mirabegron on lipolysis do not translate to non-rodent species. Although mirabegron may affect non-esterified fatty acid levels following administration of a single dose, mirabegron has no discernable effect on lipid metabolism, glucose metabolism or body temperature upon repeated administration in healthy subjects and/or in diabetes mellitus patients.

Safety pharmacology programme

Central nervous system findings in rats and mice included decreased locomotor activity, decreased grip strength, lateral position, palpebral closure, and at higher doses deep respiration, decreased muscle tone, prone position, and loss of righting reflex. CNS depression was reported at exposures close to clinical exposures. These findings were transient and no relevant CNS findings were identified in the cynomolgus monkey at significantly higher exposures than those proposed clinically.

Assessment of mirabegron on hERG current in HEK293 revealed an Ikr inhibition of 14.7% at 30 µmol/L although this concentration was more than 600-fold the unbound C_{max} at the maximum recommended human dose (MRHD). Mirabegron metabolites M5 and M16 inhibited hERG current, with respective IC_{50} values of 21 and 31 µmol/L, and 17.3% for M14, although at concentrations considerably higher than the human expected C_{max}. The observed effects of mirabegron on cardiac muscle action potential were not significant, although M5 at 3 µmol/L prolonged slightly APD_{30} by 6.1% and shortened APD_{30-90} by 7.9%, while concentrations of 30 µmol/L prolonged APD_{30} by 5.6% and APD_{90} by 4.7%. M16 prolonged APD_{90} by 5.0% at 30 µmol/L. Assessment of mirabegron on the effect on arterially perfused canine ventricular wedge preparations did not reveal demonstrable pro-arrhythmic effects of mirabegron and its metabolites.

Following oral administration in the dog, a reduction in QT interval was observed at 10 mg/kg; when corrected for heart rate, an increase in QTc interval was apparent (at ≥0.3 mg/kg) upon application of Bazett's or Van der Water equations, while no effect on QTc was reported upon application of the Matsunaga equation. The Applicant has supplied references in order to support the use of the Matsunaga equation as opposed to the Van de Water equation (Matsunaga et al., 1998; Miyazaki, 2002). In the monkey, an increase in PR and QRS interval was noted at 100 mg/kg and no effects were reported on QT/QTcB/QTcF interval or body temperature following single oral administration of up to 100 mg/kg. However, the 52 week repeated dose study conducted in both males and females has demonstrated sporadic increases QTcB interval at 30 mg/kg. The corresponding C_{max} (at Week 52) was ~11-fold higher than that proposed clinically; hence, these data do not indicate any potential for QT prolongation in man at the proposed clinical dose of 50 mg. A post authorisation safety study to further characterise the cardiovascular safety of mirabegron has been requested (see Clinical Safety), as detailed in the Risk Management Plan.

Oral administration to conscious dogs and monkeys showed that mirabegron caused an increase in heart rate. In the dog, mirabegron (at ≥0.03 mg/kg) increased heart rate (and shortened PR interval), at doses lower than those proposed clinically. Systolic and mean arterial blood pressures were also significantly decreased at 0.3 to 10 mg/kg. In the cynomolgus monkey, mirabegron increased heart rate at 10 mg/kg (C_{max} approx 29.6-fold higher than that observed at the MRHD).

Single intravenous administration of mirabegron to conscious dogs caused death due to ventricular fibrillation at 10 mg/kg) and ECG findings were reported from doses of 0.3 mg/kg (HED corresponds to 0.2-fold MRHD). Other findings included increased heart rate, decreased mean blood pressure, absent P-wave, prolonged QRS interval, and ventricular tachycardia. The Applicant suggests that increases in heart rate observed in rats, dogs, and monkeys are mediated via cross activation of the beta 1-adrenoceptor (beta 1-AR). Heart rate increases and ECG changes together with histopathological findings were only reported in dogs at lethal doses while histopathological findings observed in the heart in monkeys were limited to the fat tissue surrounding the heart (small adipocytes and multivacuolated cytoplasm) with no histopathological findings in the cardiomyocytes. In humans at the MRHD the heart rate increase was limited to approximately 1 bpm. In non clinical studies at doses where smaller increases in heart rates were observed, no histopathological findings were noted.

Studies carried out in cynomolgus monkeys receiving a single oral dose of mirabegron, did not reveal effects on the respiratory system. Mirabegron administration to dogs increased respiratory rate and decreased partial pressure of carbon dioxide in blood at 3 mg/kg. The mechanistic process underlying this event in dogs was not investigated as it was only reported in one species and was not observed in humans at doses up to 6-fold higher than the MRHD.

In vitro, mirabegron inhibited contraction of guinea-pig ileum at concentrations below the proposed clinical C_{max} (free). There is evidence to suggest that the administration of β_3 agonists (of comparable potency) is associated with a decrease in gastrointestinal motility, nonetheless the Applicant has demonstrated that although mirabegron inhibited contraction of the guinea pig ileum *in vitro*, no effects on gastrointestinal transit were reported *in vivo*, in the mouse, rat, dog or monkey. More importantly, repeated administration for 7 days at 50 or 100 mg/day had no effect on gastrointestinal transit in man.

Even though there was no effect on urine excretion in rats receiving single dose administration of mirabegron at low doses, higher doses of ≥ 10 mg/kg, revealed that urine volume and the amount of electrolytes excreted was variable with time and dosing. In the rat, mirabegron at ≥10 mg/kg (equivalent to ≥1.9-fold the human equivalent dose) reduced the levels of sodium, potassium and chloride excreted into the urine during the first 3 hours post-dose. In rat toxicity studies of a longer duration, (26 week) effects on electrolytes and urine volume were also observed. Given that the intrinsic activity of mirabegron for the β_1-receptor is higher in the rat and the absence of effects in dogs and monkeys, the CHMP consider these effects to be due to cross activation of the β_1 receptor.

Pharmacodynamic drug interactions

No specific pharmacodynamic drug interaction studies were conducted, which is accepted. The potential for pharmacodynamic interactions between mirabegron and concomitantly administered medicinal products has been addressed in the Clinical Dossier with clinical data.

2.3.3. Pharmacokinetics

The analytical methods used were validated and considered to be sufficiently accurate.

Absorption

Mirabegron absorption was studied after single and repeated dose administration in fasted and non fasted males (rat, mouse and dog). The absorption profile in females was generally consistent with that observed in male rats after oral administration.

Mirabegron was well and rapidly absorbed in the species tested. In rats the mean *in situ* absorption into each loop of gastrointestinal tract was variable with the highest values reported in the small intestine accounting for duodenum, jejunum, and ileum were 55.5%, 61.7%, and 65.9% of absorption respectively and the lowest in the stomach and colon at 7.1% and 15.1%, respectively.

Mean peak plasma concentrations in a single dose administration study in fasted rats and monkeys were observed at 3 h and 0.25 h post-dose, respectively. The AUC_{inf} of mirabegron in plasma was low for both species accounting for 18 and 5% of total radioactivity in plasma confirming that metabolites accounted for a significant proportion of the drug-related material.

Absolute bioavailability in rats was 23.0%, 48.4%, and 75.7% at doses of 3, 10, and 30 mg/kg, respectively, and in dogs 41.8%, 64.6%, and 77.1% at doses of 0.25, 0.5, and 1 mg/kg, respectively.

A single oral dose study in fasted and fed dogs revealed that the mean t_{max} value for mirabegron administered was independent of the feeding status; however, C_{max} and AUC_{inf} values under fed conditions were 78.5% and 65.8%, respectively, of those under the fasted conditions, suggesting that mirabegron absorption was reduced in the presence of food.

Repeated dosing of mirabegron in non fasted male rats for 21 days indicate that the AUC_{24h} and C_{max} increased with dose and that steady state was achieved by Day 17.

Distribution

When single doses of mirabegron were intravenously administered to rats (1 mg/kg) and dogs (0.1 mg/kg), total body clearance (CL_{tot}) was high for both species at 47.4 and 37.2 mL/min/kg, respectively. Also, the steady state distribution volume (V_{ss}) was large in both species at 10.3 and 14.3 L/kg, respectively, indicating that mirabegron is extensively distributed.

Plasma protein binding of mirabegron *in vivo* in man was 71%. Albumin was estimated to be the main human plasma protein responsible for the binding of mirabegron, followed by alpha 1-acid glycoprotein.

Mirabegron distribution to erythrocytes was reported and the *in vitro* blood/plasma radioactivity concentration ratio of ^{14}C-mirabegron was fairly similar for all species; ranging from 1.41 to 1.43 in humans.

Radioactivity distributed to all organs with the lowest value reported in the GI tract. The highest was found in the liver and kidney and the lowest in the cerebrum and cerebellum remaining low after repeated administration. In albino and pigmented rats, at 168 and 360 hours post-dose, most tissues showed less than 10% of their peak radioactivity concentrations. Pigmented rats showed 18-fold higher peak values of radioactivity in the eyeball compared to that observed in albino rats and the elimination half-life of radioactivity from the eyeball was estimated to be 157 days. A high percentage of the radioactivity corresponded to metabolites (with no pharmacological activity).

In pregnant rats, low levels of mirabegron-derived components crossed the placental barrier and were transferred to the fetus. Mirabegron-derived components were excreted into the milk.

Metabolism

Mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, glucuronidation, and amide hydrolysis. The metabolic rate was faster in cynomolgus monkeys, followed by dogs and rats, then humans. Metabolites generated by human microsomes were also formed by at least one of the animal species examined. A total of 18 metabolites from mirabegron were identified in plasma, urine and/or bile from male mice, rats, cynomolgus monkeys and humans. In human urine and plasma, ten and eight metabolites were identified respectively. All the metabolites found in human plasma were also observed either in rat or cynomolgus monkey plasma, suggesting that both species are relevant species for toxicity studies.

Excretion

After oral administration of ^{14}C-mirabegron at 10 mg/kg in the rat, elimination of radioactivity accounted for 94.1% of the total radioactivity (18.8% in the urine and 75.3% in the feces). When the same dose was administered to the monkey, the overall radioactivity recovered accounted for 101% (46.8% in urine and 54.2% in feces) while in bile duct cannulated male rat, the excretion rate of radioactivity was 37.3% in the urine and 29.4% in the bile suggesting that enterohepatic circulation occurs in this species. In humans, urine and fecal excretion accounted for 55.0% and 34.2% respectively.

2.3.4. Toxicology

Single dose toxicity

Mirabegron was administered to fasting rats at single oral doses of 300, 500, and 800 mg/kg and observed for mortality and general conditions for 14 days. The lethal dose of mirabegron was ≥ 800 mg/kg. Other findings reported in the study included hypoactivity, salivation and lacrimation in all groups. Chromodacryorrhea was observed at 300 mg/kg and prone position together with loss of body weight at ≥ 500 mg/kg, while clonic convulsion was reported at 800 mg/kg. Necropsy of one dead male at 800 mg/kg revealed a pale liver. Histopathological examination showed hepatocyte hypertrophy and vacuolar degeneration around the liver lobule.

Mirabegron was also administered to dogs as a single oral dose of 0, 0.3, 3, or 30 mg/kg to one male and one female beagle dog per group. The lethal dose of mirabegron was ≥ 30 mg/kg. Skin reddening and increased heart rate was observed in all groups. Vomiting was reported in the 30 mg/kg group. Histopathological examination revealed focal acinar dilatation/ disruption in the zygomatic gland at 0.3 and 3 mg/kg while necrosis of the zygomatic gland was reported at 30 mg/kg.

Repeat dose toxicity

Mirabegron was extensively studied in oral repeated dose studies in mice (two weeks), rats (26 weeks), dogs (two weeks) and monkeys (52 weeks). Additional short term studies were also carried out by intravenous repeated dose administration in rats and monkeys.

Table 1: Repeated Dose Toxicity Studies with Mirabegron

Species /strain duration	Method of Administration	Dose (mg/kg) †	GLP	TK
Mouse/Crj:B6C3F$_1$ 2 weeks	Oral gavage	0, 30, 100, 300	Yes	Yes
Mouse/Crj:B6C3F$_1$ 13 weeks	Oral gavage	0, 50, 100, 200	Yes	Yes
Mouse/CD1 (ICR) 5 days	Oral gavage	10, 30, 100, 300	No	No
Mouse/CD1 (ICR) 2 weeks	Oral gavage	0, 10, 30, 100	No	No
Rat/F344 DuCrj 2 weeks	Oral gavage	0, 10, 30, 100, 300	Yes	Yes
Rat/F344 DuCrj 13 weeks	Oral gavage	0, 10, 30, 100, 300	Yes	Yes
Rat/F344 DuCrj 26 weeks	Oral gavage	0, 3, 10, 30, 100	Yes	Yes
Dog/beagle 3 days	Oral/capsules	0, 20	Yes	Yes
Dog/beagle 2 weeks	Oral/capsules	0, 1, 3, 10, 20	Yes	Yes
Monkey/cynomolgus 2 weeks	Oral gavage	0, 10, 30, 60	Yes	Yes
Monkey/cynomolgus 13 weeks	Oral gavage	0, 3, 10, 30	Yes	Yes
Monkey/cynomolgus 52 weeks	Oral gavage	0, 3, 10, 30	Yes	Yes

*Nonpivotal studies;
† The underlined dose represents the no observed adverse effect level (NOAEL).
Source: Module 2.6.7 Section 6

In the mouse, repeated oral administration of mirabegron for 5 days, resulted in the death of an animal at 300 mg/kg. The animal showed decreased spontaneous movement and clonic convulsion. Dose related increase of the frequency of reduced spontaneous movement was reported; a finding that was also reported during a 2-week study, tended to diminish with repeated administration. Plasma concentration increased dose proportionally up to 100 mg/kg but thereafter the increase was less than proportional with dose. Increased food consumption and increases in red blood cell count, haemoglobin and hematocrit were reported. Blood chemistry showed non-dose or gender related changes. Liver weight was increased. In males, heart, lung and spleen weights were also increased. Decreased lipid droplet size in the brown and reduced adipocyte size with multi-vacuolated cytoplasm in the white fat were reported. Extramedullary hematopoiesis was identified in both genders at 100 mg/kg and increased pale areas of hepatocytes were reported in males. A NOAEL was not identified. There were no marked differences in C_{max} or AUC_{0-24h} on repeated dosing.

Repeated dose toxicity studies in rats revealed enzyme increases in plasma aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels at dose levels of mirabegron of ≥ 30 mg/kg. In a 13-week study, hepatocyte necrosis was observed at doses of ≥100 mg/kg; however, these findings were not observed at the same dose levels following 26 weeks of daily administration.

Decreased locomotor activity was reported at high doses of ≥ 100 mg/kg/day in a 2 week study and prone position was noted at 3 mg/kg in males and 10 mg/kg in females (systemic exposures of 0.3 and 1.7-fold the human exposure at MRHD, respectively). Decreased platelet counts were seen in all rat studies at 100 mg/kg and alterations in reticulocyte counts at 300 mg/kg although the latter was only observed during a 2-week repeated dose study. Triglycerides were decreased in rat studies from doses of 10 mg/kg (2.7-fold of the exposure at the MRHD). Reversible eosinophilic changes were noted in liver hepatocytes of rats administered mirabegron. Electron microscopic evaluation of this finding suggested that the eosinophilic changes were the result of a decrease in the number of glycogen particles in the hepatocytes.

Renal effects of mirabegron were limited to changes in urine volume and electrolyte excretion in rats and were probably due to the pharmacological effects of the drug.

Studies in the dog were of short duration and the main findings were of a cardiovascular nature. Skin reddening and ventricular tachycardia (and subsequent death) at 20 mg/kg were reported. At ≥ 10 mg/kg, a clear increase in heart rate was reported, together with ECG increases in P wave duration, QRS interval and T wave amplitude prolongation and a reduction in P-R interval. Swelling around the eyes, ocular discharge and/or reddened sclera and the microscopic pathology findings of degeneration/inflammation of the zygomatic salivary gland were reported at ≥ 3 mg/kg. At 20 mg/kg, vacuolation in the liver was observed in males and myocardial degeneration of the left ventricle in females. Endocardial hemorrhage in the left ventricle of the heart, periportal vacuolation of the liver, focal areas of loss of blood in the red pulp of the spleen, and hemorrhage/congestion of the thymus were observed in females at 20 mg/kg that died during the treatment period. The implications of cardiovascular findings have been discussed previously. As the 20 mg/kg dose was lethal to some of the animals it could not be repeatedly administered to surviving animals. In a 3-day study in dogs, slight increases of liver enzymes and hepatocellular hypertrophy were noted at a lethal dose; these changes were reversible in surviving animals.

Repeated dose studies in the cynomolgus monkey demonstrated ventricular tachycardia at 60 mg/kg. In a 13-week study, ventricular tachycardia was reported in one animal at 30 mg/kg/day at one time point and was confirmed in a 52-week repeated-dose monkey study at the same dose. The PR interval tended to be prolonged in both males and females at ≥ 10 mg/kg. Following IV administration, transient ventricular tachycardia and prolongation of the PR interval was observed at ≥ 1 mg/kg/day, as well as a slight transient prolongation of the QRS interval at 3 mg/kg/day.

Genotoxicity

Mirabegron as assessed by the bacterial reverse mutation test, the human peripheral blood lymphocyte chromosomal aberration test and the rat micronucleus test was not genotoxic.

Carcinogenicity

Repeated administration of mirabegron to mice and rats for 104 weeks did not reveal a potential to cause carcinogenicity at doses up to 100 mg/kg.

Reproduction Toxicity

Studies to evaluate the effect of mirabegron on fertility and early embryonic development in the rat revealed no effects on male fertility up to 100 mg/kg, although it has been reported that 14 males at 300 mg/kg died. It should be noted that half of the untreated females that copulated with the males in this group were non-pregnant and the numbers of corpora lutea, implantations and live embryos were lower in 3 pregnant non treated females. In female rats at 300 mg/kg, prolonged diestrus was observed, as was a decrease in the number of corpora lutea, implantations and live fetuses. A reduction in the size of the prostate, seminal vesicles and uterus was noted during the repeated dose studies in the rat. In addition, regression of the X-zone adrenal glands in the female was noted following repeated oral administration for 13 weeks. The Applicant has clarified that the effects on reproduction are evident at lethal doses only and that fertility changes were reported at exposures that were 156- and 204- fold higher than the human exposure at MRHD in males and females respectively. Moreover, in the monkey, no effects on ovulation frequency or in male and female reproductive organs were reported in the 52-week study. The reduction in fertility and the effects on the seminal vesicles may be secondary to the general condition of the animals. The regression of the X-zone in the adrenal glands of the female rat, was a finding that could not be confirmed in any of the other studies.

Reduced fetal body weight, delayed ossification, wavy ribs and other skeletal anomalies were noted in rat embryofetal studies at exposures that are higher than those proposed clinically. Reduced fetal body weight, dilated aorta, cardiomegaly and increased post-implantation loss were noted during the rabbit embryofetal development study. The exposures at the NOAEL for embryo development are below those proposed clinically. The applicant has conducted follow-up investigative studies and the data suggest the observed cardiovascular malformations and post-implantation loss may be due to the activity of mirabegron or its metabolites at the β1-adrenoceptor. Therefore Mirabegron is not recommended during pregnancy and in women of childbearing potential not using contraception. This is clearly labelled in the relevant parts of the SmPC.

In a rat pre- and postnatal development study, mirabegron had no effects on reproductive function of the dams at doses up to 100 mg/kg/day, and up to 30 mg/kg/day for the offspring.

Toxicokinetic data

See paragraphs above.

Local Tolerance

Local tolerance studies suggest that mirabegron was not irritant to rabbit skin following dermal application, but was irritant to the ocular mucosa of rabbits. Following intravenous administration of mirabegron, edema and erythema were observed at the injection site.

In vitro studies revealed that mirabegron does not have the potential to cause hemolysis at the concentrations tested.

In vivo studies in guinea pigs indicate that mirabegron shows a moderate skin sensitizing potential in the adjuvant/patch test and the Buehler test.

Due to the characteristics and intended use of mirabegron, concerns related to dependence potential are not expected.

Other toxicity studies

The assessment of impurities was outlined in the quality dossier. The specification limit for the major impurity, YM181687 was set to 1%. The Applicant performed a qualification study with levels of Impurity YM181687 as high as 1.51%, including a 2-week toxicity study in rats. The study is considered acceptable as an increasing level of impurity YM181687 neither increased the toxicity nor changed the toxicity profile of mirabegron. The Applicant has also provided additional data (DEREK analysis) which demonstrates that YM181687 does not display an alert for genotoxicity.

Mirabegron does not absorb light at the wavelengths in the range of 290-700 nm. Thus, there is no need for photosafety testing with this product.

2.3.5. Ecotoxicity / environmental risk assessment

The Applicant has performed an environmental risk assessment for mirabegron. During the Phase I of the assessment, the calculation of the predicted environmental concentration (PEC) has resulted in a $PEC_{surfacewater}$ above 0.01 µg/L, and consequently a Phase II environmental fate and effect analysis was carried out. The assessment of “Aerobic Transformation in Aquatic Systems’ study (OECD 308) was not

carried out according to OECD recommendations. Although the guideline requests to conduct both aerobic and anaerobic transformation the study only included data on aerobic transformation. The Applicant justified the lack of including an anaerobic assessment in the study as the 'Questions and Answers on 'Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use' (EMA/CHMP/SWP/44609/2010), states that this type of study would not be required for this type of medicinal product. This was considered acceptable and no further clarification with respect to the ERA is warranted.

Substance (INN/Invented Name): Mirabegron					
CAS-number (if available): 223673-61-8					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log P_{ow}	OECD107	≤2.0			Potential PBT N
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log P_{ow}	**Media** / pH 4 / pH 7 / pH 10 — **$Log_{10} P_{ow}$** / - 0.4 / 0.3 / 2.0			not B
PBT-statement :	The compound is not considered as PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.25	µg/L			> 0.01 threshold Y
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 306…	K_F^{ads} = 21.2 - 197 K_{Foc}^{ads} = 440 - 29500 K_F^{des} = 51.1 - 320			Medium to very high potential for binding to soil; low potential for binding sludge; degree of irreversibility to the adsorption
Ready Biodegradability Test	OECD 301	Mean O_2 consumption Day 19: 10% Day 28: 21%			not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 1.1-1.2 $DT_{50, sediment}$ =20-111 $DT_{50, whole\ system}$ =1.2-1.3 % shifting to sediment =10			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	4.34	mg/L	Species: *Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	1.01	mg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	10.1	mg/L	Species: *Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	100	µg/L	

2.3.6. Discussion on non-clinical aspects

The Applicant has carried out an extensive non clinical development program related to the requested indication.

In vitro, mirabegron has substantially higher affinity for the β_3 adrenoceptor, when compared to the β_1 and β_2 adrenoceptors. No functional agonism at the β_1 or β_2 receptors occurred at concentrations that were at least 21-fold higher than that observed clinically. The results from studies with rat bladder strips suggest a relaxant effect mediated by β_3-ARs.

In vivo studies in anesthetized rats revealed that mirabegron decreased the resting intravesical pressure and also decreased the frequency of rhythmic bladder contractions without affecting the contraction force. Given that the three β-adrenoceptor subtypes (i.e. β_1, β_2 and β_3) are expressed in human detrusor muscle, the Applicant has provided some evidence that the observed relaxation in the human bladder may be mediated by the β_3-receptor. However, not all of the mechanistic aspects have been demonstrated experimentally; hence, the CHMP recommended performing additional mechanistic studies post authorisation to elucidate whether human bladder relaxation induced by mirabegron is indeed mediated via the β_3-receptor.

Oral administration to conscious dogs and monkeys showed that mirabegron caused an increase in heart rate. In the dog, mirabegron (at ≥0.03 mg/kg) increased heart rate (and shortened PR interval) at doses lower than those proposed clinically. Systolic and mean arterial blood pressures were also significantly decreased at 0.3 to 10 mg/kg. In the cynomolgus monkey, mirabegron increased heart rate at 10 mg/kg (C_{max} approx 29.6 fold higher than that observed at the MRHD).

After single intravenous administration of mirabegron to conscious dogs, heart rate increases and ECG changes together with histopathological findings were only reported in dogs at lethal doses while histopathological findings observed in the heart in monkeys were limited to the fat tissue surrounding the heart (small adipocytes and multivacuolated cytoplasm) with no histopathological findings in the cardiomyocytes. In humans at the MRHD the heart rate increase was limited to approximately 1 bpm.

Non clinical studies in dogs and monkeys did not indicate any potential for QT prolongation in man at the proposed clinical dose of 50 mg. However, as sporadic increases in QTC_B were observed following repeated administration to the monkey (where the C_{max} was ~11-fold higher than that proposed clinically) and as an increase in QT prolongation has been observed at supra therapeutic doses in man, the Applicant was requested to conduct a post-authorisation study to further evaluate cardiovascular safety in man (see Clinical Safety), details of which has been included in the Risk Management Plan.

Mirabegron absorption was studied after single and repeated dose administration in fasted and non fasted males (rat, mouse and dog). Mirabegron was well and rapidly absorbed in the species tested.

Repeated dosing of mirabegron in non fasted male rats for 21 days indicate that the AUC_{24h} and C_{max} increased with increasing doses and steady state was achieved by Day 17.

In pregnant rats, low levels of mirabegron-derived components crossed the placental barrier and were transferred to the fetus. Reduced fetal body weight, dilated aorta, cardiomegaly and increased post-implantation loss were noted during the rabbit embryofetal development study at exposures that are higher than those proposed clinically and occurred at doses associated with maternal toxicity. However, the exposures at the NOAEL for embryo development are below those proposed clinically. Furthermore, mirabegron-derived components were excreted into the milk of rodents; hence, the SmPC clearly states that mirabegron is not recommended during pregnancy and in women of childbearing potential not using contraception, and that mirabegron should not be administered during breast feeding.

Genotoxicity and carcinogenicity studies have shown no genotoxic or carcinogenic potential *in vivo*.

Based on environmental risk assessment studies, mirabegron is unlikely to represent a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data which have been provided on the pharmacodynamic, pharmacokinetic and toxicological aspects of this application are sufficient to support the proposed indication. The SmPC adequately describes the information currently available. Regarding the mechanism of action, the CHMP recommends to carry out additional mechanistic studies in order to clarify whether mirabegron–induced bladder relaxation is mediated via the β_3-receptor in humans.

The cardiovascular safety will be further characterised through the measures identified in the risk management plan, particularly a post-authorisation safety study (see Clinical Safety). The observed embryofetal toxicity in pregnant rats and rabbits occurred at doses higher than those proposed clinically and the observed malformations are thought to be mediated via activation of the β_1-receptor. As a precautionary measure, the SmPC clearly states that mirabegron is not recommended during pregnancy and in women of childbearing potential not using contraception.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development program consists of 41 studies in patients with OAB, patients with lower urinary tract symptoms (LUTS)/ bladder outlet obstruction (BOO), or patients with type 2 diabetes mellitus. For a detailed description of the clinical data package relevant for the applied indication see chapter 2.5 Clinical efficacy.

The initial clinical development program examined an indication of type 2 diabetes mellitus and was subsequently discontinued due to the absence of efficacy demonstrated in this population based on proof of concept studies. A total of 29 phase 1 studies and 12 phase 2 and 3 studies (9 in patients with OAB, 1 in patients with LUTS/BOO and 2 in patients with type 2 diabetes mellitus) have been conducted globally in Europe, the US, Canada, Japan, Australia/New Zealand and South Africa.

The primary studies to support efficacy of mirabegron were designed consistent with Committee for Medicinal Products for Human Use (CHMP) guidance for the clinical investigation of medicinal products for urinary incontinence. Further, the company received national scientific advice from national Competent Authorities. In general, the recommendations from the authorities were followed.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

There was a routine inspection for the product Betmiga (EMEA/H/C/002388) conducted at three investigator sites in relation to the pivotal clinical studies 178-CL-047 and 178-CL-074. In summary, the data presented in the concerning clinical study reports are accurately described and hence the data can be considered for the evaluation of the marketing authorisation application.

2.4.2. Pharmacokinetics

The pharmacokinetics of mirabegron in plasma and urine were studied in healthy young and elderly volunteers, patients suffering from overactive bladder, diabetes mellitus, and patients with renal or hepatic impairment.

A total of 29 studies were included to evaluate the pharmacokinetics of mirabegron. Mirabegron and M5, M8, M11, M12, M13, M14, M15 and M16 metabolites were determined in plasma, urine, and feces. Standard procedures for non-compartmental pharmacokinetic analysis were applied. Three population pharmacokinetic analyses were performed.

Absorption

Mirabegron absorption is likely to be dose dependent. In the popPK analysis the total bioavailability of 50 mg of mirablegron (OCAS-M formulation) was reported to be around 20%. However, a more than proportional increase in the bioavailability as a function of dose was reported. The higher the dose, the higher the proportion of the dose that is absorbed probably due to the saturation of active transport enzymes, and Pg-P. The absolute bioavailability of mirabegron OCAS tablets was shown to decrease with decreasing in vitro release rate. Administration of OCAS tablets with three different dissolution rates (OCAS-H (fast release), OCAS-M (Phase 3 OCAS) and OCAS-L (slow release)) demonstrated that the absolute bioavailability was highest for the fast release tablet and lowest for the slow release tablet. Mean absolute bioavailability estimates for OCAS-H, OCAS-M and OCAS-L tablets were 43%, 35% and 30%, respectively, at a dose of 50 mg (study 178-CL-076).

The absolute bioavailability (F) of a single oral dose of mirabegron OCAS under fasted conditions increased with dose, resulting in a more than dose proportional increase in Cmax and AUC with increasing oral dose from 50 to 150 mg. F averaged 24.3% for the 50 mg dose and 45.2% for the 150 mg dose (study 178-CL-033).

The food effect on mirabegron absorption is clear. With 50 mg tablets, the ratio and 90% CI values for AUCinf and Cmax of mirabegron were 17% lower (90% CI of the GM ratio: 74.16, 93.42) and 45% lower (90% CI of the GM ratio: 43.69, 68.65), respectively, after high-fat breakfast. Low-fat breakfast reduced the mean AUCinf and Cmax by 51% and 75%, respectively. The differential effect of a high-fat and low-fat meal on the bioavailability of mirabegron may be explained by a higher fraction that is adsorbed to contents of a low-fat breakfast, in particular cereal, compared with a high-fat breakfast. In addition, the differences in the specific constituents between high- and low-fat meals may differentially affect uptake and efflux transport of mirabegron from the gastrointestinal tract. The effect of food depends on the quantity of fat, and it is also different depending on the gender (women show a higher increase in bioavailability when the drug is taken with food).

There were no apparent differences in the magnitude of the food effect between Western and Japanese healthy volunteers or between males and females. There were no food restrictions in the primary phase 3 studies; efficacy and safety of the proposed therapeutic dose of 50 mg was established in these studies with the administration of mirabegron with or without food. Mirabegron can be taken with or without food.

Distribution

Mirabegron has a large volume of distribution of approximately 1670 mL indicating extensive distribution. Mirabegron is moderately bound (approximately 71%) to human plasma proteins, including albumin and alpha-1 acid glycoprotein. Small changes were observed in patients with mild, moderate or severe renal impairment and those observed for mild or moderate hepatic impairment

however, it is not probable that these changes have any clinical relevance considering the relative change and the high volume of distribution of mirabegron.

Mirabegron distributes to red blood cells. However no clinical effect is expected even if the erythrocyte concentration decreases. The volume of distribution of mirabegron of around 1670 mL across studies indicates that mirabegron highly distributes in the organism.

Elimination

The excretion process is independent of dose or administration route and is not altered with repeated dosing. Part of the renal excretion is through active secretion.

The total body clearance (CL) from plasma is estimated to be approximately 57 L/h. Blood clearance is estimated to be approximately 41 L/hr, which is about half the liver blood flow.

Based on population PK analysis the effective half-life of mirabegron was determined to be 19.0 hours. This is shorter than the estimates for the terminal t1/2 obtained in the clinical mass balance study and the studies which use a prolonged sampling schedule suggesting that the terminal t1/2 comprises a small fraction of the total AUCinf.

Renal clearance was decreased in subjects with renal impairment and in elderly subjects, in particular in elderly females, in comparison to the respective control groups, consistent with the generally lower renal capacity in these subjects.

All circulating mirabegron metabolites represented a larger percentage of the parent exposure after oral administration of mirabegron compared to IV administration, suggesting that mirabegron undergoes intestinal and/or hepatic first-pass metabolism following oral administration.

Metabolite-to-parent AUC ratios were relatively constant across multiple oral doses of 25 to 200 mg qd, indicating that the metabolism of mirabegron is not saturable over this dose range.

No studies have been performed to determine whether differences in the pharmacogenetics regarding the UGT, and CYP enzymes other than CYP2D6 would have any effect on the metabolism of mirabegron. it is predicted from the urinary excretion data that the UGT system metabolizes approximately 10% of the absorbed drug dose. Of the 10 metabolites observed in human urine, 6 metabolites were formed via glucuronidation, 3 primary (M11, M13 and M14) and 2 secondary glucuronides (M12 and M15) and one tertiary glucuronide (M17). An exploratory in vitro study with recombinant UGTs and a panel of human liver microsomes (correlation study) identified UGT2B7 as the primary UGT forming the major metabolite, M11, with limited contribution of UGT1A1, the UGT that has been associated with clinically relevant genotypic variations. Considering the unimodal distribution of the values of the ratios of the AUCs of M11 to parent (MRp) and the low percentage of mirabegron that could be metabolized by UDP-glucuronosyl-transferases it is unlikely that pharmacogenetic variation in UGTs or inhibitors or inducers of glucuronidation have a significant effect on mirabegron pharmacokinetics.

The affinity of the metabolites detected in plasma for the beta-3-adrenoceptor was much smaller than that reported for mirabegron. Although no protein binding of the metabolites have been performed, considering the plasma concentrations and the affinity for the beta-3 adrenoceptor it is not likely that any of them contribute to the observed effect.

Dose proportionality and time dependencies

No deviations from dose proportionality in mirabegron PK parameters were observed after single-dose intravenous administration of mirabegron. After oral administration, a greater than dose-proportional

increase in mirabegron Cmax and AUC was observed, due to an increase in absolute bioavailability with increasing dose.

In the overall population of males and females, a 2-fold increase in dose increased mirabegron Cmax and AUCtau by approximately 2.9- and 2.6-fold, respectively, within the dose range of 25 mg to 200 mg. Similar fold increases were obtained for males and females separately. Mirabegron metabolites also demonstrated a more than dose proportional increase in Cmax and AUCtau after multiple mirabegron doses (25 to 200 mg qd), similar to that observed with the parent compound, indicating that the greater than dose-proportional increase in mirabegron exposure is not caused by saturable first-pass metabolism.

Steady state plasma concentrations were achieved within 7 days of once daily dosing with mirabegron. Comparison between AUCtau values following a single dose and at steady state indicated a 2-fold accumulation of mirabegron with once daily dosing. No time-dependency was observed at the proposed therapeutic dose of 50 mg. At doses of 100 mg and 200 mg, a small increase (less than 20%) in AUCtau at steady state compared with single dose AUCinf was observed, suggesting that mirabegron may exhibit time-dependent PK at supratherapeutic doses. The changes are considered not clinically relevant.

Special populations

Impaired renal function

In patients with severe renal impairment there was an increase in Cmax and AUC; the increases were 92% (90% CI: -3%, 281%) and 118% (90% CI: 30%, 267%), respectively compared to the values estimated for healthy volunteers. The suggested reduction of the dose to 25 mg once daily in patients with severe renal impairment or in those patients with mild or moderate renal impairment and concomitant administration of potent CYP3A inhibitors is accceptable.

Impaired hepatic function

In vitro and in vivo data suggested that mirabegron is cleared through multiple metabolic pathways and possibly biliary excretion of unchanged drug.

Study 178-CL-039 an open-label, single-dose parallel group study was conducted to assess the single dose pharmacokinetics and protein binding of 100 mg of mirabegron in 32 male and female subjects with mild and moderate hepatic impairment in relation to healthy subjects. The results showed that Absorption of mirabegron was delayed in subjects with hepatic dysfunction compared to those with normal hepatic function. The t1/2 was increased in mildly impaired subjects to about 68 hours compared to 57 hours in healthy controls. A similar finding was not observed in subjects with moderate hepatic impairment where the t1/2 was not substantially different from matched controls (mean values, 51 and 54 hours, respectively). No clear relationship was evident between individual Cmax and AUCinf values and the scores of the 5 parameters included in the Child-Pugh scale. In subjects with mild hepatic impairment (Child-Pugh Class A), mean mirabegron Cmax and AUCinf were increased by 9% and 19% relative to volunteers with normal hepatic function. In volunteers with moderate hepatic impairment (Child-Pugh Class B), mean Cmax and AUCinf values were 175% and 65% higher.

Gender

Mirabegron Cmax and AUCtau were approximately 44% to 38% higher, respectively, in females compared with males. The magnitude of the gender differences is attenuated with correction for body weight. Weight-normalized values for Cmax and AUCtau were approximately 23% and 18% higher in females compared to those in males. This remaining increased exposure is attributed to a higher absolute bioavailability of mirabegron in females compared to males. The t1/2 tended to be longer in females (mean values, 59.0 to 67.9 hr) compared with males (mean values, 56.3 to 60.0 hr).

Race

There are limited data regarding the influence of different ethnic origin on the pharmacokinetics of mirabegron However, results from the TQT study 178-CL-077 which included a similar number of White/Caucasian volunteers and Black or African American volunteers did not show an effect of race on the pharmacokinetics of mirabegron.

Genetic polymorphism

In spite of the low number of ultrarapid and poor metabolizers for CYP2D6, no dose adjustment appear to be necessary in poor metabolizers for CYP2D6, however AUC and Cmax in ultra-rapid metabolizers are reduced to half in intermediate and extended metabolizers. At doses of 50, 100 and 200 mg in Study 178-CL-077, mean AUCtau of mirabegron was approximately 30%, 43% and 9% lower, respectively, in volunteers with the UM phenotype compared to volunteers with the EM phenotype. Mean Cmax was approximately 30% and 47% lower, respectively, in volunteers with the UM phenotype compared to volunteers with the EM phenotype at doses of 50 and 100 mg, respectively, while for the 200 mg dose, mean Cmax values were similar.

Elderly

The effect of age on mirabegron pharmacokinetics was specifically evaluated in Study 178-CL-031. A Double-blind, randomized, placebo-controlled, exploratory study to investigate the pharmacokinetics, safety and tolerability of multiple doses of mirabegron OCAS-M in healthy young male and female subjects and healthy elderly male and female subjects. No relevant differences were notable between the young and elderly groups apart from the age.

No consistent differences in mirabegron Cmax and AUCtau were found in elderly versus young subjects. Terminal elimination half-life tended to be longer in elderly subjects (mean values, 60 to 68 hours) compared with young subjects (mean values, 55 to 60 hours), but the differences were generally not more than a few hours.

Population PK analysis of phase 2 and 3 data indicated that age affected mirabegron exposure. The typical AUC was predicted to be 11% higher in a subject aged 90 years compared to a typical OAB subject aged 60 years. Dose adjustment based on age is not necessary.

Weight

The magnitude of the observed mirabegron exposure differences between male and female volunteers and between Japanese and Western volunteers was attenuated with correction for body weight. Population PK analysis of phase 2 and 3 data confirmed that body weight affected mirabegron exposure. Relative to a subject with a body weight of 70 kg, AUCtau was about 53% higher in a subject with a body weight of 30 kg and approximately 17% lower in a subject with a body weight of 100 kg. The increase in exposure with lower body weight is less than would be achieved if the dose were doubled (resulting in a 190% and 160% increase in Cmax and AUC, respectively). Given documented safety of mirabegron at a 100 mg dose (twice the proposed therapeutic dose), the effect of body weight on plasma exposure is considered not clinically significant. Dose adjustment based on body weight is not necessary.

The influence of weight (including other body size measures such as body mass index, lean body mass and height) has been investigated across a number of population PK analyses using data from healthy subjects and patients with OAB who received IR or OCAS formulations [178-PK-003, 178-PK-012, 178-PK-015]. In the population PK analysis of phase 2 and 3 data [178-PK-015], a 10% increase in weight was found to increase mirabegron CL and central volume of distribution by 5%. Relative to a subject with a body weight of 70 kg, AUCtau increased by 52.8 % for a body weight of 30 kg and decreased by 16.5% for a body weight of 100 kg. Dose adjustment based on body weight, according to this analysis is not necessary.

Pharmacokinetic interaction studies

In vitro data suggest that mirabegron is mainly metabolized by CYP3A4, but also by CYP2D6 and UGT. CYP3A4 inhibitors reduce mirabegron metabolism. Studies of mirabegron using human liver microsomes and recombinant human CYP enzymes showed that mirabegron is a moderate and time-dependent inhibitor of CYP2D6 and a weak inhibitor of CYP3A. Mirabegron inhibited P-gp-mediated drug transport at high concentrations.

The coadministration of mirabegron with potent CYP3A4 inhibitors increases mirabegron plasma concentrations. Mean mirabegron Cmax and AUCinf values were increased when coadministered with ketoconazole (a potent CYP3A4 inhibitor) by 45% and 81%, respectively. However, these changes are not considered to have clinical relevance. Only when the mirabegron is coadministered with potent CYP3A inhibitor in patients with mildly impaired hepatic metabolism or mild / moderate renal impairment the concentrations of mirabegron increase in such a manner that a dose reduction from 50 mg to 25 mg seems appropriate.

Following coadministration of mirabegron with rifampin (CYP3A4 inductor) maximum concentration and AUC were decreased 35-40% with respect to the values obtained when mirabegron was administered alone. This reduction could be due to a decreased bioavailability of mirabegron through induction of intestinal and first-pass metabolism mediated by CYP and UGT enzymes. In addition, rifampin may have also induced intestinal P-gp efflux of mirabegron. The effect of rifampin on mirabegron exposure was generally greater in females than in males. No interaction with clinical relevance is likely between mirabegron and CYP3A4 inductors.

No dose adjustment is claimed for mirabegron when coadministered with inhibitors of CYP2D6, although no study has been performed using this type of drugs, it is based on the fact that *in vitro* data indicates a minor involvement of CYP2D6 and the lack of changes in the pharmacokinetics of mirabegron in PMs for this isoenzyme.

Two drug interaction studies were performed to investigate whether mirabegron inhibits cytochrome P450 (CYP) 2D6 in vivo (160 mg immediate release [IR] once a day [qd], Study 178-CL-005; and 100 mg OCAS qd, Study 178-CL-058). Coadministration of mirabegron with substrates of CYP2D6 (desipramine and metoprolol) resulted in small modifications of the pharmacokinetics of mirabegron. However Cmax and AUC of desipramine and metoprolol were increased by 79% and 241% respectively when coadministered with mirabegron. It is taken into account that both drug-drug interaction studies investigated supratherapeutic doses of mirabegron. Drugs that are CYP2D6 substrates are not expected to require dose adjustment, except for drugs with a narrow therapeutic index that are significantly metabolized by CYP2D6. Therefore a cautionary statement reflecting this is included into the SmPC.

Considering the results obtained when co administering mirabegron with warfarin it is not likely an interaction between mirabegron and CYP2C9 substrates.

In order to establish that there is no risk to patients who may take mirabegron in combination with drugs that utilize the P-gp transporter, the effect of mirabegron on the pharmacokinetics of digoxin, a known substrate for P-gp, was studied in healthy volunteers. In the presence of mirabegron, mean increases in digoxin AUClast and Cmax of 27% and 29% were observed after a single digoxin dose (0.25 mg). The same results were obtained in an exploratory analysis when subjects were included as random effects instead of fixed effects. The confidence intervals for the ratios for both AUClast and Cmax exceed the pre-specified interval of 0.80 – 1.25, thus a clinically relevant effect of mirabegron on digoxin pharmacokinetics cannot be excluded. Since there was a 28% difference in plasma exposure (Cmax and AUC) for mirabegron between males and females, the effect of sex on the interaction of mirabegron and digoxin was assessed. The ANOVA model which explored sex effects and treatment by sex interactions for ratios of AUClast or Cmax showed non-significant p-values for main effects of sex and for the interaction term. The potential for inhibition of P-gp by mirabegron is adequately reflected in the SmPC.

2.4.3. Pharmacodynamics

The PD effects of mirabegron were investigated throughout the clinical development programme in healthy volunteers and patients with overactive bladder. Pharmacodynamic studies were conducted to explore the cardiovascular effects and intra-ocular pressure effects of mirabegron. In addition, 2 Thorough QT (TQT) studies were conducted.

Mechanism of action

Mirabegron is a selective agonist for human beta 3-adrenoceptor (beta 3-AR) which is dominant in the human detrusor muscle. Activation of the beta-AR in the bladder trigone facilitates urine storage through flattening and lengthening of the bladder base. Mirabegron dose-dependently increased cyclic adenosine 3', 5'-monophosphate (cAMP) concentrations in bladder tissues isolated from rats and showed a potent relaxant effect in isolated rat and human bladder strips pre-contracted with carbachol at low contraction tonus. It decreased the resting intravesical pressure in a rat model and in anesthetised rats; mirabegron decreased the frequency of rhythmic bladder contractions without affecting the force of the rhythmic bladder contractions.

Primary and Secondary pharmacology

The relationship between plasma concentrations of mirabegron and its effects on the overactive bladder have been shown in three different PK/PD analysis (178-PK-005, 178-PK-009 and 178-PK-015). In the three analyses individual plasma exposure to mirabegron were obtained from a previously developed pharmacokinetic model (study 178-PK-015). In all of them an Emax model best fitted the relationship between mirabegron AUC and the number of micturitions with respect to the baseline level and the modification of the volume of urine voided (with respect to baseline level). In those analyses it was shown that mirabegron reduces the number of incontinent episodes, although the effect is not related to the degree of exposure to mirabegron. The primary pharmacology study in male patients (≥ 45 years of age) with lower urinary tract symptoms (LUTS) and bladder outlet obstruction (BOO) showed bladder relaxation with mirabegron during the filling phase and inhibition of the frequency of non-voiding activity, without impairing voiding efficiency. This study provides supportive evidence of the mechanism of action in patients. Further the endpoints in the phase 2 and 3 clinical studies, especially mean voided volume, demonstrate an effect on urine storage capacity. The CHMP acknowledges the data provided on the mechanism of action. However, the population where voiding

urodynamic measurements were performed is different from the overactive bladder population and the data do not demonstrate an unequivocal mechanism of action on the human bladder in vivo. Therefore the applicant was asked to develop a plan for studies to unequivocally elucidate the mechanism of action of mirabegron post authorisation.

In healthy subjects mirabegron increased heart rate and reduced SV while CO remained essentially unchanged. Coadministration of propranolol or bisoprolol attenuated the mirabegron-stimulated decrease in SV. However, these two antagonists are not selective of beta3-AR and thus it is difficult to clarify whether the cardiac effects of mirabegron are mediate by beta 1, beta 2 or beta3-AR.

Regarding the QTC, a PK/PD model was developed including an effect compartment, plus linear relationship between changes in QTc and plasma concentrations in the biophase to explore the predicted change in the QTc after the administration of 100 and 200 mg of mirabegron in males and females. The drug is able to produce a change higher than 5 msec at both doses, in females. Predictions have been performed for 50 mg doses in females, and in patients suffering from different degrees of renal or hepatic impairment. According to the model women are more sensitive to changes in the QTc than men at similar plasma concentrations. TQT results are discussed under Clinical Safety - Laboratory Findings - ECG.

Even though the exposure of mirabegron depends on the age, renal impairment, hepatic impairment and coadministration with potent CYP3A4 inhibitors, under no conditions did the upper 1-sided 95% confidence interval for the mean ddQTc interval exceed 10 msec. Maximal ddQTc intervals did not increase more than 30 msec in any virtual subject under any conditions. 95% of subjects had maximal QTc intervals less than 500 msec for all simulation groups, except for 75 year old females with mild renal impairment, mild hepatic impairment and taking ketoconazole who had maximal ddQTc values of 500.4 msec (95th percentile). In conclusion mirabegron 50 mg dose does not raise safety concerns related to the potential QT prolongation when factors such as gender or age (which may influence the exposure to mirabegron) are considered under usual circumstances.

The population PK/PD analyses found small mean effects of mirabegron exposure on blood pressure in patients with overactive bladder, restricted to males in the case of systolic blood pressure and to younger patients in the case of diastolic blood pressure. Simulations of SBP showed that for 50 and 100 mg daily doses in male OAB patients, mean increases from baseline of 0.80 and 1.75 mmHg respectively could be expected at steady state. Simulations of DBP showed that for 50 and 100 mg daily doses in OAB patients aged 18 to 50 years, mean increases from baseline of 0.40 and 0.80 mmHg respectively could be expected at steady state. Simulations performed to predict the effect of mirabegron on SBP or DB in women over 55 years in situations mimicking possible renal or hepatic impairment showed that there will be no clinically significant changes in SBP and DBP unless mirabegron is coadministered with potent CYP3A inhibitors. In that case mirabegron dose reduction to 25 mg as labeled in the SmPC is reasonable.

Pharmocodynamic drug interaction studies with tamusolin, metformin and warfarin show that that PD interactions are unlikely when administered together with mirabegron. Results from specific ocular safety assessments in phase 1 studies, including a study performed with a non-contact air-puff tonometer [178-CL-031], do not demonstrate an effect on IOP and do not show clinically significant changes in visual acuity or fundoscopy at mirabegron doses up to 400 mg as a single dose or 300 mg/day as multiple doses over 10 consecutive days [178-CL-034].

2.4.4. Discussion on clinical pharmacology

After oral administration, a greater than dose-proportional increase in mirabegron Cmax and AUC was observed, due to an increase in absolute bioavailability with increasing dose. In the overall population

of males and females, a 2-fold increase in dose increased mirabegron Cmax and AUCtau by approximately 2.9- and 2.6-fold, respectively, within the dose range of 25 mg to 200 mg. Similar fold increases were obtained for males and females separately. The applicant indicates that the target exposure range of mirabegron is based on the plasma exposure observed with mirabegron 50 mg and is bracketed by the exposure observed with the 2 doses on either side evaluated in the program, namely 25 mg and 100 mg. The definition of this range is based on the demonstrated efficacy within this range in the absence of dose-dependent safety signals when the dose is varied between 25 mg and 100 mg. This indicates that the degree of difference in mirabegron exposure caused by an intrinsic or extrinsic factor that is of no clinical consequence is a 2.6-fold change in AUC or a 2.9-fold change in Cmax in either direction.

In vitro data suggest that mirabegron is mainly metabolized by CYP3A4, but also by CYP2D6 and UGT. The coadministration of mirabegron with potent CYP3A4 inhibitors increases mirabegron plasma concentrations. Mean mirabegron Cmax and AUCinf values were increased when coadministered with ketoconazole (a potent CYP3A4 inhibitor) by 66% and 100%, respectively, in females. However, these changes are not considered to have clinical relevance.

Coadministration of mirabegron with substrates of CYP2D6 (desipramine and metoprolol) resulted in small modifications of the pharmacokinetics of mirabegron. However Cmax and AUC of desipramine and metoprolol were increased around 2 and 3 fold respectively when coadministered with mirabegron. Therefore cautionary statements were included into the SmPC for the concomitant use of drugs with a narrow therapeutic index that are significantly metabolized by CYP2D6.

With respect to Pg-P substrates, the interaction was studied with digoxin. Changes in the pharmacokinetics of digoxin were observed. Since digoxin is considered a narrow therapeutic index drug it was included into the SmPC that, for patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should be prescribed initially. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect.

Following single dose administration of 100 mg mirabegron in volunteers with mild hepatic impairment (Child-Pugh Class A), mean mirabegron Cmax and AUCinf were increased by 9% and 19% relative to volunteers with normal hepatic function. In volunteers with moderate hepatic impairment (Child-Pugh Class B), mean Cmax and AUCinf values were 175% and 65% higher. A reduction of the dose to 25 mg once daily in patients with moderate hepatic impairment is recommended. Further the CHMP considered that also patients with mild hepatic impairment concomitantly receiving strong CYP3A4 inhibitor could have mirabegron plasma exposure around or outside the acceptable upper boundary. Therefore, a dose reduction to 25 mg for patients with mild hepatic impairment concomitantly receiving strong CYP3A inihitors was included into the SmPC; use of mirabegron in patients with moderate hepatic impairment who concomitantly receive strong CYP3A inihitors is not recommended according to the SmPC.

Similarly patients with severe renal impairments showed an increase in Cmax and AUC superior to 100% with respect to the values estimated for healthy volunteers. Therefore recommendation for reduction of the dose to 25 mg once daily in patients with severe renal impairment or in those patients with mild or moderate renal impairment if concomitantly receiving a potent CYP3A inhibitors was included into the SmPC.

Regarding the QTC, a PK/PD model was developed. Even though the exposure of mirabegron depends on the age, renal impairment, hepatic impairment and coadministration with potent CYP3A4 inhibitors, under no conditions did the upper 1-sided 95% confidence interval for the mean ddQTc interval exceed 10 msec. Maximal ddQTc intervals did not increase more than 30 msec in any virtual subject under any conditions. 95% of subjects had maximal QTc intervals less than 500 msec for all simulation groups,

except for 75 year old females with mild renal impairment, mild hepatic impairment and taking ketoconazole who had maximal ddQTc values of 500.4 msec (95th percentile). In conclusion mirabegron 50 mg dose does not raise safety concerns related to the potential QT prolongation when factors such as gender or age (which may influence the exposure to mirabegron) are considered under usual circumstances.

2.4.5. Conclusions on clinical pharmacology

In terms of the potential for pharmacokinetic interactions, mirabegron exposure increased when applied with CYP3A4 inhibitors and substrates of CYP2D6. Further with respect to interaction with Pg-P substrates, changes in the pharmacokinetics of digoxin were observed. Appropriate cautionary statements and, when applicable, dose reductions, were included into the SmPC. Although the available information on the mechanism of action is considered sufficient by the CHMP, the applicant is recommended to explore it further, particularly in light of the available clinical efficacy data. With regard to cardiovascular safety, the proposed dose does not raise safety concerns related to the potential QT prolongation when factors such as gender or age are considered; further data will be generated as detailed in the risk management plan (see clinical safety).

2.5. Clinical efficacy

The efficacy of mirabegron in the treatment of patients with symptoms of overactive bladder (OAB), including urge urinary incontinence, urgency, and urinary frequency was evaluated in 9 studies, including:

· 1 phase 2a proof-of-concept study (178-CL-008),
· 2 supportive phase 2b studies (178-CL-045 and 178-CL-044),
· 3 primary phase 3 studies (178-CL-046, 178-CL-047 and 178-CL-074),
· 1 supportive phase 3 study (178-CL-048),
· 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).

The phase 3 program evaluated doses of 25, 50, or 100 mg mirabegron orally once daily.

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Reports of Efficacy and Safety Studies								
E/S	178-CL-044 Belgium, Czech Republic, Denmark, France, Germany, Hungary, Italy, Netherlands, Norway, Poland, Russia, Spain, Sweden, United Kingdom	Dose-response efficacy; safety and tolerability of mirabegron	Phase 2b, randomized, double-blind, parallel group, placebo- and active-controlled, dose ranging	Treatment groups: placebo, mirabegron 25, 50, 100 or 200 mg, or tolterodine SR 4 mg Mirabegron OCAS 25, 50, 100, 200 mg tablet or matching placebo po; once daily fed (after breakfast) tolterodine SR 4 mg capsule (overencapsulated) or matching placebo po; once daily fed (after breakfast)	928†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Complete; Full
E/S PK	178-CL-045 Japan	Dose-response efficacy; safety and tolerability of mirabegron	Phase 2, randomized, double-blind, placebo-controlled, parallel group	Treatment groups: placebo, mirabegron 25, 50, or 100 mg Mirabegron OCAS 25, 50, 100 mg qd or matching placebo tablet po; once daily fed (after breakfast)	842†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Complete; Full

E/S POC	178-CL-008 Belgium, Czech Republic, Denmark, Germany, Spain, Sweden, United Kingdom	Efficacy, safety, tolerability, population PK; proof of concept	Phase 2a, randomized, double-blind, parallel group, placebo-controlled and active-controlled	Treatment groups: placebo, mirabegron IR 100 or 150 mg bid, or tolterodine MR 4 mg Mirabegron IR 100 mg or 150 mg tablet po (total daily doses of 200 or 300 mg); twice daily with food (after breakfast and after dinner) tolterodine MR 4 mg capsule (overencapsulated) po; once daily in the morning with food (after breakfast)	262†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 4-week double-blind treatment period	Complete; Full
E/S	178-CL-046 Europe‡ and Australia	Efficacy and safety of mirabegron compared to placebo and tolterodine SR	Phase 3, randomized, double-blind, placebo-controlled and active-controlled	Treatment groups: placebo, mirabegron 50 or 100 mg, or tolterodine SR 4 mg Mirabegron OCAS 50 or 100 mg tablet or matching placebo po; once daily with or without food tolterodine SR 4 mg capsule (overencapsulated) or matching placebo po; once daily with or without food	1987†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Complete; Full
E/S	178-CL-047 Canada United States	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo-controlled	Treatment groups: placebo, mirabegron 50 or 100 mg Mirabegron OCAS 50 or 100 mg tablet or matching placebo po; once daily with or without food	1329†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Complete; Full
E/S	178-CL-048 Japan	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo- and active-controlled	Treatment groups: placebo, mirabegron 50 mg, or tolterodine SR 4 mg Mirabegron OCAS 50 mg tablet or matching placebo po; once daily with food (after breakfast) tolterodine SR 4 mg capsule (overencapsulated) or matching placebo po; once daily with food (after breakfast)	1139†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Complete; Full
E/S	178-CL-074 Canada, Czech Republic, Denmark, Finland, Germany, Hungary, Norway, Portugal, Slovakia, Spain, Sweden, United States	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo-controlled	Treatment groups: placebo, mirabegron 25 or 50 mg Mirabegron OCAS 25 or 50 mg tablet or matching placebo po; once daily with or without food	1306†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Complete; Full
E/S	178-CL-049 Europe§ Canada United States Australia New Zealand South Africa	Long term safety	Phase 3, randomized, double-blind, active-controlled	Treatment groups: Mirabegron 50 or 100 mg, or tolterodine ER mg Mirabegron OCAS 50 or 100 mg tablet or matching placebo po; once daily with or without food tolterodine ER 4 mg capsule (overencapsulated) or matching placebo po; once daily with or without food	2452†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12 month double-blind treatment period	Complete; Full
E/S	178-CL-051 Japan	Long term safety	Phase 3, open-label	Treatment group: Mirabegron (titration) Mirabegron OCAS 50 mg po, dose escalation to 100 mg allowed after 8 weeks (improve efficacy); once daily fed (after breakfast)	204 enrolled	Adults with overactive bladder	52 weeks	Complete; Full

2.5.1. Dose response study(ies)

2 supportive phase 2b studies (178-CL-045 and 178-CL-044) were conducted to assess the dose-response relationship of mirabegron on efficacy in patients with OAB. Doses from 25 mg to 200 mg were included in these studies.

	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered / compl.	Duration
178-CL-044	97/Belgium, Czech Republic, Denmark, France, Germany, Hungary, Italy, Netherlands, Norway, Poland, Russian Federation, Spain, Sweden, United Kingdom	Phase 2b, randomized, double-blind, parallel, placebo- and active controlled	Placebo oral, qd Mirabegron 25 mg, oral, qd Mirabegron 50 mg, oral, qd Mirabegron 100 mg, oral, qd Mirabegron 200 mg, oral, qd Tolterodine ER 4 mg, oral, qd	Efficacy and Safety, Dose Range Finding	169/157 169/153 169/153 169/161 167/151 85/82	12 weeks
178-CL-045	60/Japan	Phase 2b, randomized, double-blind, parallel, placebo controlled	Placebo oral, qd Mirabegron 25 mg, oral, qd Mirabegron 50 mg, oral, qd Mirabegron 100 mg, oral, qd	Efficacy and Safety, Dose Range Finding	214/198 211/200 208/195 209/196	12 weeks

Quantitative symptoms were the basis for the preliminary assessment of the efficacy and the dose-response relationship. Little differences in terms of effect appear to be between 25 and 200 mg dosages, showing a flat dose effect curve. OAB patients experienced a reduction of 1.9 (25 mg) to 2.2 (200 mg) of daily micturitions and 1.2 to 1.3 (25-200 mg) of incontinence episodes. A similar pattern was followed by the other defining condition symptoms urgency and nocturia.

From the safety point of view the selection of the dose for Phase III appears to be driven by the adverse beta-adrenergic effects, in which a clearer dose-effect relationship was determined. This effect is mainly apparent on heart rate. A dose-dependent pulse rate increase was observed, being significant over 100 mg.

In conclusion, dose selection for Phase 3 was based on both tolerability and efficacy grounds, although the more clear relationship with the dose level is related to safety. As a consequence, mirabegron 200 mg was no longer tested. Doses of 25 mg, 50 mg and 100 mg were selected for confirmatory studies.

2.5.2. Main study(ies)

Three pivotal Phase3 randomized, double blind, placebo controlled, parallel group 12-week studies support the use of mirabegron 25 mg, 50 mg and 100 mg in the treatment of OAB (Studies CL-046, CL-047 and CL-074). Data from these three studies was integrated for pooled-analyses.

Pivotal studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
E/S	178-CL-046 Europe‡ and Australia	Efficacy and safety of mirabegron compared to placebo and tolterodine SR	Phase 3, randomized, double-blind, placebo-controlled and active-controlled	Treatment groups: placebo, mirabegron 50 or 100 mg, or tolterodine SR 4 mg Mirabegron OCAS 50 or 100 mg tablet or matching placebo po; once daily with or without food tolterodine SR 4 mg capsule (overencapsulated) or matching placebo po; once daily with or without food	1987†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12-week double-blind treatment period
E/S	178-CL-047 Canada United States	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo-controlled	Treatment groups: placebo, mirabegron 50 or 100 mg Mirabegron OCAS 50 or 100 mg tablet or matching placebo po; once daily with or without food	1329†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12-week double-blind treatment period
E/S	178-CL-074 Canada, Czech Republic, Denmark, Finland, Germany, Hungary, Norway, Portugal, Slovakia, Spain, Sweden, United States	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo-controlled	Treatment groups: placebo, mirabegron 25 or 50 mg Mirabegron OCAS 25 or 50 mg tablet or matching placebo po; once daily with or without food	1306†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12-week double-blind treatment period

These studies had the following design features in common:

- Patients participated in a 2-week single-blind placebo run-in period followed by a 12-week double-blind, placebo-controlled treatment period.
- Patients completed a 3-day micturition diary during the 3 days prior to each study visit.
- Eligible patients were female and male adults who had symptoms of OAB (urinary frequency and urgency with or without incontinence) for at least 3 months and
- Eligible patients experienced frequency of micturition on average ≥ 8 times per 24-hour period and at least 3 episodes of urgency (grade 3 or 4) with or without incontinence during the 3-day micturition diary period collected during the run-in period.

The studies were conducted with similar statistical methodology. Including:

- The same co-primary efficacy endpoints
    - change from baseline to final visit in mean number of incontinence episodes per 24 hours based on a 3-day micturition diary and
    - change from baseline to final visit in mean number of micturition per 24 hours based on a 3-day micturition diary.
- The same key secondary efficacy endpoints including 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; and change from baseline to week 4 in mean number of micturitions per 24 hours.

Study 178-CL-046

This was a phase III randomized, double-blind, parallel group, placebo- and active-controlled, multinational, multicenter study. A total of 189 sites in Europe and Australia enrolled patients for the study.

Methods

Study Participants

Male and female patients at least 18 years of age who had symptoms of OAB for more than 3 months were eligible for inclusion. Patients were excluded if they had significant stress incontinence or mixed stress/urgency incontinence with stress as the predominant factor; an indwelling catheter; evidence of a symptomatic urinary tract infection (UTI), chronic inflammation, bladder stones, previous pelvic radiation therapy or previous or current malignant disease of the pelvic organs; or severe hypertension (defined as a sitting average systolic blood pressure [SBP] ≥ 180 mm Hg and/or average diastolic blood pressure [DBP] ≥ 110 mm Hg). Additionally, patients were excluded if they practiced intermittent self-catheterization; received nondrug treatment including electro-stimulation therapy; or used medications intended to treat OAB, prohibited medications, or restricted medications without meeting conditions for use.

At baseline patients had to have experienced a micturition frequency on average ≥ 8 times per 24-hour period during the 3-day micturition diary period, experienced at least 3 episodes of urgency (grade 3 or 4) with or without incontinence during the 3-day micturition diary period and had to continue to meet all screening eligibility criteria. Patients were excluded if they had an average total daily urine volume > 3000 mL as recorded in the 3-day micturition diary period; they had serum creatinine of > 150 mcmol/L, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times the upper limit of normal range or gamma glutamyl transferase (GGT) > 3 times the upper limit of normal, as assessed in screening samples and considered clinically significant by the investigator; or severe hypertension (defined as a sitting average systolic blood pressure [SBP] ≥ 180 mm Hg and/or average diastolic blood pressure [DBP] ≥ 110 mm Hg); or they had a clinically significant abnormal electrocardiogram (ECG).

Treatments

- Mirabegron tablets: 50 mg and 100 mg. One mirabegron tablet (and matching placebo for the other dose) was administered each morning (qd) by mouth with a glass of water with or without food to patients randomized to receive mirabegron 50 or 100 mg. Lot numbers: K0700248 (50 mg tablet); L0700011 (100 mg tablet).

- Two placebo tablets to match mirabegron 50 mg and 100 mg were administered to patients randomized to placebo each morning (qd) by mouth with a glass of water with or without food. Lot number: K0700232 (placebo to match mirabegron 50 mg tablet); K0700243 (placebo to match mirabegron 100 mg tablet)

- an active control, and placebo tablets to match tolterodine SR 4 mg capsules were administered qd by mouth with a glass of water with or without food to patients randomized to receive tolterodine SR 4 mg. Batch number: A705314A (tolterodine SR 4 mg capsules); BX1000891 and BX1001013 (placebo to match tolterodine SR 4 mg capsules).

Objectives

Primary: To assess the efficacy of mirabegron 50 and 100 mg versus placebo in the treatment of patients with symptoms of OAB.

Secondary: To assess the safety and tolerability of mirabegron 50 and 100 mg versus placebo in the treatment of patients with symptoms of OAB and to place the efficacy and safety of mirabegron in context with a standard treatment for OAB, tolterodine ER 4 mg.

Outcomes/endpoints

The co-primary efficacy variables included:

- Change from baseline to Final Visit in the mean number of incontinence episodes per 24 hours based on a 3 day micturition diary
- Change from baseline to Final Visit in the mean number of micturition per 24 hours based on a 3 day micturition diary

The key secondary efficacy variables included; 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 and change from baseline to week 4 in mean number of micturition per 24 hours based on a 3 day micturition diary.

Safety variables included; treatment-emergent adverse events (TEAEs); events adjudicated by the independent cardiovascular adjudication committee; TEAEs of interest (i.e., hypertension, QTc prolongation, cardiac arrhythmias, urinary retention/acute urinary retention, hypersensitivity, syncope, seizure, hepatic events and renal and urinary events); clinical laboratory evaluations (i.e., haematology and serum chemistry); Vital signs; ECGs and post-void residual volume (PVR)

Additional Secondary Endpoints

- 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 micturition per24 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

In addition, 2 responder analyses based on incontinence episodes were performed at week 4, week 8, week 12 and Final Visit using the FAS-I data set. The 2 responder definitions were as follows:

- Zero incontinence episodes: A responder was defined as a subject with 0 incontinence episodes post-baseline
- Reduction in incontinence episodes: A responder was defined as a subject with a ≥ 50% decrease from baseline in mean number of incontinence episodes per 24 hours

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

- 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 the TS-VAS
- Change from baseline to week 4, week 8, week 12 and Final Visit in number of physician visits for the subject's bladder condition (excluding study-related visits)

In addition, for change from baseline in PPBC, analyses were performed at week 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

Sample size

The sample size of pivotal studies was planned to provide about 90% power to detect a reduction of 0.7 in the mean number of micturitions per 24 hours over placebo in the mirabegron group at a 2-sided significance level of 0.05. Both mirabegron doses were compared with placebo by means of the Dunnett's test, which takes into account multiplicity, and the sample size calculation was based on this test. The standard deviation of the primary efficacy variable was assumed to be 2.7.

The sample size calculation for the mean number of incontinence episodes was based on nonparametric methods since the results of Study 178-CL-044 indicated that the assumption of normality might not be valid.

Only patients who were incontinent at baseline were included in the analysis of incontinence episodes. From Study 178-CL-044, it was estimated that this constituted about 65% of the population. The probability that a patient on mirabegron would respond better than a patient on placebo was 60.8%.

Since the 2 variables are positively correlated (Spearman rank correlation 0.31), the overall power is between 87% and 90%. A dropout rate of 20% during the placebo run-in period was assumed.

Randomisation

Patients were randomized after all baseline assessments were performed and eligibility for randomization was established. Patient numbers and randomized treatment were allocated by the CIRT system.

Patients who met the inclusion criteria and did not meet the exclusion criteria at the end of the single-blind, placebo run-in period, were randomized to 1 of the 4 treatment groups (mirabegron 50 mg, mirabegron 100 mg, placebo, or tolterodine SR 4 mg) in a 1:1:1:1 ratio using a computer-generated randomization scheme prepared by Pierrel Research Europe GmbH. Randomization was stratified by country.

Blinding (masking)

During the placebo run-in period, patients were blinded to the identity of study drug. During the double-blind treatment and follow-up periods, the investigator, study site personnel, patients, sponsor and the sponsor's representatives were blinded to the identity of the randomized drug assignment.

Statistical methods

A full description of the planned statistical methodology was provided in the Statistical Analysis Plan (SAP) which was finalised before the treatment codes were unblinded. The SAP included a number of changes made to the statistical methods described in the protocol.

The following analysis sets were pre-specified:

- Run-in Period Analysis Set (RPAS): all patients who took at least one dose of the single-blind placebo run-in study drug;
- Randomized Analysis Set (RAS): all randomized patients;
- Full Analysis Set (FAS): 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 post-baseline visit diary with a micturition measurement;
- FAS Incontinence (FAS-I): all FAS patients who had at least one incontinence episode at baseline;
- Per Protocol Set (PPS): FAS patients who did not deviate from the list of pre-specified major protocol violations;
- PPS Incontinence (PPS-I): All PPS patients who had at least one incontinence episode at baseline;
- Intent-to-Treat (ITT) Analysis Set: all randomized patients who took at least one dose of double-blind study drug and who had a baseline diary with micturition measurements;

- ITT Incontinence (ITT-I) Analysis Set: all randomized patients who took at least one dose of double-blind study drug and who had micturition measurements and at least one incontinence episode in the baseline diary;
- Safety Analysis Set (SAF): all randomized patients who took at least one dose of double-blind study drug.

As patients could be randomised without an incontinence episode in the baseline diary, a separate FAS definition based on micturition and incontinence episodes was defined as FAS-I. The populations for analyses of the co-primary efficacy endpoints and key secondary efficacy endpoints included the FAS and FAS-I.

Two-co-primary efficacy variables, both based on a micturition diary completed by the patients on the 3 study days immediately before visits at Weeks 4, 8 and 12, were defined as follows:

- Change from baseline to end of treatment (Final Visit) in mean number of micturition per 24 hours;
- Change from baseline to end of treatment (Final Visit) in mean number of incontinence episodes per 24 hours.

In addition three key secondary efficacy variables were:

- 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 micturition per 24 hours;
- change from baseline to Week 4 in mean number of incontinence episodes per 24 hours.

The additional secondary endpoints of Treatment Satisfaction Visual Analog Scale (TS-VAS), HRQL scores as assessed by the Overactive Bladder Questionnaire (OAB-q), and Patient Perception of Bladder Condition (PPBC) were used to collect and analyse subjective outcome measures. A responder analysis was specified for the reduction in incontinence episodes with a responder being defined as a patient that had at least a 50% decrease from baseline in the number of episodes per 24 hours.

All statistical comparisons were made using two-sided tests at the 5% significance level and were testing the treatment difference compared with placebo. The primary comparisons for the co-primary and secondary efficacy variables were between each mirabegron group and placebo with a secondary comparison between tolterodine and placebo. No formal statistical testing was performed to assess the difference between the mirabegron 50 mg and 100 mg groups or between each mirabegron group and the tolterodine group.

Missing data for the Final Visit were handled using last observation carried forward (LOCF) methods. All efficacy analyses using Final Visit included data that were measured within 7 days of the last dose of study drug. For all efficacy analyses, to be included in an analysis at a specific time-point the patient needed to have a measurement at that time-point; therefore no values were imputed.

Since there were two co-primary efficacy variables and 3 key secondary efficacy variables, the multiplicity between the variables was controlled at the Type I error rate at the 5% significance level using a stepwise parallel gate-keeping procedure, a hierarchical testing procedure. At each of the five

stages, the difference between a mirabegron dose group and placebo had to be statistically significant before that mirabegron dose group proceeded to the next stage. The stages and efficacy variables that were evaluated were as follows:

- Stage 1: incontinence episodes at the Final Visit
- Stage 2: micturition at the Final Visit
- Stage 3: volume voided per micturition at the Final Visit
- Stage 4: incontinence episodes at week 4
- Stage 5: micturition at week 4

Since two mirabegron treatment groups were compared with placebo, the Hochberg procedure was performed at the 5% significance level to adjust for multiplicity within each stage described above. If only one of the mirabegron dose groups proceeded to the next stage for any efficacy variable, then the comparison between mirabegron and placebo was assessed at the 2.5% significance level. Since the comparison between tolterodine and placebo was a secondary analysis, no adjustment for multiplicity was necessary.

The stratified rank analysis of covariance (ANCOVA) was used for hypothesis testing and calculating the pair-wise p-values. The least squares mean estimates and two-sided 95% CIs for mean changes from baseline within treatment group, as well as the mean change from baseline in the difference between each mirabegron treatment group and placebo and between tolterodine and placebo, were derived from the corresponding ANCOVA model with all treatment groups in the model.

Change from baseline to Final Visit (co-primary efficacy variable) and to Week 4 (key secondary efficacy variable) in mean number of incontinence episodes per 24 hours was analysed using a separate stratified rank analysis of covariance (ANCOVA) for each pair-wise treatment group difference of interest. The response variable was standardised ranks on change from baseline to Final Visit value for the stratified rank ANCOVA with baseline standardised ranks and gender as covariates and geographical region as a stratum.

Change from baseline to Final Visit (co-primary efficacy variable) and to Week 4 (key secondary efficacy variable) in mean number of micturition per 24 hours was analysed using an ANCOVA including treatment, gender and geographical region as fixed factors and baseline as a covariate. This ANCOVA model also was used to analyse the change from baseline to Final Visit in mean volume voided per micturition. Within the framework of this ANCOVA model, point estimates and two-sided 95% CIs for the mean change from baseline within each treatment group, as well as for the difference in mean change from baseline between each mirabegron treatment group and placebo and between tolterodine and placebo, were calculated.

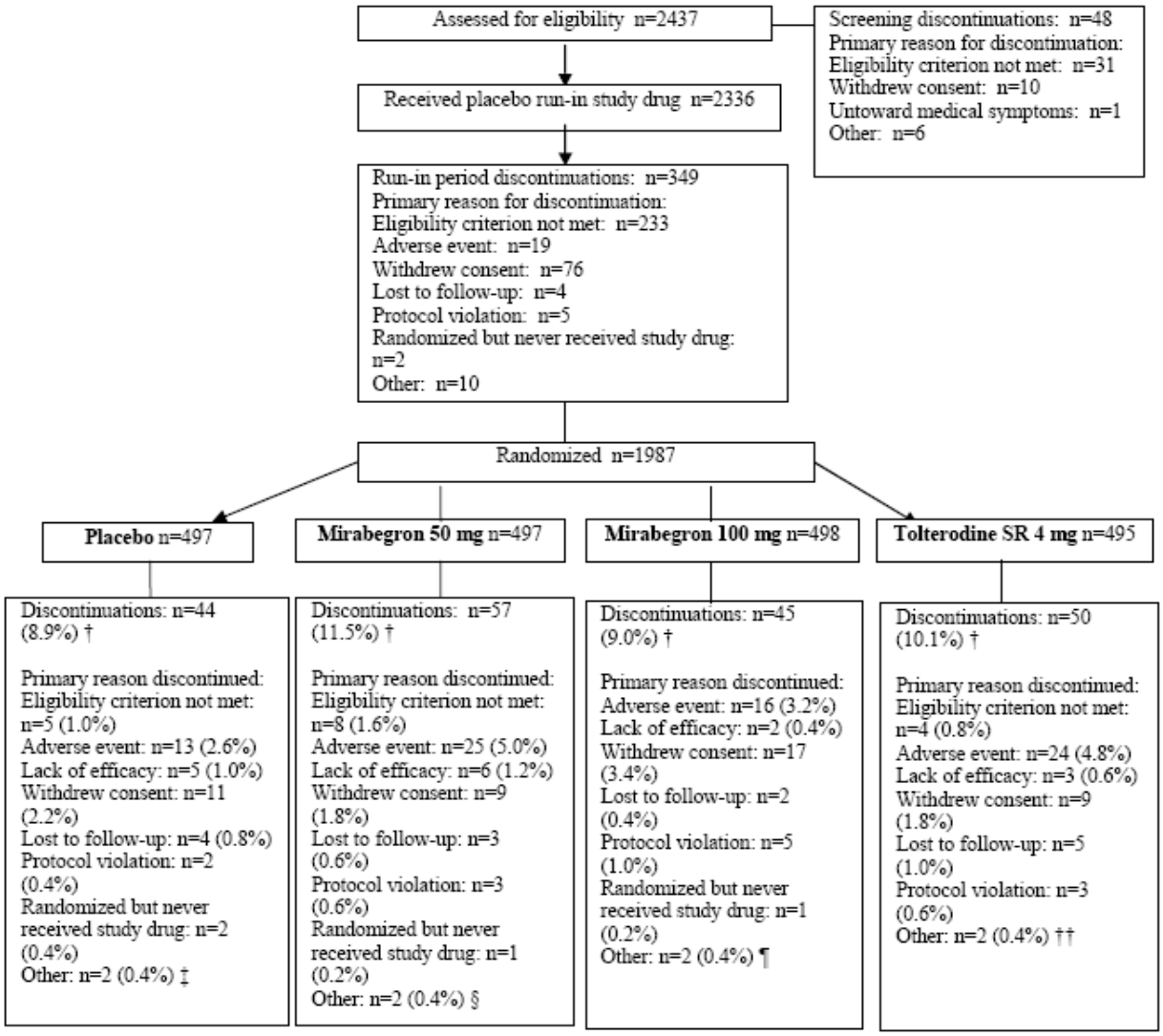
To assess the robustness of the primary efficacy analysis, the modelling of the co-primary efficacy variables was repeated using various sensitivity analyses using repeated measures methodology. These sensitivity analyses included investigation of outliers and where appropriate additional analyses were planned excluding outliers. An outlier was defined as an observation for which the residual is more than three interquartile ranges above the 75th percentile or below the 25th percentile.

The co-primary efficacy variables were also analysed for the following subgroups: race, age, gender and geographical region.

Results

Participant flow

Figure 1 Patient Disposition



All patients.

† Discontinuations are those reported for patients in the Randomized Analysis Set.

‡ Other reasons for discontinuation in the placebo group were personal reasons and blood pressure was too difficult to measure.

§ Other reasons for discontinuation in the mirabegron 50 mg group were unable to commit to study schedule due to work commitments and patient wanted to go to Italy for family reasons and could not return in time to begin the study.

¶ Other reasons for discontinuation in the mirabegron 100 mg group were patient was excluded in error and patient had to move to another town in Spain.

Recruitment

First Subject Enrolled – Last Subject Last Visit: 28 April 2008 - 24 March 2009

Conduct of the study

Reasons for exclusion of patients from the PPS and PPS-I comprised major protocol violations that affected the co-primary efficacy variables and the key secondary efficacy variable of volume voided per micturition. These included eligibility criteria that were not met, administration of incorrect study drug, poor study drug compliance (defined as < 70% of study taken during the double-blind treatment period), inadequate duration of treatment during the placebo run-in period or double-blind treatment period (defined as < 53 days recorded for the last diary day of the Final Visit), use of prohibited concomitant medication during the placebo run-in period or the double-blind treatment period, and unblinding of treatment for double-blind study drug. Approximately 11% of patients in the FAS and 12% of patients in the FAS-I were excluded from the PPS and PPS-I, respectively. The percentage of patients excluded from the PPS and PPS-I was comparable across all treatment groups. The most frequently cited reason for exclusion reflected an inadequate duration of treatment during the double-blind treatment period (i.e., the last diary day of the Final Visit was < 53 days); the percentage of patients excluded for this reason for the PPS and PPS-I was 3.8% and 4.1% for the placebo group, 6.1% and 6.5% for the mirabegron 50 mg group, 4.2% and 4.3% for the mirabegron 100 mg group and 3.8% and 3.0% for the tolterodine SR 4 mg group

Baseline data

Demographic and baseline characteristics were consistent across treatment groups for patients in the SAF population. Overall, 72.2% of patients were female. The majority (62.9%) of patients were < 65 years of age and 91.3% were < 75 years of age. Overall, 99.1% of patients were white. Mean body mass index across all treatment groups was 27.8 kg/m2. Demographic and baseline characteristics were similar across treatment groups in the FAS and FAS-I. 72.0% and 83.4% of patients were female (FAS and FAS-I, respectively). In the FAS, mean age was 59.1 years and 37.1% of patients were ≥ 65 years of age. The overall mean duration of OAB symptoms was 79.3 and 88.0 months in the FAS and FAS-I, respectively. Overall, approximately one-half of patients had received previous OAB antimuscarinic therapy (49.6% and 56.5% in the FAS and FAS-I, respectively).

Table 1 Summary of Patient Demographics and Baseline Characteristics, SAF

Parameter	Placebo (n=494)	Mirabegron 50 mg (n=493)	Mirabegron 100 mg (n=496)	Tolterodine SR 4 mg (n=495)	Total (n=1978)
Sex (n, %)					
Male	138 (27.9%)	136 (27.6%)	141 (28.4%)	134 (27.1%)	549 (27.8%)
Female	356 (72.1%)	357 (72.4%)	355 (71.6%)	361 (72.9%)	1429 (72.2%)
Age (years)					
Mean (SD)	59.2 (12.30)	59.1 (12.36)	59.0 (12.71)	59.1 (12.89)	59.1 (12.56)
Age group (years) (n, %)					
< 65	313 (63.4%)	315 (63.9%)	313 (63.1%)	303 (61.2%)	1244 (62.9%)
≥ 65	181 (36.6%)	178 (36.1%)	183 (36.9%)	192 (38.8%)	734 (37.1%)
< 75	450 (91.1%)	447 (90.7%)	450 (90.7%)	458 (92.5%)	1805 (91.3%)
≥ 75	44 (8.9%)	46 (9.3%)	46 (9.3%)	37 (7.5%)	173 (8.7%)
Race (n, %)					
White	490 (99.2%)	488 (99.0%)	492 (99.2%)	490 (99.0%)	1960 (99.1%)
Black or African American	2 (0.4%)	1 (0.2%)	1 (0.2%)	3 (0.6%)	7 (0.4%)
Asian	0	2 (0.4%)	2 (0.4%)	2 (0.4%)	6 (0.3%)
Other †	2 (0.4%)	2 (0.4%)	1 (0.2%)	0	5 (0.3%)
BMI (kg/m^2)					
n	493	493	495	495	1976
Mean (SD)	27.8 (4.96)	27.5 (4.86)	28.0 (4.95)	27.8 (4.96)	27.8 (4.93)
Geographical region (n, %)					
Eastern Europe	225 (45.5%)	222 (45.0%)	224 (45.2%)	226 (45.7%)	897 (45.3%)
Western Europe‡	269 (54.5%)	271 (55.0%)	272 (54.8%)	269 (54.3%)	1081 (54.7%)

All randomized patients who took at least 1 dose of double-blind study drug (Safety Analysis Set [SAF]). The denominators for the percentage calculations of categorical variables are the number of patients with nonmissing values. Body mass index (BMI) = weight (kg)/height (m^2).

† Other race: placebo: Romanian and Ghanaian; mirabegron 50 mg: Pakistani and American Indian; mirabegron 100 mg: Latin.

‡ For the purposes of this summary, Australia was included within the Western Europe category. A list of countries included in each geographical region (Eastern Europe or Western Europe) is provided [see Appendix 1 of the SAP, Appendix 13.1.9].

Source: Table 12.1.2.1.1 and Appendix 13.2.4.1

Table 8 Overactive Bladder History, FAS

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

All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). The percentage for each category was calculated using the number of patients with nonmissing values for the denominator.

OAB: overactive bladder.

† Types of OAB were defined as follows: urgency incontinence = urge incontinence only; mixed = mixed stress/urge incontinence with urge as a predominant factor; frequency = frequency/urgency without incontinence.

‡ Patients could choose > 1 reason for discontinuation of previous OAB drug.

Source: Table 12.1.2.2.2

Numbers analysed

Analysis Set, n (%)	Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Tolterodine SR 4 mg	Total
Randomized analysis set	497 (100.0%)	497 (100.0%)	498 (100.0%)	495 (100.0%)	1987 (100.0%)
Full analysis set	480 (96.6%)	473 (95.2%)	478 (96.0%)	475 (96.0%)	1906 (95.9%)
Full analysis set incontinence	291 (58.6%)	293 (59.0%)	281 (56.4%)	300 (60.6%)	1165 (58.6%)
Intent-to-treat analysis set	493 (99.2%)	492 (99.0%)	496 (99.6%)	495 (100.0%)	1976 (99.4%)
Intent-to-treat analysis set incontinence	299 (60.2%)	309 (62.2%)	294 (59.0%)	311 (62.8%)	1213 (61.0%)
Per protocol analysis set	425 (85.5%)	417 (83.9%)	426 (85.5%)	426 (86.1%)	1694 (85.3%)
Per protocol analysis set incontinence	251 (50.5%)	256 (51.5%)	247 (49.6%)	267 (53.9%)	1021 (51.4%)
Safety analysis set	494 (99.4%)	493 (99.2%)	496 (99.6%)	495 (100.0%)	1978 (99.5%)

The percentage of patients in each analysis set is based on the Randomized Analysis Set.

The percentage of patients randomised who had reported at least one episode of incontinence in the baseline diary is approximately 60%, similar across the treatment groups.

Outcomes and estimation

Primary endpoints

Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 Hours

Approximately 60% of patients in the FAS in each treatment group had 1 or more episodes of incontinence during the 3-day diary period at baseline. Mirabegron 50 mg and 100 mg groups demonstrated statistically significant greater reductions from baseline to Final Visit compared to placebo in the mean number of incontinence episodes per 24 hours (difference from placebo: -0.41 and -0.29, mirabegron 50 mg and mirabegron 100 mg). The reduction in the mean number of incontinence episodes per 24 hours (difference from placebo: -0.10) as compared to placebo for the tolterodine SR 4 mg group was not statistically significant.

Table 17 Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 Hours, FAS-I

		Mirabegron		
	Placebo (n=291)	50 mg (n=293)	100 mg (n=281)	Tolterodine SR 4 mg (n=300)
Baseline				
Mean (SE)	2.67 (0.140)	2.83 (0.165)	2.89 (0.147)	2.63 (0.148)
Median	2.00	2.00	2.33	1.67
Range	0.3 – 13.3	0.3 – 16.7	0.3 – 14.0	0.3 – 11.7
Final Visit				
Mean (SE)	1.54 (0.145)	1.22 (0.133)	1.37 (0.134)	1.42 (0.145)
Median	0.67	0.33	0.33	0.33
Range	0.0 – 17.7	0.0 – 17.7	0.0 – 19.3	0.0 – 14.7
Change from Baseline				
Mean (SE)	-1.13 (0.126)	-1.62 (0.137)	-1.51 (0.128)	-1.21 (0.137)
Median	-1.00	-1.00	-1.33	-1.00
Range	-11.7 – 10.0	-12.0 – 5.7	-11.3 – 9.7	-10.3 – 9.3
ANCOVA Model †				
Adjusted mean change from baseline (SE)	-1.17 (0.113)	-1.57 (0.113)	-1.46 (0.115)	-1.27 (0.112)
95% two-sided CI	(-1.39, -0.95)	(-1.79, -1.35)	(-1.68, -1.23)	(-1.49, -1.05)
Mean difference vs placebo (SE)		-0.41 (0.160)	-0.29 (0.162)	-0.10 (0.159)
95% two-sided CI		(-0.72, -0.09)	(-0.61, 0.03)	(-0.42, 0.21)
P-value ‡		0.003#	0.010#	0.11

All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement and at least 1 incontinence episode in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (Full Analysis Set Incontinence [FAS-I]).

† The analysis of covariance (ANCOVA) model included treatment group, sex and geographical region as fixed factors and baseline as a covariate.

‡ Nominal P-values were from pairwise comparisons vs placebo within the stratified rank ANCOVA, a nonparametric analysis.

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

Change from Baseline to Final Visit in Mean Number of Micturition per 24 hours

Each mirabegron group demonstrated a statistically significant decrease in the reduction from baseline to Final Visit in mean number of micturition per 24 hours compared to placebo with the multiplicity adjustment. The magnitude of reduction in the mirabegron 100 mg group was lower than that observed in the mirabegron 50 mg group. The adjusted mean difference versus placebo for the tolterodine SR 4 mg group (-0.25) was not statistically significant.

Table 18 Change from Baseline to Final Visit in Mean Number of Micturitions per 24 Hours, FAS

	Placebo (n=480)	Mirabegron 50 mg (n=473)	Mirabegron 100 mg (n=478)	Tolterodine SR 4 mg (n=475)
Baseline				
Mean (SE) Median Range	11.71 (0.143) 11.00 5.3 – 25.0	11.65 (0.137) 11.00 6.7 – 25.7	11.51 (0.124) 11.00 6.7 – 23.3	11.55 (0.128) 11.00 6.0 – 22.7
Final Visit				
Mean (SE) Median Range	10.35 (0.144) 10.00 4.3 – 24.3	9.70 (0.139) 9.00 4.0 – 25.3	9.76 (0.144) 9.00 4.0 – 24.0	9.97 (0.162) 9.33 3.7 – 35.7
Change from Baseline				
Mean (SE) Median Range	-1.37 (0.115) -1.17 -13.0 – 6.7	-1.94 (0.116) -1.67 -14.0 – 7.3	-1.75 (0.110) -2.00 -9.0 – 8.7	-1.57 (0.123) -1.67 -10.3 – 13.0
ANCOVA Model †				
Adjusted mean change from baseline (SE)	-1.34 (0.110)	-1.93 (0.111)	-1.77 (0.110)	-1.59 (0.111)
95% two-sided CI	(-1.55, -1.12)	(-2.15, -1.72)	(-1.99, -1.56)	(-1.80, -1.37)
Mean difference vs placebo (SE)		-0.60 (0.156)	-0.44 (0.156)	-0.25 (0.156)
95% two-sided CI		(-0.90, -0.29)	(-0.74, -0.13)	(-0.55, 0.06)
P-value ‡		<0.001#	0.005#	0.11

All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]).

† The analysis of covariance (ANCOVA) model included treatment group, sex and geographical region as fixed factors and baseline as a covariate.

‡ Nominal P-values were from pairwise comparisons vs placebo within the ANCOVA model, a parametric analysis.

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

Source: Table 12.3.1.2

Key Secondary endpoints

Table 5 Overview of Key Secondary Efficacy Results, FAS and FAS-I

Change from Baseline to Final Visit in Mean Volume Voided (mL) per Micturition (FAS)			
	Mirabegron 50 mg (n=472)	**Mirabegron 100 mg (n=478)**	**Tolterodine SR 4 mg (n=475)**
Mean difference from placebo (SE) 95% CI	11.9 (2.83) (6.3, 17.4)	13.2 (2.82) (7.7, 18.7)	12.6 (2.83) (7.1, 18.2)
P-values‡	<0.001#	<0.001#	<0.001&
Change from Baseline to Week 4 in Mean Number of Incontinence Episodes per 24 Hours (FAS-I)			
	Mirabegron 50 mg (n=293)	**Mirabegron 100 mg (n=281)**	**Tolterodine SR 4 mg (n=299)**
Mean difference from placebo (SE) 95% CI	-0.39 (0.167) (-0.71, -0.06)	-0.38 (0.169) (-0.71, -0.05)	-0.35 (0.166) (-0.68, -0.03)
P-values†	0.002#	0.002#	0.019&
Change from Baseline to Week 4 in Mean Number of Micturitions per 24 Hours (FAS)			
	Mirabegron 50 mg (n=471)	**Mirabegron 100 mg (n=477)**	**Tolterodine SR 4 mg (n=474)**
Mean difference from placebo (SE) 95% CI	-0.40 (0.136) (-0.66, -0.13)	-0.52 (0.136) (-0.79, -0.26)	-0.33 (0.136) (-0.60, -0.06)
P-values‡	0.004#	<0.001#	0.016&

All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement and at least 1 incontinence episode in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (FAS Incontinence [FAS-I]).

† Nominal P-values were from pairwise comparisons vs placebo within the stratified rank analysis of covariance (ANCOVA).

‡ Nominal P-values were from pairwise comparisons vs placebo within the ANCOVA model.

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

& Statistically significantly superior compared to placebo at the 0.05 level without multiplicity adjustments.

After 12 weeks of treatment patients receiving mirabegron experienced a statistically significant reduction in the number of micturitions and the incontinence episodes. This positive effect was also translated into the main secondary endpoints. In general, effect size is deemed as modest. Doses of 50 mg and 100 mg do not separate from each other in terms of efficacy. Exploratory comparison between mirabegron and tolterodine showed numerical differences in favour of mirabegron.

Additional secondary endpoints

- Statistically significant greater reductions from baseline to week 4, week 8 and week 12 compared to placebo in the mean number of incontinence episodes per 24 hours and mean number of micturition per 24 hours were observed for mirabegron 50 mg and 100 mg. The tolterodine SR 4 mg group only demonstrated statistically significant greater reductions from baseline to week 4 compared to placebo for these parameters.

- Statistically significant greater reductions from baseline to week 4, week 8 and week 12 compared to placebo in the mean volume voided per micturition were observed for mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg.

- The mirabegron 50 mg group demonstrated statistically significant greater improvements from baseline to Final Visit compared to placebo in the mean number of urgency episodes (grade 3 or 4) per 24 hours (using the patient Perception of Intensity of Urgency Scale) and mean number of nocturia episodes per 24 hours for mirabegron 50 mg.

- The tolterodine SR 4 mg group also demonstrated statistically significant greater improvements from baseline to Final Visit compared to placebo in the mean number of urgency episodes (grade 3 or 4) per 24 hours.

- For the TS-VAS, the mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg groups demonstrated statistically significant greater increases from baseline to Final Visit compared to placebo.

- For the OAB-q:

    - The mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg groups demonstrated statistically significant greater improvements from baseline to Final Visit compared to placebo in the Symptom Bother scale.

    - The mirabegron 50 mg and 100 mg groups demonstrated statistically significant greater improvements from baseline to Final Visit compared to placebo in the HRQL dimensions of Coping, Concern and in mean total HRQL score. The mirabegron 100 mg group also demonstrated statistically significant greater improvements from baseline to Final Visit compared to placebo in the HRQL dimension of Sleep and Social Interaction.

    - The tolterodine SR 4 mg group did not demonstrate statistically significant improvement from baseline to Final Visit compared to placebo for any of these OAB-q parameters.

Ancillary analyses

Ancillary analyses

Sensitivity analyses were performed to assess the robustness of the primary efficacy analyses.

- Repeated Measurement Analysis of Mean Number of Incontinence Episodes per 24 Hours, FAS-I

In the repeated measurement analysis of the mean number of incontinence episodes per 24 hours, the adjusted mean difference versus placebo and 95% CIs for both mirabegron 50 mg and 100 mg groups at week 12 were similar to those at the Final Visit in the primary analysis. Both mirabegron groups demonstrated statistically significantly superior mean reduction of incontinence episodes compared to the placebo group as early as week 4 and their effectiveness was maintained throughout the treatment period (weeks 8 and 12).

- Repeated Measurement Analysis of Mean Number of Micturition per 24 Hours, FAS

In the repeated measurement analysis of the mean number of micturition per 24 hours, the adjusted mean difference versus placebo and 95% CIs for both mirabegron 50 mg and 100 mg groups at week 12 were similar to those at the Final Visit in the primary analysis. Both mirabegron groups demonstrated statistically significantly superior mean reduction of micturition compared to the placebo group as early as week 4 and their effectiveness was maintained throughout the treatment period (weeks 8 and 12). The P-values at week 12 from the repeated measurement analysis were P< 0.001 for the mirabegron 50 mg and P=0.006 for the mirabegron 100 mg group. Tolterodine SR 4 mg demonstrated a statistically significantly superior mean reduction of micturition compared to placebo at the week 4 and week 8 time points.

- Sensitivity Analysis of Mean Number of Incontinence Episodes per 24 Hour, PPS-I

In the PPS-I, the adjusted mean difference versus placebo in the number of incontinence episodes per 24 hours from baseline to Final Visit was -0.40 in the mirabegron 50 mg group and -0.29 in the mirabegron 100 mg group. Each mirabegron group demonstrated a statistically significant difference in the reduction from baseline to Final Visit compared to placebo in the mean number of incontinence episodes per 24 hours]. In the PPS-I, the adjusted mean difference versus placebo in the number of incontinence episodes per 24 hours from baseline to Final Visit was -0.17 in the tolterodine SR 4 mg group, this was not statistically significant.

- Sensitivity Analysis of Mean Number of Micturition per 24 Hours, PPS

One of the inclusion criteria was a mean of ≥ 8 micturition per 24 hours at baseline. The sensitivity analyses in the PPS excluded patients who did not meet this criterion at baseline. In this sensitivity analysis, the adjusted mean differences versus placebo in the number of micturition per 24 hours were -0.71 and -0.50 for the mirabegron 50 mg and 100 mg groups, respectively. Each mirabegron group demonstrated a statistically significant difference in the reduction from baseline to Final Visit compared to placebo in the mean number of micturition per 24 hours (see table below). The adjusted mean differences versus placebo in the number of micturition per 24 hours were -0.40 for the tolterodine SR 4 mg group. This was statistically significant.

Responder Analysis

Reduction in Incontinence Episodes

At the Final Visit, the percentage of responders was greater in the mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg groups than in the placebo group. The difference versus placebo was 11.9%, 7.5% and 8.2% for the mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg groups. The corresponding odds ratio for mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg was 1.75, 1.45 and 1.44, respectively; statistical significance was achieved for all 3 active treatment groups

Zero Incontinence Episodes

The percentage of responders for zero incontinence episodes was greater in the active treatment groups than in placebo and the difference versus placebo in all active treatment groups at the Final visit was 4.5%, 3.2% and 6.8% for mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg.

Study 178-CL-047

This was a randomised, parallel group, placebo-controlled, double-blind, double-dummy, multinational, multicenter study conducted in patients with symptoms of OAB syndrome (urinary frequency and

urgency with or without incontinence) of at least 3 months' duration. The study was conducted at 132 sites in the United States (115 sites) and Canada (17 sites).

Methods

After screening (day -21 to day -14), patients were enrolled in a 2-week, single-blind, placebo run-in period that ended at baseline (week 0). At baseline, patients meeting inclusion criteria and not meeting exclusion criteria were randomly assigned in a 1:1:1 ratio to receive mirabegron 50 mg, mirabegron 100 mg or a matching placebo qd for a 12-week, double-blind, placebo-controlled treatment period that consisted of visits at weeks 4, 8 and 12 and a 30-day follow-up telephone contact or visit.

Study Participants

As in study 178-CL-046

Treatments

- Mirabegron tablets: 50 mg and 100 mg. One mirabegron tablet (and matching placebo for the other dose) was administered each morning (q.d) by mouth with a glass of water with or without food to patients randomized to receive mirabegron 50 or 100 mg. Lot numbers: K0700248 (50 mg tablet); L0700011 (100 mg tablet).
- Two placebo tablets to match mirabegron 50 mg or 100 mg were administered each morning (q.d) by mouth with a glass of water with or without food to patients randomized to placebo. Lot number: K0700232 (placebo to match mirabegron 50 mg tablet); K0700243 (placebo to match mirabegron 100 mg tablet)

Objectives

- The primary objective of the study was to assess the efficacy of mirabegron 50 mg q.d and mirabegron 100 mg qd against placebo in the treatment of patients with symptoms of overactive bladder (OAB).
- The secondary objective was to assess the safety and tolerability of mirabegron 50 mg q.d and mirabegron 100 mg qd against placebo in the treatment of patients with symptoms of OAB.

Outcomes/endpoints

The endpoints are essentially the same as study 178-CL-046

Sample size

The sample size was determined as in study 178-CL-046

Randomisation

As in study 178-CL-046

Blinding (masking)

As in study 178-CL-046

Statistical methods

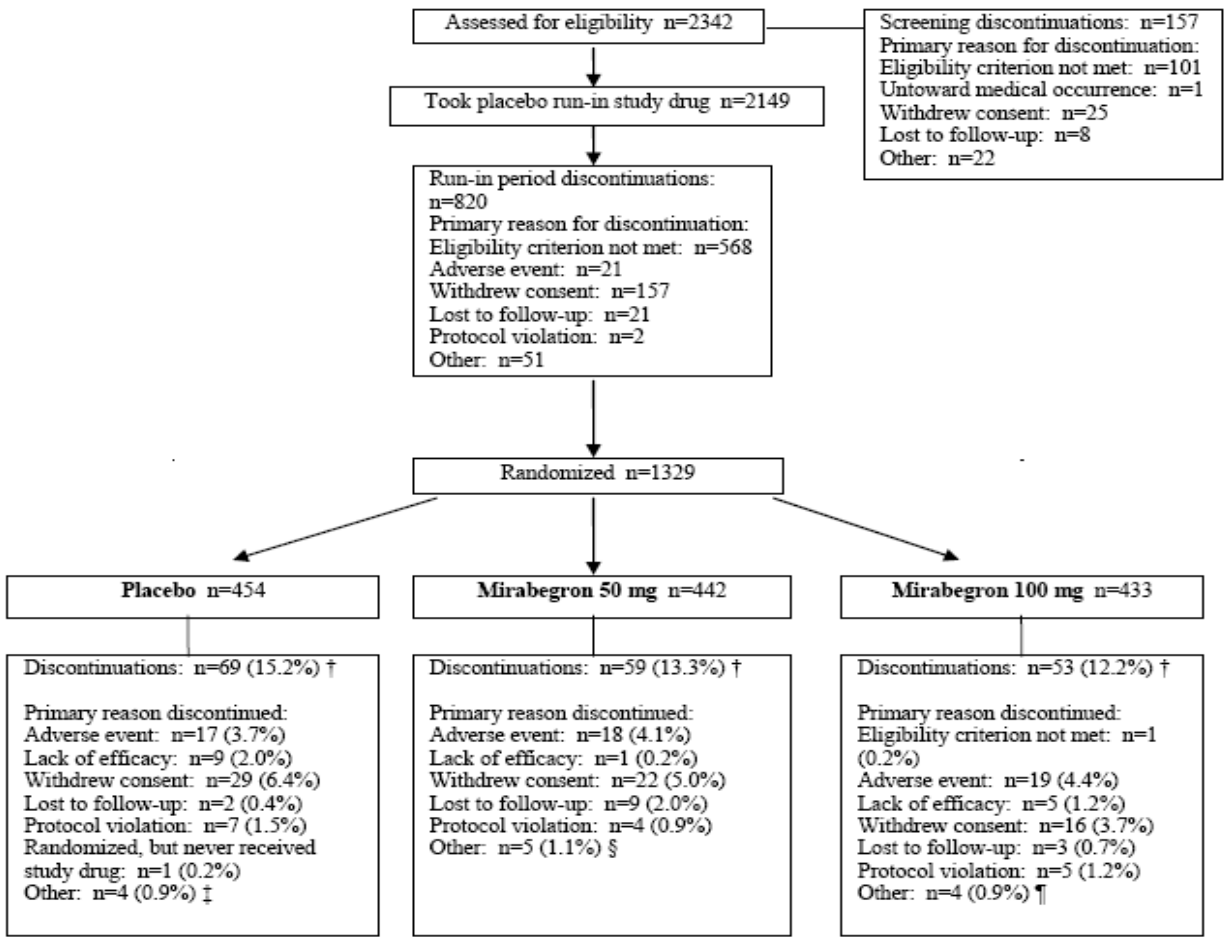
The statistical methods used were essentially the same as used in study 178-CL-046

Results

Participant flow

A total of 2342 patients were screened, 2306 patients entered the placebo run-in period, 2149 patients took placebo run-in study drug, and 1329 patients were randomized into the study and 1328 received double-blind study medication (SAF population).

Figure 1 Patient Disposition



All patients.

† Discontinuations are those reported for patients in the Randomized Analysis Set.

‡ Other reasons for discontinuation in the placebo group included noncompliance with diary completion; inability to complete diary correctly; error by study site personnel and investigator decision to withdraw patient.

§ Other reasons for discontinuation in the mirabegron 50 mg group included extreme weather and hazardous travel conditions precluded attendance at site visits; noncompliance with study schedule, diary completion and study drug; family emergency caused patient to run out of study drug; withdrawal by investigator due to visit delay such that patient had not taken study drug for 12 days and average urinary output exceeded baseline exclusion criterion.

¶ Other reasons for discontinuation in the mirabegron 100 mg group included withdrawal by investigator; scheduling for excluded procedure; withdrawal by investigator due to noncompliance with protocol and incarceration with concomitant noncompliance with study drug.

Recruitment

First Subject Enrolled – Last Subject Last Visit: 28 March 2008 - 22 April 2009

Conduct of the study

Five patients were identified as having been enrolled into the study twice. Enrolment occurred at 10 unique sites for these patients. One patient was a screen failure at 1 site and a run-in failure at a different site and the other 4 patients were randomized twice and received 2 double-blind study drug treatment assignments. These 4 patients were therefore analyzed as 8 unique patients for both efficacy and safety.

Reasons for exclusion of patients from the PPS and PPS-I comprised major protocol violations that affected the co-primary efficacy variables and the key secondary efficacy variable of volume voided per micturition. These included eligibility criteria that were not met, administration of incorrect study drug, poor study drug compliance (defined as < 70% during the double-blind treatment period) and inadequate duration of treatment. For the placebo run-in period, inadequate duration of treatment was defined as placebo treatment < 9 days during the placebo run-in period until the last diary day before randomization. For the double-blind treatment period, inadequate duration of treatment was defined as last diary day of the Final Visit 3-day micturition diary < 53 days during the double-blind treatment period.

Approximately 12% of patients in the FAS and 11% of patients in the FAS-I were excluded from the PPS and PPS-I, respectively. In all treatment groups, the most frequently cited reason for exclusion reflected an inadequate duration of treatment during the double-blind treatment period (i.e., last diary day of the Final Visit was < 53 days); the percentage of patients excluded for this reason for the PPS and PPS-I was 6.5% in the placebo group (for both the PPS and PPS-I), 6.4% and 7.7% in the mirabegron 50 mg group and 3.4% and 3.7% in the mirabegron 100 mg group.

Baseline data

Generally, demographic and baseline characteristics were similar across treatment groups. Overall, approximately 75% and 82% of patients were female in the FAS and FAS-I, respectively. In the FAS, the mean age was 60.2 years and 39.7% of patients were ≥ 65 years of age. The overall mean duration of OAB symptoms was approximately 90 months in the FAS and FAS-I. The majority of patients had received previous OAB antimuscarinic therapy (approximately 56% and 60% in the FAS and FAS-I, respectively). Approximately 65% of patients in both analysis sets who had received previous OAB antimuscarinic therapy cited insufficient effect as a reason for discontinuation, while poor tolerability was cited by approximately 22% of these patients.

Table 1 Demographic Characteristics, SAF

Parameter	Placebo (n=453)	Mirabegron 50 mg (n=442)	Mirabegron 100 mg (n=433)	Total (n=1328)
Sex (n, %)				
Male	108 (23.8%)	120 (27.1%)	113 (26.1%)	341 (25.7%)
Female	345 (76.2%)	322 (72.9%)	320 (73.9%)	987 (74.3%)
Age (years)				
Mean (SD)	60.1 (13.79)	59.2 (13.53)	61.0 (13.25)	60.1 (13.54)
Age group (years) (n, %)				
< 65	273 (60.3%)	274 (62.0%)	253 (58.4%)	800 (60.2%)
≥ 65	180 (39.7%)	168 (38.0%)	180 (41.6%)	528 (39.8%)
< 75	385 (85.0%)	382 (86.4%)	360 (83.1%)	1127 (84.9%)
≥ 75	68 (15.0%)	60 (13.6%)	73 (16.9%)	201 (15.1%)
Race (n, %)				
White	395 (87.2%)	391 (88.5%)	381 (88.0%)	1167 (87.9%)
Black or African American	47 (10.4%)	32 (7.2%)	37 (8.5%)	116 (8.7%)
Asian	6 (1.3%)	12 (2.7%)	8 (1.8%)	26 (2.0%)
Other	5 (1.1%) †	7 (1.6%) ‡	7 (1.6%) §	19 (1.4%)
Ethnicity (n, %)				
Hispanic/Latino	26 (5.7%)	23 (5.2%)	32 (7.4%)	81 (6.1%)
Non-Hispanic/Non-Latino	427 (94.3%)	419 (94.8%)	401 (92.6%)	1247 (93.9%)
BMI (kg/m^2)				
n	452	442	433	1327
Mean (SD)	30.4 (7.36)	30.0 (6.59)	30.2 (7.06)	30.2 (7.01)
Geographical region (n, %)				
Northeastern US	78 (17.2%)	73 (16.5%)	77 (17.8%)	228 (17.2%)
Midwestern US	61 (13.5%)	59 (13.3%)	53 (12.2%)	173 (13.0%)
Southern US	156 (34.4%)	147 (33.3%)	147 (33.9%)	450 (33.9%)
Western US	116 (25.6%)	116 (26.2%)	113 (26.1%)	345 (26.0%)
Canada	42 (9.3%)	47 (10.6%)	43 (9.9%)	132 (9.9%)

All randomized patients who took at least 1 dose of double-blind study drug (Safety Analysis Set [SAF]). The denominators for the percentage calculations of categorical variables were the number of patients with nonmissing values. BMI = weight (kg)/height (m^2).

BMI: body mass index; US: United States.

† Other races in the Placebo group included Hispanic, White/American Indian; American Indian/Alaska native (n = 2); White and Black/African American.

‡ Other races in the mirabegron 50 mg group included American Indian/Alaska native (n = 5) and native Hawaiian/other Pacific islander (n = 2).

§ Other races in the mirabegron 100 mg group included American Indian/Alaska native (n = 4); native American, Ethiopian, Caucasian; native Hawaiian/other Pacific islander and East Indian.

Source: Table 12.1.2.1.1

Table 7 Overactive Bladder History, FAS and FAS-I

Parameter	FAS			FAS-I		
		Mirabegron			Mirabegron	
	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

All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement and at least 1 incontinence episode in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (FAS Incontinence [FAS-I]). The percentage for each category was calculated using the number of patients with nonmissing values for the denominator.

OAB: overactive bladder.

† Types of OAB were defined as follows: urgency incontinence = urge incontinence only; mixed = mixed stress/urge incontinence with urge as a predominant factor; frequency = frequency/urgency without incontinence.

‡ Patients could choose > 1 reason for discontinuation of previous OAB drug.

Source: Table 12.1.2.2.2 and Table 12.1.2.2.3

Numbers analysed

Table 2 Summary of Analysis Sets

Analysis Set, n (%)	Placebo	Mirabegron		Total
		50 mg	100 mg	
Randomized analysis set	454 (100.0%)	442 (100.0%)	433 (100.0%)	1329 (100.0%)
Full analysis set	433 (95.4%)	425 (96.2%)	412 (95.2%)	1270 (95.6%)
Full analysis set incontinence	325 (71.6%)	312 (70.6%)	296 (68.4%)	933 (70.2%)
Intent-to-treat analysis set	453 (99.8%)	442 (100.0%)	433 (100.0%)	1328 (99.9%)
Intent-to-treat analysis set incontinence	339 (74.7%)	326 (73.8%)	309 (71.4%)	974 (73.3%)
Per protocol analysis set	380 (83.7%)	372 (84.2%)	372 (85.9%)	1124 (84.6%)
Per protocol analysis set incontinence	286 (63.0%)	271 (61.3%)	270 (62.4%)	827 (62.2%)
Safety analysis set	453 (99.8%)	442 (100.0%)	433 (100.0%)	1328 (99.9%)

The percentage of patients in each analysis set is based on the Randomized Analysis Set.

The percentage of patients randomised who had reported at least one episode of incontinence in the baseline diary is approximately 70%, fairly similar in each of the treatment groups.

Outcomes and estimation

Primary endpoints

Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 Hours

Each mirabegron group demonstrated a statistically significant difference in reduction from baseline to Final Visit in the mean number of incontinence episodes per 24 hours compared to placebo with the multiplicity adjustment. The mirabegron 100 mg group achieved a numerically greater adjusted mean difference in reduction from baseline to Final Visit versus placebo than the mirabegron 50 mg group.

Table 14 Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 Hours, FAS-I

	Placebo (n=325)	Mirabegron 50 mg (n=312)	Mirabegron 100 mg (n=296)
Baseline			
Mean (SE)	3.03 (0.171)	2.77 (0.150)	2.69 (0.142)
Median	2.00	2.00	2.00
Range	0.3 to 25.7	0.3 to 18.0	0.3 to 15.3
Final Visit			
Mean (SE)	1.81 (0.152)	1.33 (0.133)	1.14 (0.128)
Median	0.67	0.33	0.33
Range	0.0 to 17.0	0.0 to 15.0	0.0 to 17.7
Change from Baseline			
Mean (SE)	-1.22 (0.152)	-1.44 (0.126)	-1.56 (0.130)
Median	-1.00	-1.00	-1.33
Range	-25.7 to 6.7	-18.0 to 6.3	-13.7 to 8.7
ANCOVA Model †			
Adjusted mean change from baseline (SE)	-1.13 (0.112)	-1.47 (0.114)	-1.63 (0.117)
95% two-sided CI	(-1.35, -0.91)	(-1.69, -1.25)	(-1.86, -1.40)
Mean difference vs placebo (SE)		-0.34 (0.160)	-0.50 (0.162)
95% two-sided CI		(-0.66, -0.03)	(-0.82, -0.18)
P-value ‡		0.026#	< 0.001#

All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement and at least 1 incontinence episode in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (FAS Incontinence [FAS-I]).

† The analysis of covariance (ANCOVA) model included treatment group, sex and geographical region as fixed factors and baseline as a covariate.

‡ P-values were from pairwise comparison vs placebo within the stratified rank ANCOVA, a nonparametric analysis.

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

Change from Baseline to Final Visit in Mean Number of Micturition per 24 Hours

Each mirabegron group demonstrated a statistically significant difference in reduction from baseline to Final Visit in the mean number of micturition per 24 hours compared to placebo with the multiplicity adjustment. The mirabegron 100 mg group achieved a numerically greater adjusted mean difference in reduction from baseline to Final Visit versus placebo than the mirabegron 50 mg group.

Table 15 Change from Baseline to Final Visit in Mean Number of Micturitions per 24 Hours, FAS

	Placebo (n=433)	Mirabegron 50 mg (n=425)	Mirabegron 100 mg (n=412)
Baseline			
Mean (SE)	11.51 (0.157)	11.80 (0.168)	11.66 (0.167)
Median	10.67	11.00	11.00
Range	3.7 to 40.3	5.7 to 33.3	7.3 to 35.3
Final Visit			
Mean (SE)	10.51 (0.164)	10.09 (0.175)	9.91 (0.166)
Median	10.00	9.33	9.67
Range	3.0 to 28.7	2.0 to 34.0	1.0 to 31.3
Change from Baseline			
Mean (SE)	-1.00 (0.140)	-1.71 (0.145)	-1.75 (0.159)
Median	-1.00	-1.67	-1.67
Range	-15.3 to 14.0	-20.0 to 9.0	-20.7 to 17.7
ANCOVA Model †			
Adjusted mean change from baseline (SE)	-1.05 (0.132)	-1.66 (0.133)	-1.75 (0.135)
95% two-sided CI	(-1.31, -0.79)	(-1.92, -1.40)	(-2.01, -1.48)
Mean difference vs placebo (SE)		-0.61 (0.188)	-0.70 (0.189)
95% two-sided CI		(-0.98, -0.24)	(-1.07, -0.33)
P-value ‡		0.001#	< 0.001#

All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]).

† The analysis of covariance (ANCOVA) model included treatment group, sex and geographical region as fixed factors and baseline as a covariate.

‡ P-values were from pairwise comparison vs placebo within the ANCOVA model, a parametric analysis.

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

Key Secondary Endpoints

For the key secondary efficacy endpoints, the mirabegron 50 and 100 mg groups showed statistically significantly greater increases from baseline to final visit compared with placebo in mean volume voided per micturition, statistically significantly greater reductions from baseline to week 4 (the first measured time point) compared with placebo in mean number of incontinence episodes per 24 hours and the mean number of micturition per 24 hours.

Table 4 Overview of Key Secondary Efficacy Results, FAS and FAS-I

Change from Baseline to Final Visit in Mean Volume Voided per Micturition (FAS)		
	Mirabegron 50 mg	**Mirabegron 100 mg**
n	424	412
Mean difference from placebo (SE)	11.1 (3.43)	11.0 (3.45)
95% CI	(4.4, 17.9)	(4.2, 17.7)
P-values	0.001#	0.002#
Change from Baseline to Week 4 in Mean Number of Incontinence Episodes per 24 Hours (FAS-I)		
	Mirabegron 50 mg	**Mirabegron 100 mg**
n	309	293
Mean difference from placebo (SE)	-0.48 (0.166)	-0.46 (0.168)
95% CI	(-0.80, -0.15)	(-0.79, -0.13)
P-values	0.003#	<0.001#
Change from Baseline to Week 4 in Mean Number of Micturitions per 24 Hours (FAS)		
	Mirabegron 50 mg	**Mirabegron 100 mg**
n	422	409
Mean difference from placebo (SE)	-0.42 (0.182)	-0.60 (0.183)
95% CI	(-0.77, -0.06)	(-0.96, -0.24)
P-values	0.022#	0.001#

All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement and at least 1 incontinence episode in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (FAS Incontinence [FAS-I]).

* Nominal P-values (incontinence episodes) are from pairwise comparisons vs placebo within the stratified rank analysis of covariance (ANCOVA). Nominal P-values (volume voided and micturitions) are from the ANCOVA model.

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

Additional secondary endpoints

The mirabegron 50 and 100 mg treatment groups demonstrated statistically significant improvements from baseline to final visit compared with placebo in mean level of urgency, mean number of urgency incontinence episodes and mean number of episodes of urgency grade 3 or 4. For the subjective improvement assessments, mirabegron 50 and 100 mg demonstrated statistically significant improvement from baseline to final visit compared with placebo in TS-VAS, PPBC, mean number of pads used per 24 hours, the Symptom Bother Score and HRQL Total Score.

Ancillary analyses

- Repeated Measurement Analysis of Mean Number of Incontinence Episodes per 24 Hours, FAS-I

In the repeated measurement analysis of the mean number of incontinence episodes per 24 hours, the adjusted mean difference versus placebo and 95% CIs for both mirabegron 50 mg and 100 mg groups at week 12 were similar to those at the Final Visit in the primary analysis. Both mirabegron groups demonstrated statistically significantly superior mean reduction of incontinence episodes compared to the placebo group as early as week 4 and their effectiveness was maintained throughout the treatment period (weeks 8 and 12).

- Repeated Measurement Analysis of Mean Number of Micturition per 24 Hours, FAS

In the repeated measurement analysis of the mean number of micturition per 24 hours, the adjusted mean difference versus placebo and 95% CIs for both mirabegron 50 mg and 100 mg groups at week

12 were Both mirabegron groups demonstrated statistically significantly superior mean reduction of micturition compared to the placebo group as early as week 4 and their effectiveness was maintained throughout the treatment period (weeks 8 and 12). The P-values at week 12 from the repeated measurement analysis were P = 0.001 for the mirabegron 50 mg group and P < 0.001 for the mirabegron 100 mg group.

- Sensitivity Analysis of Mean Number of Incontinence Episodes per 24 Hour, PPS-I

In the PPS-I, the adjusted mean difference versus placebo in the number of incontinence episodes per 24 hours from baseline to the Final Visit was -0.33 in the mirabegron 50 mg group and -0.53 in the mirabegron 100 mg group. Each mirabegron group demonstrated a statistically significant difference in the reduction from baseline to Final Visit compared to placebo in the mean number of incontinence episodes per 24 hours.

- Sensitivity Analysis of Mean Number of Micturition per 24 Hours, PPS

One of the inclusion criteria was a mean of ≥ 8 micturition per 24 hours at baseline. The sensitivity analyses in the PPS excluded patients who did not meet this criterion at baseline. In this sensitivity analysis, the adjusted mean difference versus placebo in the number of micturition per 24 hours was -0.74 and -0.82 for the mirabegron 50 mg and 100 mg groups, respectively. Each mirabegron group demonstrated a statistically significant difference in the reduction from baseline to Final Visit compared to placebo in the mean number of micturition per 24 hours.

Responder Analysis

Reduction in Incontinence Episodes

At the Final Visit, the percentage of responders was greater in the mirabegron 50 mg (66.7%) and 100 mg (73.3%) groups than in placebo (59.4%). The difference versus placebo was 7.3% for the mirabegron 50 mg group and 13.9% for the mirabegron 100 mg group. Statistically significant differences compared to placebo were demonstrated for the mirabegron 100 mg group.

Zero Incontinence Episodes

At the Final Visit, the percentage of zero incontinence responders was greater in the mirabegron 50 mg (40.7%) and 100 mg (49.0%) groups than in placebo (33.8%). The difference versus placebo was 6.9% for the mirabegron 50 mg group and 15.1% for the mirabegron 100 mg group. Statistical significance was achieved for the mirabegron 100 mg group

Study 178-CL-074

A Phase III, Randomized, Double-Blind, Parallel Group, Placebo Controlled, Multicenter Study to Assess the Efficacy and Safety of the Beta-3 Agonist mirabegron (25 mg q.d and 50 mg qd) in Subjects with Symptoms of Overactive Bladder.

Methods

Study Participants

As in study 178-CL-046

Treatments

Mirabegron tablets: 25 mg and 50 mg. Lot numbers: 25 mg tablet F0800460 (North America), F0800460 (Europe) and 50 mg tablet–K0700248 (North America), L0700018 (Europe) and two placebo tablets to match mirabegron 25 mg or 50 mg. No active control is included in this study.

Objectives

- The primary objective of the study was to assess the efficacy of mirabegron (25 mg q.d and 50 mg q.d) against placebo in the treatment of patients with symptoms of overactive bladder (OAB).
- The secondary objective was to assess the safety and tolerability of mirabegron (25 mg q.d and 50 mg q.d) against placebo in the treatment of patients with symptoms of OAB.

Outcomes/endpoints

The co-primary efficacy variables included:

- 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 micturition per 24 hours based on a 3-day micturition diary

The key secondary efficacy variables (all 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 micturition 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 and change from baseline to end of treatment (final visit) in mean number of urgency episodes (grades 3 or 4) per 24 hours

Safety variables included:

- Treatment-emergent adverse events (TEAEs); events adjudicated by the independent cardiovascular adjudication committee; TEAEs of interest (i.e., hypertension, corrected QT interval (QTc) prolongation, cardiac arrhythmias, urinary retention/acute urinary retention, hypersensitivity type events, syncope type events, seizure type events, hepatic type events and renal and urinary events); Clinical laboratory evaluations (i.e., haematology, biochemistry, urinalysis and thyroid analytes); Vital signs (sitting SBP, sitting DBP and pulse rate); ECGs; Post-void residual volume (PVR) and physical examination

Sample size

The sample size was determined as in study 178-CL-046

Randomisation

After screening (day -21 to day -14), patients were enrolled in a 2-week, single-blind, placebo run-in period that ended at baseline (week 0). At baseline, patients meeting inclusion criteria and not meeting exclusion criteria were randomly assigned in a 1:1:1 ratio to receive mirabegron 25 mg, mirabegron 50 mg or a matching placebo qd for a 12-week, double-blind, placebo-controlled treatment period that consisted of visits at weeks 4, 8 and 12 and a 2 week follow-up telephone visit at the end of treatment.

Blinding (masking)

During the placebo run-in period, patients were blinded to the identity of study drug. During the double-blind treatment and follow-up periods, the investigator, study site personnel, patients, sponsor and the sponsor's representatives were blinded to the identity of the randomized drug assignment.

Statistical methods

The statistical methods used were essentially the same as used in Study 178-CL-046. However there were three additional key secondary efficacy endpoints: mean level of urgency, mean number of urgency incontinence episodes per 24 hours, and mean number of urgency episodes [grade 3 or 4] per 24 hours. These were also included in Studies 178-CL-046 and 178-CL-047 but were considered additional secondary endpoints and were not included in the hierarchical testing procedure for multiple endpoints.

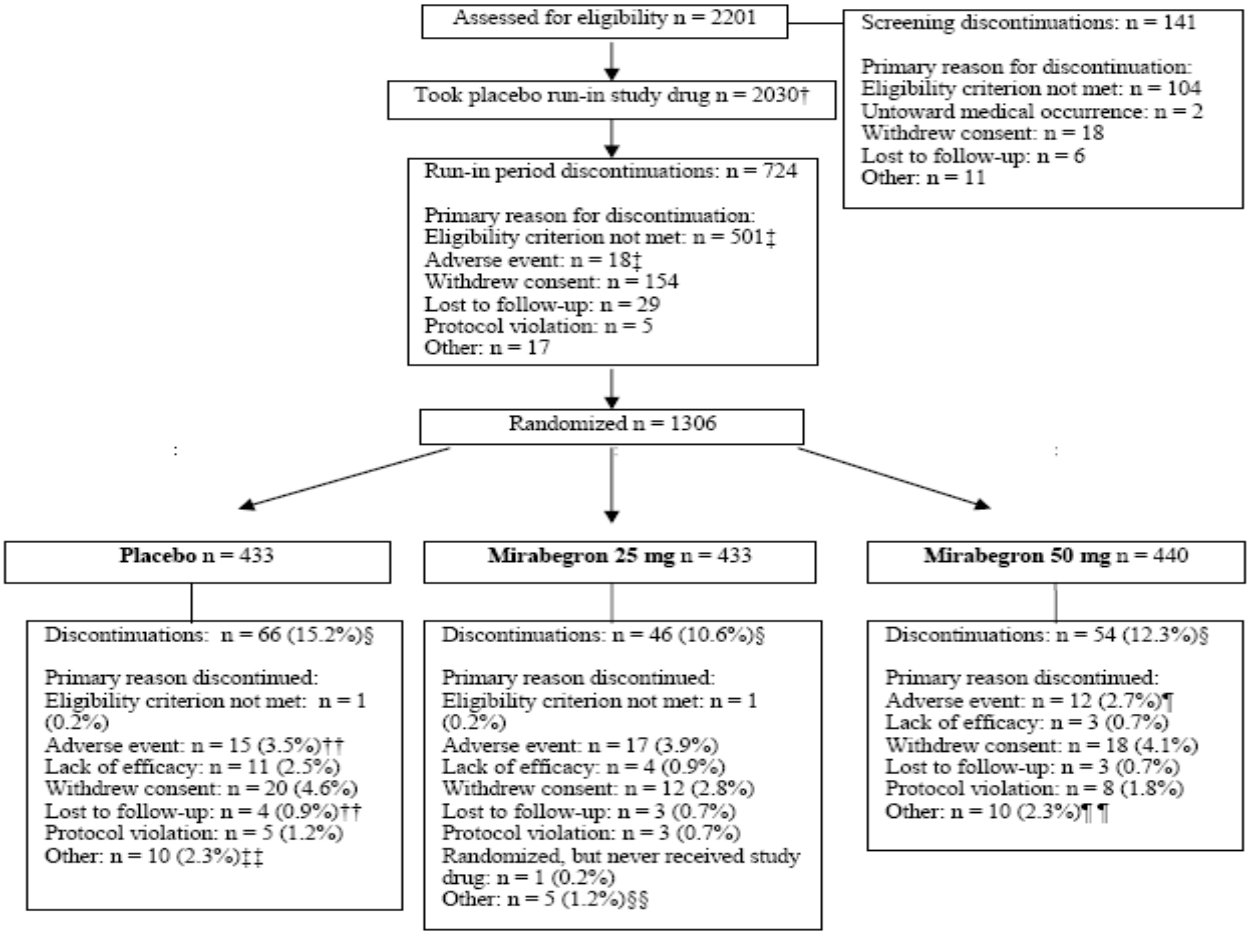
Urgency endpoints were based upon the 5-point Patient Perception of Intensity of Urgency Scale (PPIUS).

Results

Participant flow

A total of 2201 patients were screened, 2060 patients entered the placebo run-in period, 2030 patients took placebo run-in study drug, 1306 patients were randomized into the study, and 1305 patients received study drug.

Figure 1 Patient Disposition



All patients.

AE: adverse event; ECG: electrocardiogram; TEAE: treatment-emergent adverse event; UTI: urinary tract infection.

† Thirty patients returned full medication kits at baseline visit (visit 2) indicating that they did not take any study medication and thus were considered run-in failures.

‡ One patient in the run-in period (Patient No. 2197-70368) experienced a AE of urinary tract infection that led to permanent discontinuation of study drug [Appendix 13.2.7.6]. This patient is included in Figure 1 as discontinued due to eligibility criterion not met.

§ Discontinuations are those reported for patients in the Randomized Analysis Set.

¶ One patient in the mirabegron 50 mg group (Patient No. 3028-70955) reported an AE prior to start of double-blind study drug that led to permanent discontinuation of study drug; therefore, this patient is not included in the summary of patients who discontinued due to TEAEs.

†† One patient in the placebo group (Patient No. 2037-71461) experienced a TEAE of chest pain that led to permanent discontinuation of study drug. This patient is included as discontinued due to lost to follow-up in Figure 1.

‡‡ Other reasons for discontinuation in the placebo group were medications that were considered exclusionary by the medical monitor, early termination due to medical history, possibility of patient missing safety assessments at visits 5 and 6, and initial ECG conducted on wrong machine which was initially read as abnormal (and was later reread and assessed as normal after the patient was discontinued).

§§ Other reasons for discontinuation in the mirabegron 25 mg group were medications that were considered exclusionary, either by the protocol or by the medical monitor and concomitant leukopenia and thrombocytopenia.

¶¶ Other reasons for discontinuation in the mirabegron 50 mg group were medications that were considered exclusionary either by the protocol or the medical monitor, cannabis use and multiple prior UTIs.

Source: Tables 12.1.1.1, 12.1.1.3.1, 12.1.1.3.2, 12.1.1.3.3 and Appendix 13.2.1.2

Recruitment

First Subject Enrolled – Last Subject Last Visit: 28 April 2009 - 27 April 2010

Conduct of the study

19 patients (7 patients, 4 patients and 8 patients in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively) were discontinued due to taking medication that was considered exclusionary by the medical monitor. This circumstance occurred due to a more comprehensive application of the exclusion criterion with respect to concomitant medications by an interim medical monitor in the US during the study. The criterion was applied too broadly and not as intended per the protocol. Consequently, a number of medications (including CYP2D6 substrates) were disallowed that should not have been disallowed, which led to discontinuation of these patients from the study. The decision was reversed for future patients; however, the patients that were withdrawn from the study for this reason were not allowed to re-enrol. Additionally, 5 randomized patients were discontinued from the study due to protocol violations related to restricted or prohibited medications.

Nine patients were identified as having either been enrolled twice in 178-CL-074 (1 patient) or enrolled in other mirabegron studies in addition to 178-CL-074 (8 patients). Enrolment in previous mirabegron studies was an exclusion criterion in the protocol. These subjects were excluded from the PPS and PPS-I.

- Three of the 9 patients were screening or run-in failures in 178-CL-074 and were not randomized into the study.

- Two of the 9 patients received mirabegron in 178-CL-074 and had not received double-blind study medication during the previous enrolment (1 patient was previously a run-in failure at a different site in 178-CL-074 and the other patient was randomized in 178-CL-047 but never received study medication).

- Two patients received study medication in other mirabegron studies but had no overlap in double-blind treatment during 178-CL-074.

- One patient received study medication in 2 additional mirabegron studies (178-CL- 047 and 178-CL-049) and had an approximately 3-month overlap in double-blind treatment during 178-CL-074.

- One patient received mirabegron in 178-CL-074 and received placebo treatment in study 178-CL-008. The patient completed study 178-CL-008.

Reasons for exclusion of patients from the PPS and PPS-I comprised major protocol violations that affected the co-primary efficacy variables and the key secondary efficacy variable of mean volume voided per micturition. These included eligibility criteria that were not met, administration of incorrect study drug, poor study drug compliance (defined as < 70% during the double-blind treatment period), inadequate duration of treatment, unblinding of study drug, use of prohibited or restricted concomitant medication and participation in a previous mirabegron study. For the placebo run-in period, inadequate duration of treatment was defined as placebo treatment < 9 days until the last diary day before randomization. For the double-blind treatment period, inadequate duration of treatment was defined as last diary day of the final visit 3-day micturition diary < 53 days. Approximately 9% of patients in the FAS and 10% of patients in the FAS-I were excluded from the PPS and PPS-I, respectively.

Baseline data

Generally, demographic and baseline characteristics were similar across treatment groups in the FAS and FAS-I. Overall, approximately 69% and 80% of patients were female in the FAS and FAS-I, respectively. The higher proportion of female patients was the most apparent difference in demographics and baseline characteristics observed between the FAS and FAS-I populations. In the FAS, mean age was 59.1 years and 37.2% of patients were ≥ 65 years of age. The overall mean duration of OAB symptoms was approximately 94 months in the FAS and 100 months in the FAS-I. More than half of the patients had received previous OAB antimuscarinic therapy (approximately 51% and 58% in the FAS and FAS-I, respectively). Approximately 67% of patients in the FAS and 66% of patients in the FAS-I analysis sets who had received previous OAB antimuscarinic therapy cited insufficient effect as a reason for discontinuation, while approximately 26% of patients in the FAS and 28% of patients in the FAS-I cited poor tolerability.

Table 1 Summary of Patient Demographics and Baseline Characteristics, SAF

Parameter	Placebo (n = 433)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 440)	Total (n = 1305)
Sex (n, %)				
Male	132 (30.5%)	139 (32.2%)	137 (31.1%)	408 (31.3%)
Female	301 (69.5%)	293 (67.8%)	303 (68.9%)	897 (68.7%)
Age (years)	58.2	58.5	60.3	59.0
Mean (SD)	(13.73)	(12.85)	(12.22)	(12.97)
Age group (years) (n, %)				
< 65	273 (63.0%)	278 (64.4%)	272 (61.8%)	823 (63.1%)
≥ 65	160 (37.0%)	154 (35.6%)	168 (38.2%)	482 (36.9%)
< 75	388 (89.6%)	400 (92.6%)	392 (89.1%)	1180 (90.4%)
≥ 75	45 (10.4%)	32 (7.4%)	48 (10.9%)	125 (9.6%)
Race (n, %)				
White	389 (89.8%)	394 (91.2%)	400 (90.9%)	1183 (90.7%)
Black or African American	35 (8.1%)	32 (7.4%)	33 (7.5%)	100 (7.7%)
Asian	7 (1.6%)	5 (1.2%)	5 (1.1%)	17 (1.3%)
Other	2 (0.5%)†	1 (0.2%)‡	2 (0.5%)§	5 (0.4%)
Ethnicity (n, %)				
Hispanic/Latino	23 (5.3%)	24 (5.6%)	21 (4.8%)	68 (5.2%)
Non-Hispanic/Non-Latino	410 (94.7%)	408 (94.4%)	419 (95.2%)	1237 (94.8%)
BMI (kg/m^2)				
n	433	432	440	1305
Mean (SD)	29.2 (6.29)	29.8 (6.50)	29.5 (6.54)	29.5 (6.45)
Geographical region (n, %)				
Eastern Europe	75 (17.3%)	76 (17.6%)	75 (17.0%)	226 (17.3%)
Western Europe	126 (29.1%)	121 (28.0%)	120 (27.3%)	367 (28.1%)
Northeastern US	42 (9.7%)	40 (9.3%)	44 (10.0%)	126 (9.7%)
Midwestern US	23 (5.3%)	25 (5.8%)	23 (5.2%)	71 (5.4%)
Southern US	70 (16.2%)	74 (17.1%)	76 (17.3%)	220 (16.9%)
Western US	66 (15.2%)	71 (16.4%)	70 (15.9%)	207 (15.9%)
Canada	31 (7.2%)	25 (5.8%)	32 (7.3%)	88 (6.7%)

All randomized patients who took at least 1 dose of double-blind study drug (Safety Analysis Set [SAF]). The denominators for the percentage calculations of categorical variables were the number of patients with nonmissing values. BMI = weight (kg)/height (m^2).

BMI: body mass index; US: United States.

† Other races in the placebo group included White and Black and Caucasian/African American/Native American (n=1 each).

‡ Other races in the mirabegron 25 mg group included Aboriginal (n=1).

§ Other races in the mirabegron 50 mg group included American Indian/Alaska Native and Caucasian/Black American (n=1 each).

Table 9 Overactive Bladder History, FAS and FAS-I

Parameter	FAS			FAS-I		
		Mirabegron			Mirabegron	
	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

All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement and at least 1 incontinence episode in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (FAS Incontinence [FAS-I]). The percentage for each category was calculated using the number of patients with nonmissing values for the denominator.

OAB: overactive bladder.

† Types of OAB were defined as follows: urgency incontinence = urge incontinence only; mixed = mixed stress/urge incontinence with urge as a predominant factor; frequency = frequency/urgency without incontinence.

‡ Patients could choose > 1 reason for discontinuation of previous OAB drug.

Baseline characteristics are reasonable similar across the treatment groups. Majority of the subjects included were female and less than 65 years of age. The proportion of males included in this study is less than included in studies 178-CL-046 and 178-CL-047.

Numbers analysed

Table 3 Summary of Analysis Sets

Analysis Set, n (%)	Placebo	Mirabegron		Total
		25 mg	50 mg	
Run in period analysis set				2030
Randomized analysis set	433 (100.0%)	433 (100.0%)	440 (100.0%)	1306 (100.0%)
Full analysis set	415 (95.8%)	410 (94.7%)	426 (96.8%)	1251 (95.8%)
Full analysis set incontinence	262 (60.5%)	254 (58.7%)	257 (58.4%)	773 (59.2%)
Intent-to-treat analysis set	433 (100.0%)	432 (99.8%)	440 (100.0%)	1305 (99.9%)
Intent-to-treat analysis set incontinence	276 (63.7%)	271 (62.6%)	268 (60.9%)	815 (62.4%)
Per protocol analysis set	367 (84.8%)	385 (88.9%)	388 (88.2%)	1140 (87.3%)
Per protocol analysis set incontinence	227 (52.4%)	236 (54.5%)	232 (52.7%)	695 (53.2%)
Safety analysis set	433 (100.0%)	432 (99.8%)	440 (100.0%)	1305 (99.9%)

The percentage of patients in each analysis set is based on the Randomized Analysis Set.

The percentage of patients randomised who had reported at least one episode of incontinence in the baseline diary is approximately 60%, fairly similar in each of the treatment groups.

Outcomes and estimation

Primary endpoints

For the co-primary efficacy endpoints, the mirabegron 25 and 50 mg groups demonstrated statistically significantly greater reductions from baseline to final visit compared with placebo in mean number of incontinence episodes per 24 hours and the mean number of micturition per 24 hours.

Table 17 Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 Hours, FAS-I

	Placebo (n = 262)	Mirabegron 25 mg (n = 254)	Mirabegron 50 mg (n = 257)
Baseline			
Mean (SE)	2.43 (0.145)	2.65 (0.160)	2.51 (0.146)
Median	1.67	2.00	1.67
Range	0.3 - 13.7	0.3 - 21.0	0.3 - 13.5
Final Visit			
Mean (SE)	1.54 (0.151)	1.21 (0.131)	1.13 (0.128)
Median	0.67	0.33	0.33
Range	0 - 13.0	0 - 11.3	0 - 13.7
Change from Baseline			
Mean (SE)	-0.89 (0.159)	-1.44 (0.150)	-1.37 (0.143)
Median	-0.67	-1.00	-1.00
Range	-11.0 - 12.0	-18.0 - 8.7	-12.2 - 13.3
ANCOVA Model†			
Adjusted mean change from baseline (SE)	-0.96 (0.122)	-1.36 (0.124)	-1.38 (0.123)
95% 2-sided CI	(-1.19, -0.72)	(-1.60, -1.11)	(-1.62, -1.14)
Adjusted mean difference vs placebo (SE)		-0.40 (0.174)	-0.42 (0.173)
95% 2-sided CI		(-0.74, -0.06)	(-0.76, -0.08)
P-value‡		0.005#	0.001#
Statistically Significantly Superior Compared to Placebo at the 0.05 Level with Multiplicity Adjustment (Yes/No)?§		Yes	Yes

All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement and at least 1 incontinence episode in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (FAS Incontinence [FAS-I]).

ANCOVA: analysis of covariance.

† The ANCOVA model included treatment group, sex and geographical region as fixed factors and baseline as a covariate.

‡ P-values were from pairwise comparison vs placebo within the stratified rank ANCOVA, a nonparametric analysis.

§ Statistical significance was determined using a stepwise parallel gatekeeping procedure.

Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment (Hochberg Procedure).

Table 18 Change from Baseline to Final Visit in Mean Number of Micturitions per 24 Hours, FAS

	Placebo (n = 415)	Mirabegron 25 mg (n = 410)	Mirabegron 50 mg (n = 426)
Baseline			
Mean (SE)	11.48 (0.142)	11.68 (0.153)	11.66 (0.156)
Median	10.67	11.00	11.00
Range	7.3 - 26.3	6.3 - 23.3	7.7 - 37.3
Final Visit			
Mean (SE)	10.33 (0.166)	10.02 (0.153)	10.04 (0.166)
Median	9.67	9.67	9.33
Range	4.0 - 36.0	4.0 - 25.7	3.7 - 39.7
Change from Baseline			
Mean (SE)	-1.15 (0.139)	-1.66 (0.129)	-1.62 (0.130)
Median	-1.33	-1.67	-1.67
Range	-13.3 - 19.0	-11.0 - 5.3	-17.7 - 7.7
ANCOVA Model†			
Adjusted mean change from baseline (SE)	-1.18 (0.124)	-1.65 (0.125)	-1.60 (0.122)
95% 2-sided CI	(-1.42, -0.94)	(-1.90, -1.41)	(-1.84, -1.36)
Adjusted mean difference vs placebo (SE)		-0.47 (0.176)	-0.42 (0.174)
95% 2-sided CI		(-0.82, -0.13)	(-0.76, -0.08)
P-value‡		0.007#	0.015#
Statistically Significantly Superior Compared to Placebo at the 0.05 Level with Multiplicity Adjustment (Yes/No)?		Yes	Yes

All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]).

ANCOVA: analysis of covariance.

† The ANCOVA model included treatment group, sex and geographical region as fixed factors and baseline as a covariate.

‡ P-values were from pairwise comparison vs placebo within the ANCOVA model, a parametric analysis.

Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment (Hochberg Procedure).

Key Secondary endpoints

For the key secondary efficacy endpoints, the mirabegron 50 mg group in the FAS showed statistically significantly greater increases from baseline to final visit compared with placebo in mean volume voided per micturition; mirabegron 25 mg was not statistically significant compared with placebo. Since the mirabegron 25 mg group did not meet significance for mean volume voided with multiplicity adjustment, subsequent key secondary endpoints for the mirabegron 25 mg group were excluded from further hypothesis testing as part of the gate-keeping procedure. Subsequent key secondary endpoints for the mirabegron 50 mg group were evaluated at the 0.025 significance level.

The mirabegron 50 mg group had a statistically significantly greater reduction from baseline to week 4 (the first measured time point) compared with placebo in mean number of incontinence episodes per 24 hours. The mirabegron 50 mg group did not have a statistically significantly greater reduction from baseline to week 4 compared with placebo in mean number of micturition per 24 hours. For all other key secondary efficacy endpoints, statistical significance was not achieved for either mirabegron treatment group due to the gate-keeping procedure which precluded further statistical testing on subsequent endpoints in the hierarchy once a dose group failed to reach statistical significance for an efficacy variable.

Table 4 Overview of Key Secondary Efficacy Results, FAS and FAS-I

Change from Baseline to Final Visit in Mean Volume Voided per Micturition (FAS)		
	Mirabegron 25 mg (n = 410)	**Mirabegron 50 mg (n = 426)**
n	410	426
Adjusted mean difference from placebo (SE)	4.6 (3.16)	12.4 (3.13)
95% 2-sided CI	(-1.6, 10.8)	(6.3, 18.6)
P-values†	0.15	<0.001#
Change from Baseline to Week 4 in Mean Number of Incontinence Episodes per 24 Hours (FAS-I)		
	Mirabegron 25 mg (n = 254)	**Mirabegron 50 mg (n = 257)**
n	254	255
Adjusted mean difference from placebo (SE)	-0.34 (0.172)	-0.51 (0.171)
95% 2-sided CI	(-0.68, -0.01)	(-0.85, -0.17)
P-values‡	0.039	<0.001#
Change from Baseline to Week 4 in Mean Number of Micturitions per 24 Hours (FAS)		
	Mirabegron 25 mg (n = 410)	**Mirabegron 50 mg (n = 426)**
n	410	424
Adjusted mean difference from placebo (SE)	-0.18 (0.176)	-0.37 (0.174)
95% 2-sided CI	(-0.53, 0.16)	(-0.71, -0.03)
P-values†	0.30	0.035
Change from Baseline to Final Visit in Mean Level of Urgency (FAS)		
	Mirabegron 25 mg (n = 410)	**Mirabegron 50 mg (n = 426)**
n	410	426
Adjusted mean difference from placebo (SE)	-0.07 (0.040)	-0.14 (0.040)
95% 2-sided CI	(-0.15, 0.01)	(-0.22, -0.06)
P-values†	0.083	<0.001
Change from Baseline to Final Visit in Mean Number of Urgency Incontinence Episodes per 24 Hours (FAS-I)		
	Mirabegron 25 mg (n = 254)	**Mirabegron 50 mg (n = 257)**
n	247	251
Adjusted mean difference from placebo (SE)	-0.36 (0.157)	-0.39 (0.156)
95% 2-sided CI	(-0.67, -0.05)	(-0.69, -0.08)
P-values‡	0.004	0.002
Change from Baseline to Final Visit in Mean Number of Episodes with Urgency (Grade 3 or Grade 4) per 24 Hours (FAS)		
	Mirabegron 25 mg (n = 410)	**Mirabegron 50 mg (n = 426)**
n	410	426
Adjusted mean difference from placebo (SE)	-0.33 (0.219)	-0.59 (0.217)
95% 2-sided CI	(-0.76, 0.10)	(-1.01, -0.16)
P-values†	0.13	0.007

All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement and at least 1 incontinence episode in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (FAS Incontinence [FAS-I]).

ANCOVA: analysis of covariance.
† P-values were from pairwise comparisons vs placebo within the ANCOVA model.
‡ P-values were from pairwise comparison vs placebo within the stratified rank ANCOVA.
# Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment(Hochberg Procedure).

Additional secondary endpoints

For the subjective improvement assessments, mirabegron 25 mg demonstrated statistically significant improvement in change from baseline to final visit in TS-VAS. Mirabegron 25 mg did not demonstrate statistically significant improvement in change from baseline to final visit in Symptom Bother Score, HRQL Total Score, PPBC, or mean number of pads used per 24 hours. Mirabegron 50 mg demonstrated statistically significant improvement in change from baseline to final visit in TS-VAS and in Symptom Bother Score, but not in HRQL Total Score, PPBC, or mean number of pads used per 24 hours.

Ancillary analyses

- Repeated Measurement Analysis of Mean Number of Incontinence Episodes per 24 Hours, FAS-I

In the repeated measurement analysis of the mean number of incontinence episodes per 24 hours, the adjusted mean change from baseline to week 12 for the placebo group was greater than that at the final visit in the primary analysis. Therefore, although the adjusted mean change (and 95% CI) from baseline to week 12 for the mirabegron groups in the repeated measurement analysis were similar to those at final visit in the primary analysis, the adjusted mean differences versus placebo for both mirabegron groups (mirabegron 25 mg: -0.32 [0.169]; mirabegron 50 mg: -0.37 [0.169]) were slightly smaller compared to the primary analysis (mirabegron 25 mg: -0.40 [0.174]; mirabegron 50 mg: -0.42 [0.173]). In the repeated measurement analysis, the reduction in the mean number of incontinence episodes was statistically significantly greater in mirabegron 25 mg group compared to placebo at week 4 (P = 0.048) and week 8 (P = 0.014) and approached statistical significance at week 12 (P = 0.058). The mirabegron 50 mg group demonstrated statistically significant reduction in the mean number of incontinence episodes compared to placebo at weeks 4, 8 and 12 (P-values of 0.003, 0.016 and 0.030, respectively).

- Repeated Measurement Analysis of Mean Number of Micturition per 24 Hours, FAS

In the repeated measurement analysis of the mean number of micturition per 24 hours, the adjusted mean change from baseline to week 12 for the placebo group was greater than that at the final visit in the primary analysis. Therefore, although the adjusted mean change (and 95% CI) from baseline to week 12 for the mirabegron groups in the repeated measurement analysis were similar to those at final visit in the primary analysis, the adjusted mean differences versus placebo for both mirabegron groups (mirabegron 25 mg: -0.35 [0.171]; mirabegron 50 mg: -0.32 [0.171]) were slightly smaller compared to the primary analysis mirabegron 25 mg: -0.47 [0.176]; mirabegron 50 mg: -0.42 [0.174]). In the repeated measurement analysis, the mirabegron 25 mg group demonstrated statistically significant reductions in the mean number of micturition compared to the placebo group at weeks 8 and 12 (P-values of 0.004 and 0.042, respectively). The reduction in the mean number of micturition was statistically significantly greater in the mirabegron 50 mg group compared to placebo at week 4 (P = 0.032) and week 8 (P = 0.006) and approached statistical significance at week 12 (P = 0.063).

- Sensitivity Analysis of Mean Number of Incontinence Episodes per 24 Hour, PPS-I

In the PPS-I, the adjusted mean difference versus placebo in the number of incontinence episodes per 24 hours from baseline to the final visit was -0.32 and -0.39 in the mirabegron 25 mg and 50 mg groups, respectively. Each mirabegron group demonstrated a statistically significant difference in the reduction from baseline to final visit compared to placebo in the mean number of incontinence episodes per 24 hours.

- Sensitivity Analysis of Mean Number of Micturition per 24 Hours, PPS

In this sensitivity analysis, the adjusted mean difference versus placebo in the number of micturition per 24 hours was -0.34 and -0.31 for the mirabegron 25 mg and 50 mg groups, respectively. Compared to placebo, the reduction from baseline to final visit in the mean number of micturition per 24 hours for both mirabegron groups approached statistical significance [Table 19].

- Other Sensitivity Analyses

The results of all other sensitivity analyses were consistent with those presented for the primary analyses of the co-primary efficacy variables.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections). Of note, only results on co-primary endpoints and the key secondary endpoint of mean volume voided are presented. Relevant results of secondary parameters are included in other sections of the report.

Table 1. Summary of Efficacy for trial 178-CL-046

Title: A Randomized, Double-Blind, Parallel Group, Placebo and Active Controlled, Multicenter Study to Assess the Efficacy and Safety of Mirabegron in Subjects with Symptoms of Overactive Bladder			
Study identifier	178-CL-046		
Design	Randomized, Double-Blind, Parallel Group, Placebo and Active Controlled, Multicenter Study		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		First Subject Enrolled – Last Subject Last Visit: 28 April 2008 - 24 March 2009 2 weeks Not applicable
Hypothesis	superiority of each mirabegron dose group versus placebo or tolterodine versus placebo		
Treatments groups	Placebo		Placebo tablets, PO, qd, 12 weeks, Randomized N=497
	Mirabegron 50 mg		Mirabegron tablets 50 mg, PO, qd, 12 weeks, Randomized N=497
	Mirabegron 100 mg		Mirabegron tablets 100 mg, PO, qd, 12 weeks, Randomized N=498
	Tolterodine SR 4 mg		Tolterodine SR 4 mg capsules, PO, qd, 12 weeks, Randomized N=495
Endpoints and definitions	Coprimary endpoint	Incontinence episode frequency	Change from baseline to Final Visit (end of treatment) in mean number of incontinence episodes per 24 hours based on a 3-day micturition diary.
	Coprimary endpoint	Micturition frequency	Change from baseline to Final Visit (end of treatment) in mean number of micturitions per 24 hours based on a 3-day micturition diary.
	Key secondary endpoint	Volume voided per micturition	Change from baseline to Final Visit (end of treatment) in mean volume voided per micturition based on a 3-day micturition diary.
	Key secondary endpoint	Incontinence episode frequency	Change from baseline to Week 4 in mean number of incontinence episodes per 24 hours based on a 3-day micturition diary.
	Key secondary endpoint	Micturition frequency	Change from baseline to Week 4 in mean number of micturitions per 24 hours based on a 3-day micturition diary.
Database lock	23 October 2009		

Results and Analysis					
Analysis description	**Coprimary analysis - Incontinence episode frequency**				
Analysis population and time point description	The Full Analysis Set-Incontinence (FAS-I): all Full Analysis Set (FAS) patients who had at least 1 incontinence episode at baseline. Time point: Final Visit				
Descriptive statistics and estimate variability†	Treatment group	Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Tolterodine SR 4 mg
	Number of subjects, FAS-I	291	293	281	300
	Adjusted mean change from baseline	-1.17	-1.57	-1.46	-1.27
	Standard Error	0.113	0.113	0.115	0.112
	95% 2-sided CI	(-1.39, -0.95)	(-1.79, -1.35)	(-1.68, -1.23)	(-1.49, -1.05)
Effect estimate per comparison†	Adjusted mean difference from placebo		-0.41	-0.29	-0.10
	Standard Error		0.160	0.162	0.159
	95% 2-sided CI		(-0.72, -0.09)	(-0.61, 0.03)	(-0.42, 0.21)
	P value‡		0.003*	0.010*	0.11
Notes	Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from that of treatment groups. † Estimates are based on an ANCOVA model, which included treatment group, gender and geographical region as fixed factors and baseline as a covariate. ‡ Nominal P values are from pairwise comparison vs placebo within the stratified rank ANCOVA, a nonparametric analysis. * Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustment.				
Analysis description	**Coprimary analysis - Micturition frequency**				
Analysis population and time point description	Full Analysis Set (FAS): all randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement. Time point: Final Visit				
Descriptive statistics and estimate variability†	Treatment group	Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Tolterodine SR 4 mg
	Number of subjects, FAS	480	473	478	475
	Adjusted mean change from baseline	-1.34	-1.93	-1.77	-1.59
	Standard Error	0.110	0.111	0.110	0.111
	95% 2-sided CI	(-1.55, -1.12)	(-2.15, -1.72)	(-1.99, -1.56)	(-1.80, -1.37)

Effect estimate per comparison†	Treatment group	Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Tolterodine SR 4 mg
	Adjusted mean difference from placebo		-0.60	-0.44	-0.25
	Standard Error		0.156	0.156	(0.156)
	95% 2-sided CI		(-0.90, -0.29)	(-0.74, -0.13)	(-0.55, 0.06)
	P value‡		<0.001*	0.005*	0.11
Notes	Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from that of treatment groups. † Estimates are based on an ANCOVA model, which included treatment group, gender and geographical region as fixed factors and baseline as a covariate. ‡ Nominal P values are from pairwise comparisons vs placebo within the ANCOVA model, a parametric analysis. * Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustment.				
Analysis description	**Key secondary analysis - Volume voided per micturition**				
Analysis population and time point description	Full Analysis Set (FAS): see definition above. Time point: Final Visit				
Descriptive statistics and estimate variability†	Treatment group	Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Tolterodine SR 4 mg
	Number of subjects, FAS	480	472	478	475
	Adjusted mean change from baseline	12.3	24.2	25.6	25.0
	Standard Error	1.99	2.01	2.00	2.00
	95% 2-sided CI	(8.4, 16.3)	(20.3, 28.2)	(21.6, 29.5)	(21.1, 28.9)
Effect estimate per comparison†	Adjusted mean difference from placebo		11.9	13.2	12.6
	Standard Error		2.83	2.82	2.83
	95% 2-sided CI		(6.3, 17.4)	(7.7, 18.7)	(7.1, 18.2)
	P value‡		<0.001*	<0.001*	<0.001#
Notes	Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from that of treatment groups. † Estimates are based on an ANCOVA model, which included treatment group, gender and geographical region as fixed factors and baseline as a covariate. ‡ Nominal P values are from pairwise comparisons vs placebo within the ANCOVA model, a parametric 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.				

Table 2. Summary of Efficacy for trial 178-CL-047

Title: A Phase III, Randomized, Double-Blind, Parallel Group, Placebo Controlled, Multicenter Study to Assess the Efficacy and Safety of Mirabegron in Subjects with Symptoms of Overactive Bladder					
Study identifier	178-CL-047				
Design	Randomized, Double-Blind, Parallel Group, Placebo Controlled, Multicenter Study				
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		First Subject Enrolled – Last Subject Last Visit: 28 March 2008 - 22 April 2009 2 weeks Not applicable		
Hypothesis	For the coprimary endpoints, superiority of each mirabegron dose group versus placebo.				
Treatments groups	Placebo		Placebo tablets, PO, qd, 12 weeks, Randomized N=454		
	Mirabegron 50 mg		Mirabegron tablets 50 mg, PO, qd, 12 weeks, Randomized N=442		
	Mirabegron 100 mg		Mirabegron tablets 100 mg, PO, qd, 12 weeks, Randomized N=433		
Endpoints and definitions	Coprimary endpoint	Incontinence episode frequency	Change from baseline to Final Visit (end of treatment) in mean number of incontinence episodes per 24 hours based on a 3-day micturition diary.		
	Coprimary endpoint	Micturition frequency	Change from baseline to Final Visit (end of treatment) in mean number of micturitions per 24 hours based on a 3-day micturition diary.		
	Key secondary endpoint	Volume voided per micturition	Change from baseline to Final Visit (end of treatment) in mean volume voided per micturition based on a 3-day micturition diary.		
	Key secondary endpoint	Incontinence episode frequency	Change from baseline to Week 4 in mean number of incontinence episodes per 24 hours based on a 3-day micturition diary.		
	Key secondary endpoint	Micturition frequency	Change from baseline to Week 4 in mean number of micturitions per 24 hours based on a 3-day micturition diary.		
Database lock	28 September 2009				
Results and Analysis					
Analysis description	**Coprimary analysis - Incontinence episode frequency**				
Analysis population and time point description	The Full Analysis Set-Incontinence (FAS-I): all Full Analysis Set (FAS) patients (see definition below) who had at least 1 incontinence episode at baseline. Time point: Final Visit				
Descriptive statistics and estimate variability†	Treatment group		Placebo	Mirabegron 50 mg	Mirabegron 100 mg
	Number of subjects, FAS-I		325	312	296
	Adjusted mean change from baseline		-1.13	-1.47	-1.63
	Standard Error		0.112	0.114	0.117
	95% 2-sided CI		(-1.35, -0.91)	(-1.69, -1.25)	(-1.86, -1.40)

Effect estimate per comparison†	Treatment group	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
	Adjusted mean difference from placebo		-0.34	-0.50
	Standard Error		0.160	0.162
	95% 2-sided CI		(-0.66, -0.03)	(-0.82, -0.18)
	P value‡		0.026*	<0.001*
Notes	Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from that of treatment groups. † Estimates are based on an ANCOVA model, which included treatment group, gender and geographical region as fixed factors and baseline as a covariate. ‡ Nominal P values are from pairwise comparison vs placebo within the stratified rank ANCOVA, a nonparametric analysis. * Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustment.			
Analysis description	**Coprimary analysis - Micturition frequency**			
Analysis population and time point description	The Full Analysis Set (FAS): all randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement. Time point: Final Visit			
Descriptive statistics and estimate variability†	Treatment group	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
	Number of subjects, FAS	433	425	412
	Adjusted mean change from baseline	-1.05	-1.66	-1.75
	Standard Error	0.132	0.133	0.135
	95% 2-sided CI	(-1.31, -0.79)	(-1.92, -1.40)	(-2.01, -1.48)
Effect estimate per comparison†	Adjusted mean difference from placebo		-0.61	-0.70
	Standard Error		0.188	0.189
	95% 2-sided CI		(-0.98, -0.24)	(-1.07, -0.33)
	P value‡		0.001*	0.001*
Notes	Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from that of treatment groups. † Estimates are based on an ANCOVA model, which included treatment group, gender and geographical region as fixed factors and baseline as a covariate. ‡ Nominal P values are from pairwise comparisons vs placebo within the ANCOVA model, a parametric analysis. * Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustment.			
Analysis description	**Key secondary analysis - Volume voided per micturition**			
Analysis population and time point description	The Full Analysis Set (FAS): see definition above. Time point: Final Visit			

Descriptive statistics and estimate variability†	Treatment group	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
	Number of subjects, FAS	433	424	412
	Adjusted mean change from baseline	7.0	18.2	18.0
	Standard Error	2.41	2.44	2.47
	95% 2-sided CI	(2.3, 11.7)	(13.4, 22.9)	(13.1, 22.8)
Effect estimate per comparison†	Adjusted mean difference from placebo		11.1	11.0
	Standard Error		3.43	3.45
	95% 2-sided CI		(4.4, 17.9)	(4.2, 17.7)
	P value‡		0.001*	0.002*
Notes	Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from that of treatment groups. † Estimates are based on an ANCOVA model, which included treatment group, gender and geographical region as fixed factors and baseline as a covariate. ‡ Nominal P values are from pairwise comparisons vs placebo within the ANCOVA model, a parametric analysis. * Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustment.			

Table 3. Summary of Efficacy for trial 178-CL-074

Title: A Phase III, Randomized, Double-Blind, Parallel Group, Placebo Controlled, Multicenter Study to Assess the Efficacy and Safety of the Beta-3 Agonist Mirabegron (25 mg qd and 50 mg qd) in Subjects with Symptoms of Overactive Bladder					
Study identifier	178-CL-074				
Design	A Phase III, Randomized, Double-Blind, Parallel Group, Placebo Controlled, Multicenter Study				
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		First Subject Enrolled – Last Subject Last Visit: 28 Apr 2009 - 27 Apr 2010 2 weeks Not applicable		
Hypothesis	For the coprimary endpoints, superiority of each mirabegron dose group versus placebo				
Treatments groups	Placebo		Placebo tablets, PO, qd, 12 weeks, Randomized N=433		
	Mirabegron 25 mg		Mirabegron tablets 25 mg, PO, qd, 12 weeks, Randomized N=433		
	Mirabegron 50 mg		Mirabegron tablets 50 mg, PO, qd, 12 weeks, Randomized N=440		
Endpoints and definitions	Coprimary endpoint	Incontinence episode frequency	Change from baseline to Final Visit (end of treatment) in mean number of incontinence episodes per 24 hours based on a 3-day micturition diary.		
	Coprimary endpoint	Micturition frequency	Change from baseline to Final Visit (end of treatment) in mean number of micturitions per 24 hours based on a 3-day micturition diary.		
	Key secondary endpoint	Volume voided per micturition	Change from baseline to Final Visit (end of treatment) in mean volume voided per micturition based on a 3-day micturition diary.		
Database lock	28 May 2010				
Results and Analysis **(results related to the secondary endpoints are mentioned when appropriate in the corresponding section of the overview)**					
Analysis description	**Coprimary analysis - Incontinence episode frequency**				
Descriptive statistics and estimate variability†	Treatment group		Placebo	Mirabegron 25 mg	Mirabegron 50 mg
	Number of subjects, FAS-I		262	254	257
	Adjusted mean change from baseline		-0.96	-1.36	-1.38
	Standard Error		0.122	0.124	0.123
	95% 2-sided CI		(-1.19, -0.72)	(-1.60, -1.11)	(-1.62, -1.14)

Effect estimate per comparison†	Treatment group	Placebo	Mirabegron 25 mg	Mirabegron 50 mg
	Adjusted mean difference from placebo		-0.40	-0.42
	Standard Error		0.174	0.173
	95% 2-sided CI		(-0.74, -0.06)	(-0.76, -0.08)
	P value‡		0.005*	0.001*
Notes	Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from that of treatment groups. † Estimates are based on an ANCOVA model, which included treatment group, gender and geographical region as fixed factors and baseline as a covariate. ‡ Nominal P values are from pairwise comparison vs placebo within the stratified rank ANCOVA, a nonparametric analysis. * Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustment.			
Analysis description	**Coprimary analysis - Micturition frequency**			
Analysis population and time point description	The following population set was used for the analyses: • The Full Analysis Set (FAS): all randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement. Time point: Final Visit			
Descriptive statistics and estimate variability†	Treatment group	Placebo	Mirabegron 25 mg	Mirabegron 50 mg
	Number of subjects, FAS	415	410	426
	Adjusted mean change from baseline	-1.18	-1.65	-1.60
	Standard Error	0.124	0.125	0.122
	95% 2-sided CI	(-1.42, -0.94)	(-1.90, -1.41)	(-1.84, -1.36)
Effect estimate per comparison†	Adjusted mean difference from placebo		-0.47	-0.42
	Standard Error		0.176	0.174
	95% 2-sided CI		(-0.82, -0.13)	(-0.76, -0.08)
	P value‡		0.007*	0.015*
Notes	Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from that of treatment groups. † Estimates are based on an ANCOVA model, which included treatment group, gender and geographical region as fixed factors and baseline as a covariate. ‡ Nominal P values are from pairwise comparisons vs placebo within the ANCOVA model, a parametric analysis. * Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustment.			
Analysis description	**Key secondary analysis - Volume voided per micturition**			
Analysis population and time point description	The following population set was used for the analyses: • The Full Analysis Set (FAS): see definition above. Time point: Final Visit			

Descriptive statistics and estimate variability†	Treatment group	Placebo	Mirabegron 25 mg	Mirabegron 50 mg
	Number of subjects, FAS	415	410	426
	Adjusted mean change from baseline	8.3	12.8	20.7
	Standard Error	2.23	2.24	2.20
	95% 2-sided CI	(3.9, 12.7)	(8.4, 17.2)	(16.4, 25.0)
Effect estimate per comparison†	Adjusted mean difference from placebo		4.6	12.4
	Standard Error		3.16	3.13
	95% 2-sided CI		(-1.6, 10.8)	(6.3, 18.6)
	P value‡		0.15§	<0.001*
Notes	Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from that of treatment groups. † Estimates are based on an ANCOVA model, which included treatment group, gender and geographical region as fixed factors and baseline as a covariate. ‡ Nominal P values are from pairwise comparisons vs placebo within the ANCOVA model, a parametric analysis. § Since the mirabegron 25 mg group did not meet statistical significance with multiplicity adjustment for mean volume voided per micturition (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. Mirabegron 50 mg was statistically significantly superior compared with placebo at the 0.025 level. * Statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustment.			

Analysis performed across trials (pooled analyses and meta-analysis)

Primary Studies 178-CL-046, 178-CL-047 and 178-CL-074 were pooled for analyses of all primary and secondary efficacy endpoints. Methods for multiplicity adjustment for the pooled analyses are based on those established in the SAPs for Studies 178-CL-046, 178-CL-047 and 178-CL-074.

A stepwise parallel gatekeeping procedure was performed to control the Type I error rate at the 0.05 significance level for the coprimary efficacy endpoints of 1) change from baseline to final visit in mean number of incontinence episodes per 24 hours and 2) change from baseline to final visit in mean number micturitions of per 24 hours; and the key secondary efficacy endpoints of 3) change from baseline to final visit in mean volume voided per micturition, 4) change from baseline to week 4 in mean number of incontinence episodes per 24 hours, 5) change from baseline to week 4 in mean number of micturitions per 24 hours, 6) change from baseline to final visit in mean level of urgency, 7) change from baseline to final visit in mean number of urgency incontinence episodes per 24 hours and 8) change from baseline to final visit in mean number of urgency episodes (grade 3 or 4) per 24 hours.

Statistical testing was performed in 8 stages, evaluating the primary and key secondary endpoints in the order indicated above. In each stage the endpoint was evaluated and the difference between a mirabegron dose group and placebo must have been statistically significant before that mirabegron dose group proceeded to the next stage.

	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#
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.

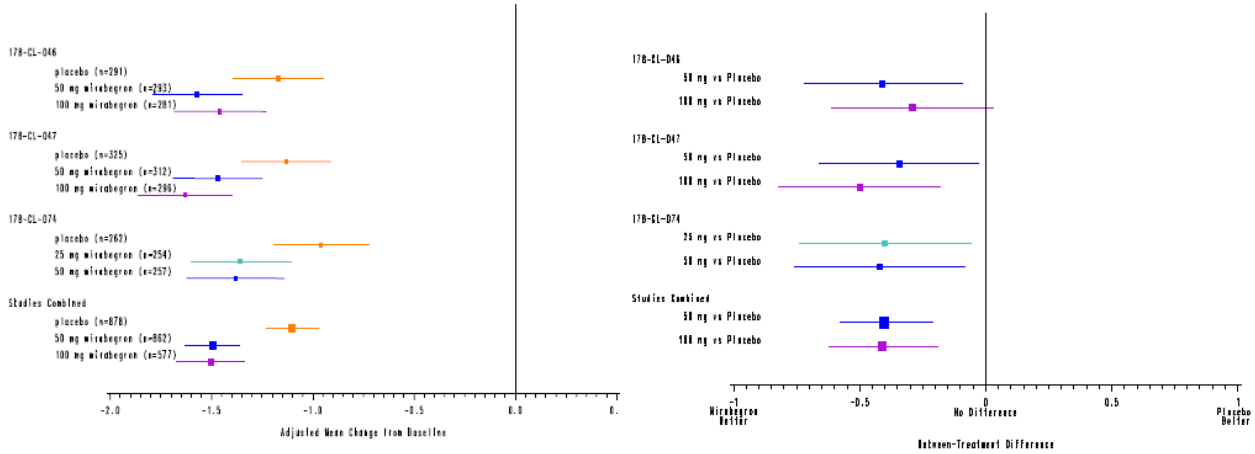
- **Incontinence**

All mirabegron treatment groups in the 12-week phase 3 primary studies demonstrated a statistically significant reduction in mean number of incontinence episodes per 24 hours at final visit compared with placebo with multiplicity adjustment. While no study required incontinence at baseline, inclusion in the FAS-I required at least one episode of incontinence in the 3-day baseline micturition diary (equating to a minimum of 0.33 episodes per 24 hours).

The mean number of incontinence episodes per 24 hours at baseline was comparable across all treatment groups in the pooled primary studies. The adjusted mean changes from baseline to final visit were -1.10, -1.49 and -1.50 for the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively [Figure 1]. The adjusted mean differences versus placebo were -0.40 (mirabegron 50 mg) and -0.41 (mirabegron 100 mg). Each mirabegron group demonstrated a statistically significant reduction from baseline to final visit in mean number of incontinence episodes per 24 hours compared with placebo with multiplicity adjustment.

Figure 1 **Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 Hours, Individual Primary Studies and Pooled Primary Studies, FAS-I**

A. Adjusted Mean Change from Baseline **B. Adjusted Mean Difference vs Placebo**



Both mirabegron 50 and 100 mg demonstrated a statistically significantly superior mean reduction of incontinence episodes compared with the placebo group as early as week 4 (the first measured time point), and their effectiveness was maintained throughout the treatment period (weeks 8 and 12).

Table 4 **Responder Analysis for Zero Incontinence Episodes at Final Visit, Pooled Primary Studies, FAS-I**

	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 5 **Responder Analysis for ≥ 50% Reduction from Baseline to Final Visit in Incontinence Episodes, Pooled Primary Studies, FAS-I**

	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*

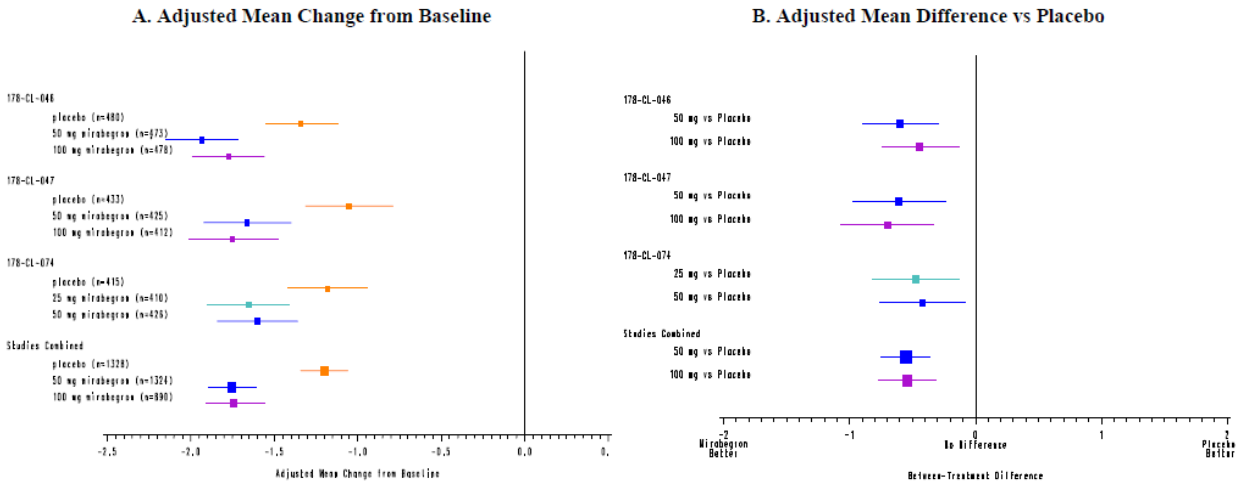
Pooled primary studies include Studies 178-CL-046, 178-CL-047 and 178-CL-074.

- **Frequency**

All mirabegron treatment groups in the 12-week phase 3 primary studies demonstrated a statistically significant reduction in mean number of micturitions per 24 hours compared with placebo with multiplicity adjustment [Figure 4].

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

Figure 4 **Change from Baseline to Final Visit in Mean Number of Micturitions per 24 Hours, Individual Primary Studies and Pooled Primary Studies, FAS**



Both mirabegron 50 and 100 mg demonstrated a statistically significantly superior mean reduction in micturitions per 24 hours compared with the placebo group as early as week 4 (the first measured time point) and their effectiveness was maintained throughout the treatment period (weeks 8 and 12).

A post-hoc evaluation of responders for reduction in micturitions (≤ 8 for mean number of micturition per 24 hours at final visit) has been carried out in the pooled analysis of primary efficacy studies.

Table 6 **Responder Analysis for 8 or Fewer Micturitions per 24 Hours at Final Visit, Pooled Primary Studies, FAS**

	Placebo (n = 1328)	Mirabegron 50 mg (n = 1324)	Mirabegron 100 mg (n = 890)
Final Visit			
Responders (n [%])	327 (24.6%)	419 (31.6%)	303 (34.0%)
Difference vs Placebo (%)		7.0%	9.4%
95% 2-sided CI for Difference†		(3.6%, 10.4%)	(5.5%, 13.3%)
Odds Ratio‡		1.57	1.69
95% 2-sided CI for Odds Ratio	--	(1.30, 1.89)	(1.37, 2.09)
P value		< 0.001*	< 0.001*

Pooled primary studies include Studies 178-CL-046, 178-CL-047 and 178-CL-074.

† 95% CIs for the difference of the proportions were based on normal approximation.

‡ Odds ratios of mirabegron over placebo, corresponding 95% CIs and P values were derived from a logistic regression model including treatment group, gender, study and baseline measurement.

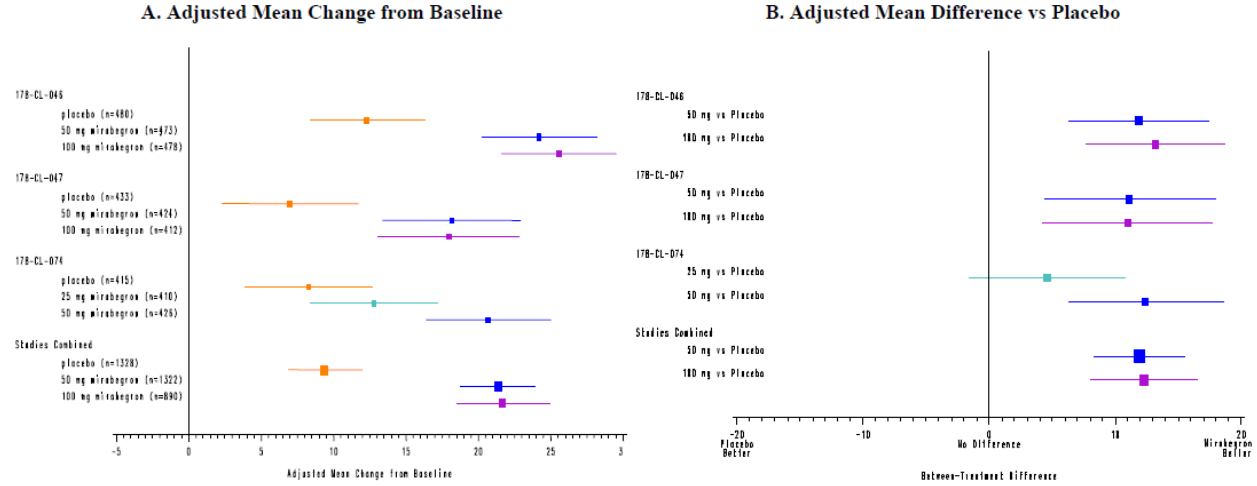
* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment.

- **Mean Volume Voided per Micturition**

All mirabegron 50 and 100 mg treatment groups in the 12-week phase 3 primary studies demonstrated a statistically significant increase from baseline in mean volume voided per micturition compared with placebo with multiplicity adjustment [Figure 7].

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

Figure 7 **Change from Baseline to Final Visit in Mean Volume Voided (mL) per Micturition, Individual Primary Studies and Pooled Primary Studies, FAS**



Both mirabegron 50 and 100 mg demonstrated a statistically significantly superior increase in mean volume voided per micturition compared with the placebo group as early as week 4 (the first measured time point) and their effectiveness was maintained throughout the treatment period (weeks 8 and 12).

- **Urgency**

All mirabegron treatment groups in the 12-week phase 3 primary studies demonstrated a reduction in mean level of urgency, the mean number of urgency incontinence episodes and the mean number of episodes with urgency grade 3 o 4 compared with placebo.

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

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

(mirabegron 100 mg). Each mirabegron group demonstrated a statistically significant reduction from baseline to final visit in mean number of urgency incontinence episodes per 24 hours compared with placebo.

The mean number of urgency episodes per 24 hours at baseline was comparable across all treatment groups in the pooled primary studies. The adjusted mean changes from baseline to final visit were -1.29, -1.93 and -1.89 for the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively. The adjusted mean differences versus placebo were -0.64 (mirabegron 50 mg) and -0.60 (mirabegron 100 mg). Each mirabegron group demonstrated a statistically significant difference in reduction from baseline to final visit in mean number of urgency episodes (grade 3 or 4) per 24 hours compared with placebo with multiplicity adjustment.

- **Nocturia**

The mean number of nocturia episodes per 24 hours at baseline was comparable across all treatment groups in the pooled primary studies. The adjusted mean changes from baseline to final visit were -0.42, -0.55 and -0.54 for the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively. The adjusted mean differences versus placebo were -0.14 (mirabegron 50 mg) and -0.12 (mirabegron 100 mg) [Table 7]. Each mirabegron group demonstrated a statistically significant reduction from baseline to final visit in mean number of nocturia episodes per 24 hours compared with placebo.

Table 7 **Adjusted Difference vs Placebo in Change from Baseline to Final Visit in Mean Number of Nocturia Episodes per 24 Hours, Individual Primary Studies and Pooled Primary Studies, FAS**

	Study 178-CL-046			Study 178-CL-047		Study 178-CL-074		Pooled Primary Studies	
Adjusted Difference vs Placebo†§	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)	Mirabegron 50 mg (n=1324)	Mirabegron 100 mg (n=890)
Mean (SE)	-0.15 (0.067)	-0.09 (0.067)	-0.04 (0.066)	-0.18 (0.091)	-0.19 (0.090)	-0.01 (0.082)	-0.04 (0.081)	-0.14 (0.046)	-0.12 (0.054)
95% 2-sided CI	(-0.28, -0.02)	(-0.22, 0.04)	(-0.17, 0.09)	(-0.36, -0.01)	(-0.37, -0.01)	(-0.17, 0.15)	(-0.20, 0.12)	(-0.23, -0.05)	(-0.23, -0.02)
P value‡	0.022*	0.20	0.52	0.043*	0.036*	0.93	0.63	0.003*	0.023*

† The ANCOVA model included treatment group, gender and geographical region as fixed factors and baseline as a covariate.

§ Estimates for the pooled primary studies are based on an analysis of covariance (ANCOVA) model, which included treatment group, gender and study as fixed factors and baseline as a covariate.

‡ Nominal P values are from pairwise comparisons versus placebo within the ANCOVA model.

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

- **Subjective Improvement Assessments**

Overactive Bladder Symptoms, Quality of Life and Treatment Benefit

The Overactive Bladder Questionnaire (OAB-q), the Patient Perception of Bladder Condition (PPBC) and the Treatment Satisfaction-Visual Analog Scale (TS-VAS) were the subjective outcome measures included in this study to evaluate treatment effects as perceived by the patient.

- The OAB-q is a self-report questionnaire with 33 items that contain the dimensions Coping, Concern, Sleep, Social Interaction and a Symptom Bother scale with 8 symptoms. Scores range from 0 to 100 with a score of 100 indicating the worst severity. A negative change indicates improvement.
- Health-Related Quality of Life Total Score and Subscales (Coping, Concern Sleep and Social Interaction). Higher scores on the HRQL subscales and total score indicated a better QoL, and a positive change in the HRQL subscale scores and total score indicated improvement.

- The PPBC scale is a global assessment tool using a 6-point Likert scale that asks patients to rate their subjective impression of their current bladder condition.
- The TS-VAS is a visual analog scale (VAS) that asks patients to rate their satisfaction with the treatment by placing a vertical mark on a line that runs from 0 (No, not at all) to 10 (Yes, completely). Positive change from baseline indicates improvement.

Mirabegron 50 mg demonstrated a statistically significant decrease (improvement) from baseline to final visit in the Symptom Bother Scale total score compared with placebo in the pooled data set [Table 1]. Further, mirabegron 50 mg demonstrated a statistically significant increase (improvement) from baseline to final visit in the HRQL total score and all its subscales including coping, concern and sleep compared with placebo except for the Social Interaction subscale.

Table 1 Overactive Bladder Questionnaire Adjusted Mean Change Scores from Baseline to Final Visit, Pooled Primary Phase 3 Studies, FAS

		Pooled Primary Studies	
Score	**Statistical Parameter**	**Placebo (n = 1328)**	**Mirabegron 50 mg (n = 1324)**
Symptom Bother Scale			
Adjusted Change from Baseline†	n Mean (SE) 95% 2-sided CI	1236 -13.98 (0.522) (-15.01, -12.96)	1237 -18.49 (0.523) (-19.51, -17.46)
Adjusted Difference vs. Placebo†	Mean (SE) 95% 2-sided CI P value	--	-4.51 (0.734) (-5.94, -3.07) < 0.001*
Health-related Quality of Life Total Score			
Adjusted Change from Baseline†	n Mean (SE) 95% 2-sided CI	1234 12.69 (0.475) (11.75, 13.62)	1237 15.15 (0.475) (14.22, 16.08)
Adjusted Difference vs. Placebo†	Mean (SE) 95% 2-sided CI P value	--	2.46 (0.667) (1.16, 3.77) < 0.001*

Coping			
Adjusted Change from Baseline†	n Mean (SE) 95% 2-sided CI	1235 14.46 (0.574) (13.34, 15.59)	1237 17.34 (0.575) (16.22, 18.47)
Adjusted Difference vs. Placebo†	Mean (SE) 95% 2-sided CI P value	--	2.88 (0.806) (1.30, 4.46) < 0.001*
Concern			
Adjusted Change from Baseline†	n Mean (SE) 95% 2-sided CI	1237 14.67 (0.542) (13.61, 15.73)	1240 17.66 (0.543) (16.59, 18.72)
Adjusted Difference vs. Placebo†	Mean (SE) 95% 2-sided CI P value	--	2.99 (0.761) (1.49, 4.48) < 0.001*
Sleep			
Adjusted Change from Baseline†	n Mean (SE) 95% 2-sided CI	1238 12.44 (0.556) (11.35, 13.53)	1240 14.68 (0.556) (13.59, 15.77)
Adjusted Difference vs. Placebo†	Mean (SE) 95% 2-sided CI P value	--	2.24 (0.780) (0.71, 3.77) 0.004*
Social interaction			
Adjusted Change from Baseline†	n Mean (SE) 95% 2-sided CI	1236 7.49 (0.415) (6.67, 8.30)	1239 8.61 (0.415) (7.80, 9.42)
Adjusted Difference vs. Placebo†	Mean (SE) 95% 2-sided CI P value	--	1.12 (0.583) (-0.02, 2.27) 0.054

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
This table was created postsubmission based on data available in Studies 178-CL-046, 178-CL-047 and 178-CL-074 in Module 5.3.5.1
All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement and at least 1 postbaseline visit diary with a micturition measurement (FAS).
--: not applicable; ANCOVA: analysis of covariance; FAS: full analysis set; HRQL: health-related quality of life; vs.: versus
Symptom Bother scores ranged from 0 to 100 (100 = worst severity). A negative change in Symptom Bother indicated improvement. HRQL Total Score indicated a better quality of life. A positive change in HRQL Total Score indicated improvement.
† Point estimates, 95% CIs and P values are from an ANCOVA model which included treatment group, gender and study as fixed factors and baseline as a covariate.
* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment.

Treatment Satisfaction-Visual Analogue Scale

Treatment satisfaction was assessed on a VAS with complete satisfaction indicated by a score of 10, with positive change from baseline indicating improvement. The mean TS-VAS score at baseline was comparable across all treatment groups. The adjusted mean changes from baseline to final visit were 1.25, 2.01 and 2.33 for the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively. The adjusted mean differences versus placebo were 0.76 (mirabegron 50 mg) and 1.08 (mirabegron 100 mg). Each mirabegron group demonstrated a statistically significant increase from baseline to final visit in TS-VAS score compared with placebo.

Table 9 Adjusted Mean Difference versus Placebo in Change from Baseline to Final Visit in TS-VAS, Pooled Primary Studies, FAS

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

† Estimates are based on an analysis of covariance (ANCOVA) model, which included treatment group, gender and study as fixed factors and baseline as a covariate. ‡ Nominal P values are from pairwise comparisons versus placebo within the ANCOVA model.
*Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment

Patient Perception of Bladder Condition, FAS

Baseline mean PPBC values were comparable across all treatment groups in each study. Mirabegron 50 and 100 mg demonstrated statistically significant improvement in PPBC compared with placebo at final visit in Studies 178-CL-046 and 178-CL-047, with adjusted mean differences versus placebo of -0.2 for mirabegron 50 mg in both Studies 178-CL-046 and 178-CL-047, and -0.2 and -0.3 for mirabegron 100 mg in Studies 178-CL-046 and 178-CL-047, respectively.

Consistency Between Objective Endpoints and Subjective Endpoints

Responderanalyses based on the pooled primary phase 3 studies are presented in order to provide a more precise estimate and additional power to detect differences between mirabegron 50 mg and placebo.

Table 8: Overall Summary of Objective and Patient Reported Efficacy Endpoints, Individual and Pooled Primary Phase 3 Studies

Endpoint		Mirabegron 50 mg Difference versus Placebo			
		178-CL-046	178-CL-047	178-CL-074	Pooled
Co-Primary Endpoints	Change from baseline to Final Visit in Mean Number of Incontinence Episodes per 24 hours	-0.41 **	-0.34 *	-0.42 **	-0.40 ***
	Change from baseline to Final Visit in Mean Number of Micturitions per 24 hours	-0.60 ***	-0.61 **	-0.42 *	-0.55 ***
Secondary Objective Responder Endpoints	Odds Ratio for Responder for Zero Incontinence Episodes at Final Visit	1.23 P=0.26	1.31 P=0.11	1.43 P=0.057	1.32 **
	Odds Ratio for Responder for ≥ 50% Reduction from baseline to Final Visit in Incontinence Episodes	1.75 **	1.34 P=0.076	1.61 *	1.54 ***
Secondary Subjective Endpoints, OAB-q	Change from baseline to Final Visit in Symptom Bother Score	-4.7 ***	-6.2 ***	-2.8 *	-4.51 ***
	Change from baseline to Final Visit in Total HRQL Score	2.3 *	4.1 **	1.2 P=0.28	2.46 ***
	Odds Ratio for Responders based on MID (10) for Symptom Bother Score	1.80 ***	1.45 *	1.08 P=0.62	1.43 ***
	Odds Ratio for Responders based on MID (10) for Total HRQL Score	1.42 *	1.91 ***	1.20 P=0.24	1.46 ***
Secondary Subjective Endpoints, PPBC	Change from baseline to Final Visit in PPBC	-0.2 *	-0.2 *	-0.0 P=0.64	-0.12 **
	Odds Ratio for Responders based on MID (1) for PPBC	1.36 *	1.16 P=0.31	1.03 P=0.87	1.18 P=0.059

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]). All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement and at least 1 incontinence episode recorded in the baseline 3-day micturition diary and at least 1 postbaseline visit diary with a micturition measurement (Full Analysis Set-Incontinence [FAS-I]).
MID: minimally important difference; PPBC: patient perception of bladder condition; HRQL: health related quality of life; ANCOVA: analysis of covariance.
For the individual primary studies adjusted mean change from baseline are from an ANCOVA model which included treatment group, gender and geographical region as fixed factors and baseline as a covariate and odds ratio and corresponding P value for the responder analyses are derived from a logistic regression model including treatment group, gender, region and baseline value. For the pooled primary studies adjusted mean change from baseline are from an ANCOVA model which included treatment group, gender and study as fixed factors and baseline as a covariate and odds ratio and corresponding P value for the responder analyses are derived from a logistic regression model including treatment group, gender, study and baseline value.
For the adjusted mean change from baseline for the incontinence endpoint, nominal P values are from pairwise comparison versus placebo within the stratified rank ANCOVA, a nonparametric analysis. For the micturition frequency co-primary endpoint, nominal P values for the adjusted mean change from baseline are from pairwise comparisons versus placebo within the ANCOVA model, a parametric analysis.
* nominal P value < 0.05; ** nominal P value <0.01; *** nominal P value < 0.001

When patients were evaluated based on achieving a response both for the objective endpoint of achieving a ≥ 50% reduction in incontinence episodes per 24 hours and being a responder based on one of the 3 patient reported indices (symptom bother score, total HRQL score or PPBC value) evaluated based on MID, mirabegron 50 mg consistently demonstrated a statistically significant greater improvement over placebo for each of these double responder analyses performed [Table 9].

The difference from placebo in the responder rates for each of the double responder analyses was higher than the differences observed in the single responder analyses.

Table 9: Results for Double Responder Analyses for Incontinence and Patient Reported Indices, Pooled Primary Phase 3 Studies, FAS-I

Double Responder Parameters				
Objective Index	**MID in Patient Reported Index**	**Statistical Parameter**	**Placebo**	**Mirabegron 50 mg**
≥ 50% reduction in incontinence episodes per 24 hours	Symptom Bother Score (≥ 10)	n	807	791
		% Responders	39.3%	54.5%
		Difference vs. Placebo (%)	--	15.2%
		95% 2-sided CI for Difference	--	(10.4%, 20.0%)
		Odds Ratio vs. Placebo ‡	--	1.87
		95% 2-sided CI for Odds Ratio‡	--	(1.53, 2.29)
		P value‡	--	< 0.001*
≥ 50% reduction in incontinence episodes per 24 hours	Total HRQL Score (≥ 10)	n	806	791
		% Responders	35.1%	46.0%
		Difference vs. Placebo (%)	--	10.9%
		95% 2-sided CI for Difference	--	(6.1%, 15.7%)
		Odds Ratio vs. Placebo‡	--	1.60
		95% 2-sided CI for Odds Ratio‡	--	(1.30, 1.97)
		P value‡	--	< 0.001*
≥ 50% reduction in incontinence episodes per 24 hours	PPBC value (≥ 1)	n	799	776
		% Responders	37.8%	44.6%
		Difference vs. Placebo (%)	--	6.8%
		95% 2-sided CI for Difference	--	(1.9%, 11.6%)
		Odds Ratio vs. Placebo‡	--	1.37
		95% 2-sided CI for Odds Ratio‡	--	(1.11, 1.68)
		P value‡	--	0.003*

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement and at least 1 incontinence episode in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (FAS-I).
A responder for ≥ 50% reduction in incontinence episodes per 24 hours was defined as a patient with a ≥ 50% reduction from baseline to final visit in mean number of incontinence episodes per 24 hours.
A responder for OAB-q parameters was defined as a patient with an improvement from baseline to final visit in HRQL Score which was at least as large as the MID (10).
A responder for PPBC was defined as a patient with an improvement from baseline to final visit in PPBC which was at least as large as the MID (1).
--: not applicable; FAS-I: Full Analysis Set-Incontinence; MID: minimally important difference; vs.: versus
95% CIs for the difference of the proportions are based on normal approximation.
‡ Odds ratios, corresponding 95% CI and the P value are derived from a logistic regression model including treatment group, gender, study and baseline values for both parameters.
* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment.
Source: data on file

When patients were evaluated based on achieving a response for the objective endpoint of a ≥ 50% reduction in incontinence episodes per 24 hours and being a responder based on two patient reported indices (Symptom Bother Score and PPBC value or total HRQL score and PPBC value) evaluated based on MID, mirabegron 50 mg consistently demonstrated a statistically significant greater improvement over placebo for the triple responder analyses performed [Table 10].

Table 10: Results for Triple Responder Analyses for Incontinence and Patient Reported Indices, Pooled Primary Phase 3 Studies, FAS-I

Triple Responder Parameters				
Objective Index	**MID for Patient Reported Indices**	**Statistical Parameter**	**Placebo**	**Mirabegron 50 mg**
≥ 50% reduction in incontinence episodes per 24 hours	Symptom Bother Score (≥ 10) and PPBC value (≥ 1)	n	742	716
		% Responders	30.5%	39.5%
		Difference vs. Placebo (%)	--	9.1%
		95% 2-sided CI for Difference	--	(4.2%, 13.9%)
		Odds Ratio vs. Placebo‡	--	1.55
		95% 2-sided CI for Odds Ratio‡	--	(1.24, 1.93)
		P value‡	--	<0.001*
≥ 50% reduction in incontinence episodes per 24 hours	Total HRQL Score (≥ 10) and PPBC value (≥ 1)	n	741	716
		% Responders	28.1%	36.5%
		Difference vs. Placebo (%)	--	8.4%
		95% 2-sided CI for Difference	--	(3.6%, 13.2%)
		Odds Ratio vs. Placebo‡	--	1.51
		95% 2-sided CI for Odds Ratio‡	--	(1.20, 1.90)
		P value‡	--	< 0.001*

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement and at least 1 incontinence episode in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (FAS-I).
A responder for ≥ 50% reduction in incontinence episodes per 24 hours was defined as a patient with a ≥ 50% reduction from baseline to final visit in mean number of incontinence episodes per 24 hours.
A responder for OAB-q parameters was defined as a patient with an improvement from baseline to final visit in HRQL Score which was at least as large as the MID (10).
A responder for PPBC was defined as a patient with an improvement from baseline to final visit in PPBC which was at least as large as the MID (1).
--: not applicable; FAS-I: Full Analysis Set-Incontinence; MID: minimally important difference; vs.: versus
95% CIs for the difference of the proportions are based on normal approximation.
‡ Odds ratios, corresponding 95% CI and the P value are derived from a logistic regression model including treatment group, gender, study and baseline values for each parameter.
* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment.
Source: data on file

Clinical studies in special populations

The applicant has not performed specific clinical studies in special populations. The consistency of treatment effects across subpopulations was evaluated using the pooled FAS and FAS-I of the three primary studies. Comparisons of subpopulations were made for the coprimary efficacy endpoints change from baseline to final visit in mean number of incontinence episodes per 24 hours and change from baseline to final visit in mean number of micturitions per 24 hours.

Pooled analyses of the coprimary efficacy endpoints by subpopulations of demographic and baseline characteristics included gender, age, race, ethnicity, body mass index (BMI) group and geographical region.

Female subjects showed greater improvements than male subjects in mean numbers of micturitions, and incontinence episodes. This could be due to a smaller effect in men (who according to pharmacokinetic parameters exhibited a lower exposure than women) or be a consequence of the smaller numbers.

Elderly patients (≥65 years; ≥75 years) experienced a greater reduction of micturitions and in incontinence episodes patient reported response than younger subjects.

Non-White subjects showed a lower reduction of incontinence episodes as well as of frequency. However the infra-representation of non-Caucasian subjects and the higher variability do not allow drawing conclusions in this regard.

A more marked placebo effect for the different endpoints is observed among naïve patients, which may be responsible of the observed differences in response.

Supportive studies

	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered / compl.	Duration
178-CL-008	35/ Belgium, Czech Republic, Denmark, Germany, Spain, Sweden, United Kingdom	Phase 2a, randomized, double-blind, parallel, placebo- and activecontrolled	Placebo Mirabegron IR 100 mg, bid Mirabegron IR 150 mg, bid Tolterodine ER 4 mg, qd	Efficacy and Safety, Proof of Concept	66/62 65/61 65/60 66/62	4 weeks
178-CL-048	93/Japan	Phase 3, randomized, double-blind, parallel, placebo- and active controlled	Placebo qd Mirabegron OCAS 50 mg, qd Tolterodine ER 4 mg, qd	Efficacy and Safety	381/350 380/349 378/355	12 weeks
178-CL-049	306/ Europe‡‡, United States, Canada, South Africa and Australia/ New Zealand	Phase 3, randomized, double-blind, parallel, active controlled, long-term study	Mirabegron OCAS 50 mg, qd Mirabegron OCAS 100 mg, qd Tolterodine ER 4 mg, qd	Long-term Safety and Efficacy	815/629 824/645 813/621	12 months
178-CL-051	26/Japan	Phase 3, open-label, uncontrolled, long-term study	Mirabegron OCAS 50 mg, qd [only] Mirabegron OCAS 100 mg, qd [used]	Long-term Safety and Efficacy	154/123 50/42	12 months

Phase 2a Proof-of-Concept Study 178-CL-008

The primary objective of the study was to assess the efficacy of mirabegron in patients with OAB in comparison with placebo. The secondary objectives of the study were to evaluate the safety and tolerability of mirabegron in patients with OAB in comparison with placebo, to compare the efficacy, safety and tolerability of mirabegron with tolterodine, and to collect population pharmacokinetics data in patients with OAB. The primary efficacy measure was change from baseline in mean number of micturition per 24 hours.

Method

After screening (day -21 to day -14), patients were enrolled in a single-blind, 2-week placebo run-in period that ended at baseline (week 0). Patients meeting the inclusion criteria and not meeting exclusion criteria were randomized to receive mirabegron IR 100 or 150 mg twice daily, placebo, or tolterodine for 4 weeks. Subsequently, patients were followed for an additional 2 weeks with single-blind placebo treatment.

Results:

The mirabegron IR 100 and 150 mg twice daily groups showed statistically significant reductions in mean number of micturition per 24 hours compared with placebo. For the tolterodine group, the estimated adjusted mean difference vs placebo was -0.40 (P = 0.2332). Repeated measures analysis also showed statistically significant reduction in mean number of micturition per 24 hours in the mirabegron IR 100 and 150 mg twice daily groups compared with placebo, whereas the difference was not statistically significant for tolterodine.

(YM178 = mirabegron)

	Placebo	YM178 100 mg bid	YM178 150 mg bid	Pooled YM178 group	Tolterodine 4 mg od
Micturitions/24 h					
FAS	**N=64**	**N=65**	**N=63**	**N=128**	**N=63**
Baseline mean (SD)	12.34 (3.51)	11.30 (2.65)	12.25 (3.62)	11.77 (3.19)	11.00 (3.06)
Change from baseline[a]	-1.32 (2.49)	-2.00 (1.76)	-2.30 (2.12)	-2.15 (1.95)	-1.27 (1.99)
Estimated difference[b]		-1.016	-1.031	-1.022	-0.399
(p-value)		0.0047*	0.0047*	0.0004*	0.2332
Mean volume voided/micturition (mL)					
FAS	**N=64**	**N=65**	**N=63**	**N=128**	**N=63**
Baseline mean (SD)	151.79 (58.34)	164.65 (62.86)	150.67 (53.49)	157.77 (58.63)	179.85 (65.21)
Change from baseline[a]	10.86 (35.99)	26.71 (51.20)	32.44 (47.67)	29.53 (49.38)	23.24 (42.18)
Estimated difference[b]		15.56	22.25	18.81	13.10
(p-value)		0.052	0.012*	0.0063*	0.1038
Incontinence episodes/24 h					
FAS	**N=41**	**N=37**	**N=41**	**N=78**	**N=41**
Baseline mean (SD)	2.41 (1.69)	2.50 (2.53)	3.57 (3.47)	3.06 (3.08)	2.95 (2.52)
Change from baseline[a]	-0.80 (1.47)	-2.01 (2.30)	-1.96 (2.64)	-1.98 (2.47)	-1.70 (2.26)
Estimated difference[b]		-1.156	-0.568	-0.806	-0.612
(p-value)		0.0081*	0.1460	0.0133*	0.1004
Nocturia episodes/24h					
FAS	**N=57**	**N=58**	**N=54**	**N=112**	**N=58**
Baseline mean (SD)	1.88 (1.16)	1.84 (0.97)	1.92 (1.08)	1.88 (1.02)	1.84 (1.08)
Change from baseline[a]	-0.25 (0.93)	-0.59 (0.73)	-0.42 (0.83)	-0.51 (0.78)	-0.37 (0.87)
Estimated difference[b]		-0.388	-0.171	-0.274	-0.196
(p-value)		0.0086*	0.2124	0.0218*	0.1547
Urge incontinence episodes/24 h					
FAS	**N=40**	**N=37**	**N=39**	**N=76**	**N=39**
Baseline mean (SD)	2.10 (1.54)	2.41 (2.50)	3.47 (3.39)	2.95 (3.02)	2.70 (2.11)
Change from baseline[a]	-0.78 (1.43)	-1.92 (2.28)	-1.89 (2.70)	-1.90 (2.49)	-1.55 (1.89)
Estimated difference[b]		-0.968	-0.353	-0.646	-0.44
(p-value)		0.0267*	0.3634	0.0445*	0.2312

The estimated differences to placebo and the corresponding p-values for the change from baseline for the primary and secondary efficacy variables at endpoint are shown below for the FAS. Statistically significant p-values ($p \leq 0.05$) are marked with an asterisk (*).

Study 178-CL-048

This study was conducted to assess the efficacy of mirabegron 50 mg versus placebo in the treatment of patients with symptoms of OAB based on mean number of micturition per 24 hours and to assess the safety and pharmacokinetics of mirabegron 50 mg. The study was also conducted to compare the efficacy and safety of mirabegron with tolterodine ER 4 mg without any formal testing for non-inferiority or superiority of mirabegron. This study was conducted in Japan.

The primary efficacy endpoint was change from baseline to final assessment in mean number of micturition per 24 hours.

Results

For the primary efficacy endpoint, the mirabegron 50 mg group demonstrated a statistically significantly greater reduction from baseline to final visit compared with placebo in mean number of micturition per 24 hours in the FAS (adjusted mean difference vs placebo: -0.86 [95% CI: -1.16, -0.57]). The adjusted mean difference between tolterodine and placebo was -0.61 [95% CI: -0.90, -0.32]).

For the secondary efficacy endpoints, the mirabegron 50 mg group showed statistically significant improvements in mean number of urgency episodes (adjusted mean difference vs placebo: -0.54 [95% CI: -0.90, -0.18] in the FAS), mean number of incontinence episodes (adjusted mean difference vs placebo: -0.42 [95% CI: -0.67, -0.17] in the subset of the FAS with incontinence at baseline), mean number of urge incontinence episodes (adjusted mean difference vs placebo: -0.36 [95% CI: -0.59, -0.12] in the subset of the FAS with incontinence at baseline), and mean volume voided per micturition (adjusted mean difference vs placebo: 14.775 mL [95% CI: 9.974, 19.576] in the FAS). For mean number of nocturia episodes, the adjusted mean difference versus placebo for mirabegron 50 mg was -0.12 (95% CI: -0.25, 0.01). The tolterodine group showed statistically significant improvements in mean number of urgency episodes (adjusted mean difference vs placebo: -0.41 [95% CI: -0.77, -0.05] in the FAS), mean number of incontinence episodes (adjusted mean difference vs placebo: -0.32 [95% CI: -0.57, -0.06] in the subset of the FAS with incontinence at baseline), mean number of urge incontinence episodes (adjusted mean difference vs placebo: -0.32 [95% CI: -0.56, -0.08] in the subset of the FAS with incontinence at baseline), and mean volume voided per micturition (adjusted mean difference vs placebo: 19.049 mL [95% CI: 14.246, 23.852] in the FAS). For mean number of nocturia episodes, the adjusted mean difference versus placebo for tolterodine was -0.10 (95% CI: -0.23, 0.03). In Study 178-CL-048, QOL scores were obtained from the King's Health Questionnaire, which patients completed covering the 2 weeks prior to each study visit. Compared with placebo, the mirabegron 50 mg group showed a statistically significant improvement in 7 of 9 QOL domain scores: domain 2 (incontinence impact [P < 0.001]), domain 3 (role limitations [P < 0.001]), domain 4 (physical limitations [P = 0.004]), domain 5 (social limitations [P = 0.005]), domain 7 (emotions [P = 0.009]), domain 8 (sleep/energy [P = 0.016]) and domain 9 (severity measures [P < 0.001]).

Study 178-CL-049

The primary objective of the study was to assess the safety and tolerability of long-term treatment with mirabegron 50 and 100 mg in patients with symptoms of OAB. The secondary objectives of the study were to assess the efficacy of long-term treatment with mirabegron 50 and 100 mg in patients with symptoms of OAB and to place the long-term safety and efficacy of mirabegron in context with a standard treatment for OAB, tolterodine.

Endpoints

The primary endpoint of the study was the frequency and severity of treatment-emergent AEs (TEAE). Efficacy analyses were secondary in this study. The efficacy endpoints assessed were change from baseline to months 1, 3, 6, 9, 12 and final visit in the following: mean number of micturition per 24 hours, mean number of incontinence episodes per 24 hours, mean volume voided per micturition, mean number of urgency incontinence episodes per 24 hours, mean number of urgency episodes (grade 3 or 4) per 24 hours, mean level of urgency, mean number of pads used per 24 hours, and mean number of nocturia episodes per 24 hours.

Results

Mirabegron 50 mg and 100 mg demonstrated numeric reductions from baseline to Final Visit in mean number of micturition per 24 hours (adjusted mean change from baseline: -1.27 and -1.41, respectively) and mean number of incontinence episodes per 24 hours (adjusted mean change from baseline: -1.01 and -1.24, respectively) as well as numeric improvements in mean volume voided per micturition (adjusted mean change from baseline: 17.5 mL and 21.5 mL, respectively). the mean change from baseline to final visit in mean number of urgency episodes (grade 3 or 4) was -1.62, -1.80 for the mirabegron 50 mg, 100 mg. Numerical improvements in mean number of urgency incontinence episodes per 24 hours were seen by month 1 and were maintained for the duration of the study. The mean change from baseline to final visit in the FAS was -1.01, -1.23 for the mirabegron 50 mg, and 100 mg. Numerical improvements in mean number of pads used per 24 hours in the FAS were seen by month 1 continued until month 9 and were maintained for the duration of the study. Numerical improvements in mean number of nocturia episodes per 24 hours from baseline to final visit were observed for mirabegron 50 mg and 100 mg, (-0.46, and -0.39 episodes respectively. Numerical improvements were seen from baseline to final visit for the mirabegron 50 mg, mirabegron100 mg, and tolterodine groups in the TS-VAS, OAB-q scores, and the PPBC scale. Improvements in these symptoms were observed by month 1, with continued improvement until at least month 3 and maintenance of the effect through month 12. Both doses of mirabegron also showed numeric improvements on the additional secondary efficacy variables. Numerically similar results and a similar course of improvement over time were observed with tolterodine ER 4 mg.

Study 178-CL-051

The primary objective of the study was to assess the safety of long-term administration (52 weeks) of mirabegron at a dose of 50 mg in patients with OAB, with the possibility of dose escalation to 100 mg. Efficacy analyses were secondary in this study.

The efficacy endpoints assessed were change from baseline to weeks 4, 8, 16, 28, 40 and 52 and final visit in the following: mean number of micturition per 24 hours, mean number of urgency episodes per 24 hours, mean number of incontinence episodes per 24 hours, mean number of urge incontinence episodes per 24 hours, mean number of nocturia episodes per 24 hours, and QOL domain scores on the King's Health Questionnaire.

Results (efficacy)

At the final assessment, all patients demonstrated a reduction in mean number of incontinence episodes (-1.38), mean number of micturition (-2.01), mean number of urgency episodes (-3.16), mean number of urge incontinence episodes (-1.33) and the mean number of nocturia episodes (-0.48). In the mirabegron 50 mg group, the reduction from baseline in all efficacy endpoints was maintained from the first assessment time point (week 8) to the final assessment (week 52). In the patients who received the increased dose of mirabegron 100 mg, the magnitude of improvements from baseline in all efficacy endpoints at week 8 was less than patients who remained on mirabegron 50 mg, but the improvements increased, and were comparable to those patients receiving mirabegron 50 mg from week 16 to final assessment. At final assessment, the respective changes from baseline in all efficacy endpoints assessed in the mirabegron 50 mg group and the group of patients who received the increased dose of mirabegron 100 mg were comparable and as follows: mean number of incontinence episodes (-1.30 and -1.56, respectively), mean number of micturition (-2.16 and -1.57, respectively), mean number of urgency episodes (-3.31 and -2.72, respectively), mean number of urge incontinence episodes (-1.32 and -1.33, respectively) and the mean number of nocturia episodes (-0.49 and -0.47, respectively). Normalization was defined as less than 8 micturition per day on average at the final assessment and resolution (0 episodes) of urge incontinence and nocturia at the final assessment. The

percentages of all mirabegron-treated patients that achieved normalization in mean number of incontinence episodes, micturitions, urgency episodes and nocturia episodes were 63.1%, 28.6%, 36.2% and 23.0% respectively. Improvements in QOL scores in all domains were observed from baseline to final assessment for all patients.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Three pivotal Phase 3 randomized, double blind, placebo controlled, parallel group 12-week studies support the use of mirabegron 25 mg, 50 mg and 100 mg in the treatment of OAB (Studies CL-046, CL-047 and CL-074). Data from these three studies was integrated for pooled-analyses.

The study design including the objectives, inclusion and exclusion criteria, and efficacy endpoints of the pivotal studies are acceptable and, in general in agreement with the CHMP Guideline (Note for Guidance on the clinical investigation of medicinal products for the treatment of urinary incontinence, CPMP/EWP/18/01).

The population of subjects participating in this trial seems adequate and representative for patients with OAB. These studies enrolled male or female subjects (18 to 95 years of age inclusive) with symptoms or signs of overactive bladder with increased urinary frequency, urgency with or without incontinence. Demographic and baseline characteristics were comparable across the 3 treatment groups. Most of the subjects randomised were females (72-83%) and White (>90%). Median ages overall ranged from 59 to 61 years. Demographic and baseline characteristics were generally similar among treatment groups within each of these trials. Patients of moderate severity were preferably recruited. Subjects had a mean of 11 to 12 micturitions per 24 hours, 2 to 3 incontinence episodes (if they were incontinent) and experienced urgency of moderate to severe intensity. Between 49% and 60% of patients reported previous antimuscarinic treatment.

Patients were treated for 12 weeks. In addition to placebo control, one of the pivotal trials also included tolterodine as active control arm.

Efficacy was primarily based on the reduction in the urinary frequency (number of micturitions) and the number of incontinence episodes. Given that incontinence was not an inclusion criterion of the pivotal trials only a subgroup of the population fulfils the “co-primary” condition. This is considered to be a deficiency in the design of the pivotal studies as when the analysis of the incontinence endpoints based upon the full ITT population (FAS) was performed the overall treatment effect was reduced.

Further the results for responder analyses (responders for zero incontinence episodes at final visit and responders for ≥ 50% reduction in incontinence episodes at final visit) in the individual studies did not always reach statistical significance. However, it is acknowledged by the CHMP that this may be due to inadequate statistical power as the studies were not planned to include sufficient patients for an analysis of responders. It is acknowledged by the CHMP that pooled results of responder analyses of studies 046, 047 and 048 showed statistical significance compared to placebo.

The perception of the patients was not part of the primary assessment of the efficacy of the product. These measures are meant to provide reassurance to the clinical relevance of the changes experienced by the quantitative outcomes. This is especially significant in such a non-life threatening condition in which the improvement of the impact of the disease on patient’s daily lives should be among the main therapeutic objectives. The CHMP is of the view that the consideration of these outcomes as primary endpoint instead of “additional secondary” outcomes would have been more appropriate.

The tools used for assessment were validated in the target population. Also, a clinically relevant change in pre-specified domains was defined.

Efficacy data and additional analyses

All studies demonstrated a statistically significant reduction in the principal variables (number of micturitions in 24 hours, number of incontinence episodes in 24 hours). Most symptoms related to secondary variables also showed a statistically significant difference from baseline after 12 weeks treatment.

- Regarding the number of micturitions the changes from baseline to final visit were -1.20 and -1.75 for the placebo and mirabegron 50 mg groups, respectively. The effect on urinary frequency shows a modest net benefit for mirabegron of 0.55 over pacebo.
- The effect of mirabegron on incontinence was assessed in a subset (about 70%) of the recruited population. The net benefit was a reduction of 0.4 incontinence episodes more than placebo. When the effect is expressed in a more meaningful way (as responder analyses) mirabegron achieves equal or less than 10% responders than placebo.

No clear dose-dependent effect has been observed. The Dose of 100 mg did not globally work better than 50 mg. The 25 mg dose exhibited a lower effect (mostly in secondary measures) than 50 mg. When subgroup populations were compared female and elderly patients showed somewhat greater improvements. Urgency and nocturia albeit reaching statistical significance appear to be less sensitive to the action of mirabegron.

Indirect comparison of the effect observed with mirabegron 50 mg on the co-primary endpoint (incontinence and micturitions) and the ones seen for fesoterodine, solifenacin, trospium chloride, darifenacine and tolterodine from publicly available sources show that the effect of mirabegron is within the range of the means values for the other products.

Table 5: Mean Difference from Placebo in Primary Endpoints for Mirabegron and Other OAB Compounds

	Mean Change from Baseline in Incontinence Episodes per Day	Mean Change from Baseline in the Number of Micturitions per Day
	Mean Difference from Placebo	Mean Difference from Placebo
Range of the Means (Literature Meta-analysis)	-0.21 to -1.08	-0.54 to -1.3
Range of the Means (Regulatory Documents)	-0.22 to -1.2	-0.40 to -1.39
Mirabegron 50 mg (95% 2-sided CI)†	-0.40 (-0.58, -0.21)	-0.55 (-0.75, -0.36)

† Estimates and 95% CIs are based on an ANCOVA model which included treatment group, gender and study as fixed factors and baseline value as a covariate for the Pooled Primary Phase 3 Studies (178-CL-046, 178-CL-047, and 178-CL-074).

Source: Chapple et al, 2008; FDA documents: Medical Review(s) Application Number 22-030 (Toviaz, Fesoterodine Fumarate) 2008, Medical Review(s) Application Number 21-518 (VESIcare, Solifenacin Succinate) 2004, Medical Review Application Number 21-595 (Sanctura, Trospium Chloride), Medical Review(s) (Parts 1, 2 and 3) 2004, Medical Review Application Number 22-103 (Sanctura XR, Trospium Chloride) 2007, Medical and Statistical Review(s) Application Number 21-513 (Enablex, Darifenacin Hydrobromide) 2004, Statistical Review(s) (Parts 1 and 2) Application Number 20-771 (Detrol, Tolterodine L-tartrate) 1998, Medical Review(s) (Parts 1 and 2) Application Number 21-228 (Detrol LA, Tolterodine) 2000.

In addition, a comparability exercise for the improvement in incontinence episodes between antimuscarinics and mirabegron was taken into account. Data for antimuscarinics where taken from a study recently published (Shamliyan et al, 20125) where the relative risk for the endpoint of

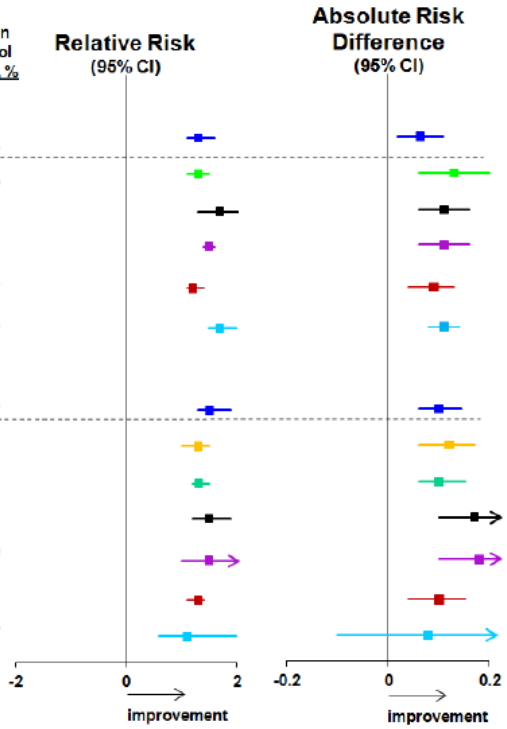
[5] Shamliyan T, Wyman JF, Ramakrishnan R, Sainfort F and Kane RL. Benefits and harms of pharmacologic treatment for urinary incontinence in women. Ann Intern Med. 2012;156:861-74.

continence (zero incontinence) and clinically important improvement in incontinence (>50% reduction in incontinence) have been calculated.

Results, again, show comparable data for the relative risk, and a slightly lower effect of mirabegron for the absolute risk difference. Limitations of such indirect comparison are acknowledged however this results suggest comparable efficacy as for other approved drugs for OAB.

Figure 1: **Comparability of Incontinence Efficacy Assessed by the Responder Analyses for Incontinence Episodes for Mirabegron and Other OAB Drugs Compared with Placebo**

	Number of Randomized, Controlled Trials	Patients in Analyses, n	Rate in Active Treatment Group, %	Rate in Control Group, %
Continence				
Mirabegron†	3	1740	44.1	37.8
Fesoterodine‡	2	2465	61.0	48.5
Oxybutynin‡	4	992	27	16
Solifenacin‡	5	6304	39.2	28.1
Tolterodine‡	4	3404	53.2	43.7
Trospium‡	4	2677	28.3	16.6
Clinical Important Improvement in Incontinence				
Mirabegron†	3	1740	69.5	59.6
Darifenacin‡	3	1011	48.4	33
Fesoterodine‡	2	1896	42	32
Oxybutynin‡	9	1244	53	32
Solifenacin‡	2	1507	60.2	42.0
Tolterodine‡	7	6119	45	37
Trospium‡	2	1176	32.4	25.4



Clinically important improvement in incontinence was defined as 50% or greater reduction in daily urinary incontinence episodes.
† data from mirabegron dossier.
‡ data from Shamliyan et al, 2012.

In this respect, also comparative effects of mirabegron with tolterodine as shown in the development program reveals an effect of similar magnitude both in short and long term treatment.

Three main measures were used to capture the subjective perception of patients with respect to the benefit of the treatment with mirabegron and the potential improvement of the condition. These instruments were based on a Visual Analogue Scale (TS-VAS), a Likert scale (PPBC) and a questionnaire about relevant aspects of the disease in the quality of life (OAB-q): bother, coping, concern, sleep and social interaction. The minimally important difference (MID) for OAB-q is considered to be 10 points; for PPBC it is considered to be one and for TS-VAS a threshold of 1cm as the smallest integer value is utilised for assessing clinical impact.

At baseline patients scored their satisfaction level (TS-VAS) from 5 to 6. After 12 weeks they improved - 1.25 with placebo and -2.0 with mirabegron 50 mg (mean differences 0.76).

With respect to the perception of the disease (PPBC) the patients initially considered that their condition represented minor to moderate problems (baseline values 3.8). The treatment with mirabegron meant an improvement of -0.2 compared to placebo.

With respect to the impact on the quality of life (OAB-q) the greatest effect was seen in the “bother” domain. However, in principle the changes from baseline with respect to placebo for the dosage finally

chosen do not reach the minimal 10-point difference on any OAB-q subscale to be considered clinically meaningful.

With respect to the fact that the modest effect is not translated into a clear perception of improvement by the patients, the CHMP acknowledges that the instruments developed to study Patient related outcomes measure different components and different domains, that some of them are specific while others are overarching in their evaluation and related to a more broad assessment. Taking these observations in mind at least a consistent trend in the majority of the domains would be necessary to conclude on an effect of mirabegron treatment on patient's perception. For mirabegron indeed a trend is seen for most of the domains in all studies. The size effect seems not to be impressive (around 8% versus placebo when the responder rate is considered) but these findings are in line with the modest effect seen on clinical endpoints.

Table 12: Overview of Results for Adjusted Mean Change from Baseline in OAB-q Parameters at the Final Visit, Individual and Pooled Primary Phase 3 Studies, FAS

Endpoint		Mirabegron 50 mg Difference versus Placebo			
		178-CL-046	178-CL-047	178-CL-074	Pooled
Secondary Subjective Endpoints, OAB-q	Symptom Bother Score	-4.7 ***	-6.2 ***	-2.8 *	-4.51 ***
	Total HRQL Score	2.3 *	4.1 **	1.2 P=0.28	2.46 ***
	Coping	2.9 *	4.1 **	1.7 P=0.20	2.88 ***
	Concern	2.6 *	5.3 ***	1.5 P=0.24	2.99 ***
	Sleeping	1.9 P=0.12	4.9 **	0.4 P=0.76	2.24 **
	Social Interaction	1.4 P=0.15	1.4 P=0.19	0.6 P=0.54	1.12 P=0.054

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (Full Analysis Set [FAS]).
For the individual primary studies adjusted mean change from baseline are from an ANCOVA model which included treatment group, gender and geographical region as fixed factors and baseline as a covariate. For the pooled primary studies adjusted mean change from baseline are from an ANCOVA model which included treatment group, gender and study as fixed factors and baseline as a covariate.
A negative change in Symptom Bother Score indicated improvement. A positive change in HRQL Total Score and the subscales of concern, coping, sleeping and social interaction indicated improvement.
P values are from pairwise comparisons versus placebo within the ANCOVA model.
* nominal P value < 0.05; ** nominal P value <0.01; *** nominal P value < 0.001
Source: Study 178-CL-046, Tables 12.3.5.17 and 12.3.5.18; Study 178-CL-047, Tables 12.3.5.17 and 12.3.5.18; Study 178-CL-074, Tables 12.3.5.19 and 12.3.5.20; Response to Day 120 Question 97.

Some reassurance can also be obtained from the analyses of responders conducted where, with different definitions of responders, the responder rate is statistically significantly better (and in a consistent way) for mirabegron than for placebo. This is of greater clinical relevance when more stringent definitions of responder based on predefined minimal important differences are used.

Table 21: Results for Double Responder Analyses for Incontinence and Patient Reported Indices, Pooled Primary Phase 3 Studies, FAS-I

Double Responder Parameters				
Objective Index	**MID in Patient Reported Index**	**Statistical Parameter**	**Placebo**	**Mirabegron 50 mg**
≥ 50% reduction in incontinence episodes per 24 hours	Symptom Bother Score (≥ 10)	n	807	791
		% Responders	39.3%	54.5%
		Difference vs. Placebo (%)	--	15.2%
		95% 2-sided CI for Difference	--	(10.4%, 20.0%)
		Odds Ratio vs. Placebo‡	--	1.87
		95% 2-sided CI for Odds Ratio‡	--	(1.53, 2.29)
		P value‡	--	< 0.001*
≥ 50% reduction in incontinence episodes per 24 hours	Total HRQL Score (≥ 10)	n	806	791
		% Responders	35.1%	46.0%
		Difference vs. Placebo (%)	--	10.9%
		95% 2-sided CI for Difference	--	(6.1%, 15.7%)
		Odds Ratio vs. Placebo‡	--	1.60
		95% 2-sided CI for Odds Ratio‡	--	(1.30, 1.97)
		P value‡	--	< 0.001*
≥ 50% reduction in incontinence episodes per 24 hours	PPBC value (≥ 1)	n	799	776
		% Responders	37.8%	44.6%
		Difference vs. Placebo (%)	--	6.8%
		95% 2-sided CI for Difference	--	(1.9%, 11.6%)
		Odds Ratio vs. Placebo‡	--	1.37
		95% 2-sided CI for Odds Ratio‡	--	(1.11, 1.68)
		P value‡	--	0.003*

Studies included: 178-CL-046, 178-CL-047 and 178-CL-074.
All randomized patients who took at least 1 dose of double-blind study drug and who had a micturition measurement and at least 1 incontinence episode in the baseline diary and at least 1 postbaseline visit diary with a micturition measurement (FAS-I).
A responder for ≥ 50% reduction in incontinence episodes per 24 hours was defined as a patient with a ≥ 50% reduction from baseline to final visit in mean number of incontinence episodes per 24 hours.
A responder for OAB-q parameters was defined as a patient with an improvement from baseline to final visit in HRQL score which was at least as large as the MID (10).
A responder for PPBC was defined as a patient with an improvement from baseline to final visit in PPBC which was at least as large as the MID (1).
--: not applicable; MID: minimally important difference; HRQL: health-related quality of life; PPBC: patient perception of bladder condition.
95% CIs for the difference of the proportions are based on normal approximation.
‡ Odds ratios, corresponding 95% CI and the P value are derived from a logistic regression model including treatment group, gender, study and baseline values for both parameters.
* Statistically significantly superior compared with placebo at the 0.05 level without multiplicity adjustment.
Source: data on file

Table 22: Results for Triple Responder Analyses for Incontinence and Patient Reported Indices, Pooled Primary Phase 3 Studies, FAS-I

Triple Responder Parameters				
Objective Index	**MID for Patient Reported Indices**	**Statistical Parameter**	**Placebo**	**Mirabegron 50 mg**
≥ 50% reduction in incontinence episodes per 24 hours	Symptom Bother Score (≥ 10) and PPBC value (≥ 1)	n	742	716
		% Responders	30.5%	39.5%
		Difference vs. Placebo (%)	--	9.1%
		95% 2-sided CI for Difference	--	(4.2%, 13.9%)
		Odds Ratio vs. Placebo‡	--	1.55
		95% 2-sided CI for Odds Ratio‡	--	(1.24, 1.93)
		P value‡	--	<0.001*
≥ 50% reduction in incontinence episodes per 24 hours	Total HRQL Score (≥ 10) and PPBC value (≥ 1)	n	741	716
		% Responders	28.1%	36.5%
		Difference vs. Placebo (%)	--	8.4%
		95% 2-sided CI for Difference	--	(3.6%, 13.2%)
		Odds Ratio vs. Placebo‡	--	1.51
		95% 2-sided CI for Odds Ratio‡	--	(1.20, 1.90)
		P value‡	--	< 0.001*

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

Long-term efficacy data of mirabegron are based on a primarily aimed safety study. Efficacy outcomes have been measured as secondary endpoints and the main evidence comes from the non-formal comparison between mirabegron (50 mg and 100 mg) and tolterodine. Although the results obtained at 12 months do not suggest a loss of efficacy, the lack of a placebo control arm and the absence of a pre-determined statistical comparison hamper reaching sound conclusions regarding the maintenance of the effect of mirabegron. However in the comparative review from publicly available sources mirabegron does not show a distinct behaviour from other medicinal products approved for that condition (i.e. antimuscarinic drugs). In this respect, comparative effects of mirabegron with tolterodine help to put in context the results as the comparison reveals an effect of similar magnitude both in short and long (52 weeks) term treatment.

2.5.4. Conclusions on the clinical efficacy

As a summary, a consistent effect is observed in favour to mirabegron for both the co-primary and the secondary endpoints that in most cases is statistically significant. The comparison with tolterodine reveals an effect of similar magnitude. In addition, the effect size on incontinence episodes and number of micturitions per day observed in indirect comparisons with antimuscarinics helps put into context the clinical benefit of mirabegron. Therefore, the magnitude of the effect of mirabegron, although modest, can be considered enough to conclude on the clinically meaningful effect of this medicinal product in the treatment of OAB.

2.6. Clinical safety

The clinical development program for mirabegron consisted of studies in 10,552 healthy volunteers, patients with OAB, male patients with lower urinary tract symptoms/bladder outlet obstruction (LUTS/BOO) or patients with type 2 diabetes mellitus. A total of 29 phase 1 studies and 12 phase 2/3 studies (9 in patients with OAB, one in patients with LUTS/BOO and 2 in patients with type 2 diabetes mellitus) have been conducted globally in Europe, United States (US), Canada, Japan, Australia/New Zealand and South Africa. The entire clinical development program is comprised of 1800 volunteers and 8752 patients (8433 patients with OAB) in support of this application. The safety of mirabegron has been investigated in 1462 volunteers in phase 1 studies and 5863 patients (5648 patients with OAB) in the phase 2/3 studies. A total of 622 of the 5648 patients with OAB received mirabegron for at least 1 year. The immediate release (IR) formulation was used for the earlier phase 1 and proof of concept (POC) studies conducted in the clinical development program; all subsequent studies used the oral controlled absorption system (OCAS) formulation.

Patient exposure

Study ID	Placebo	Mirabegron 25mg	Mirabegron 50mg	Mirabegron 100mg	Mirabegron 200mg	Total mirabegron	Tolterodine ER 4mg	Duration
178-CL-046	494		493	496		989	495	12 weeks
178-CL-047	453		442	233		875		12 weeks
178-CL-074	433	432	440			872		12 weeks
178-CL-044	169	169	169	168	167	673	85	12 weeks
178-CL-045	213	210	208	208		626		12 weeks
178-CL-048	380		379			379	378	12 weeks
178-CL-003	19				40	40		12 weeks

178-CL-004	20			40		40		12 weeks
178-CL-008	66			200mg 65	300mg 65	130	64	4 weeks
178-CL-060	65	70	65			135		14 weeks
178-CL-049		812	820			1632	812	12 months
178-CL-051	152	153	50			203		12 months

The Safety Analysis Set consists of all patients who took at least one dose of study drug. Overall, 5863 patients received at least one dose of mirabegron in the phase 2/3 clinical program. This total represents the number of unique patients in the Global Phase 2/3 Population who received mirabegron and includes the following:

4414 patients from the Global OAB 12-week Phase 2/3 Population (including the subset of 2736 patients from the EU/NA OAB 12-week Phase 3 Population);

345 patients from other phase 2 studies in type 2 diabetes mellitus, OAB and LUTS/BOO;

901 patients from the EU/NA Long-term Controlled Population who received mirabegron for the first time in Study 178-CL-049; and 203 patients from the Japan Long-term Uncontrolled Population.

Overall, 5016/5863 (85.6%) patients completed treatment with mirabegron and 847/5863 (14.4%) patients discontinued mirabegron.

The EU/NA Long-term Controlled Population comprises patients that were enrolled in Study 178-CL-049, a 12-month, double-blind phase 3 study with an active-controlled tolterodine comparator arm. Patients who completed Studies 178-CL-046 and 178-CL-047 were allowed to participate in this study after a 30-day washout period; patients naive to the mirabegron program were also allowed to participate. In this study, 812 patients treated with mirabegron 50 mg, 820 patients treated with mirabegron 100 mg and 812 patients treated with tolterodine were randomized into the study and took double-blind study drug.

A total of 629/812 (77.5%) mirabegron 50 mg, 645/820 (78.7%) mirabegron 100 mg and 621/812 (76.5%) tolterodine patients completed double-blind treatment period while 183/812 (22.5%) mirabegron 50 mg, 175/820 (21.3%) mirabegron 100 mg and 191/812 (23.5%) tolterodine patients discontinued from the study.

Adverse events

In the Global OAB 12-week Phase 2/3 Population, the most frequently reported TEAE (by PT) reported in the total mirabegron group were nasopharyngitis (mirabegron: 296/4414 [6.7%]; placebo: 141/2142 [6.6%]; tolterodine: 57/958 [5.9%]), hypertension (mirabegron: 221/4414 [5.0%]; placebo: 107/2142 [5.0%]; tolterodine: 43/958 [4.5%]) and blood glucose increased (mirabegron: 207/4414 [4.7%]; placebo: 115/2142 [5.4%]; tolterodine: 73/958 [7.6%]). One or more drug-related TEAE was reported by 906/4414 (20.5%) mirabegron, 389/2142 (18.2%) placebo and 275/958 (28.7%) tolterodine patients, with similar reporting in each of the mirabegron dose groups. The most frequently reported drug-related TEAE (by PT) in the total mirabegron group were hypertension (mirabegron: 142/4414 [3.2%]; placebo: 63/2142 [2.9%]; tolterodine: 33/958 [3.4%]), dry mouth (mirabegron: 73/4414 [1.7%]; placebo: 37/2142 [1.7%]; tolterodine:100/958 [10.4%]) and

constipation (mirabegron: 68/4414 [1.5%]; placebo: 32/2142 [1.5%]; tolterodine: 21/958 [2.2%]). In the total mirabegron group, the maximum TEAE severity was mild for 36.9%, moderate for 18.0% and severe for 4.3% of patients. The most frequently reported severe TEAE were headache (13/5863 [0.2%]), nasopharyngitis (10/5863 [0.2%]) and supraventricular extrasystoles (10/5863 [0.2%]). TEAE with missing severity (not provided by the study site) were included in the severe category. A total of 38/5863 (0.6%) mirabegron patients reported at least one TEAE with missing severity that were counted as severe. TEAE with missing severity were primarily AE associated with clinically significant changes in ECGs (for which severity was not assessed in Japan studies) or AE associated with clinical laboratory findings.

For placebo, the maximum TEAE severity was mild for 38.3%, moderate for 13.8% and severe for 3.1% of patients; for tolterodine the maximum TEAE severity was mild for 44.7%, moderate for 12.2% and severe for 3.3% of patients. The proportion of patients reporting at least one severe TEAE was similar across dose groups.

Analysis of Adverse Events by Organ System or Syndrome

Cardiovascular System

Hypertension

In the EU/NA OAB 12-week Phase 3 Population, TEAE related to hypertension were similar for the total mirabegron (230/2736 [8.4%]), placebo (117/1380 [8.5%]) and tolterodine (48/495 [9.7%]) groups. The frequency of hypertension TEAE was comparable for mirabegron doses of 50 mg (120/1375 [8.7%]) or 100 mg (58/929 [6.2%]) and was highest in mirabegron 25 mg (52/432 [12.0%]). In the EU/NA Long-term Controlled Population, the occurrence of hypertension TEAE was comparable between mirabegron 50 and 100 mg (89/812 [11.0%] and 83/820 [10.1%]) and tolterodine (86/812 [10.6%]).

QT prolongation or its sequelae

In the Global OAB 12-week Phase 2/3 Population, QTc prolongation-related TEAE were reported in 4/4414 (0.1%) total mirabegron patients, 2/2142 (0.1%) placebo patients and 2/958 (0.2%) tolterodine patients. In the EU/NA Long-term Controlled Population, QTc prolongation-related TEAE were reported in 3/812 (0.4%) mirabegron 50 mg patients, 2/820 (0.2%) mirabegron 100 mg patients and 3/812 (0.4%) tolterodine patients. TEAE in the torsades de pointes/QT prolongation SMQ was reported as SAE for 1/812 (0.1%) patient in the mirabegron 50 mg group (cardiac arrest, ventricular fibrillation and ventricular tachycardia; these concurrent CV events were adjudicated by the Cardiovascular Adjudication Committee for Clinical Trials with Mirabegron as a nonfatal myocardial infarction) and 1/812 (0.1%) patient in the tolterodine group (cardiac arrest, adjudicated by the Cardiovascular Adjudication Committee for Clinical Trials with Mirabegron to ventricular fibrillation).

Cardiac Arrhythmia, Including Tachycardia and Atrial Fibrillation

In the Global OAB 12-week Phase 2/3 Population, TEAE related to rapid pulse rate (cardiac arrhythmia, mostly tachycardia) were more frequently observed in all active treatments (2.4 to 6.6%) than placebo (1.8%). The frequency of TEAE in cardiac arrhythmia was comparable for all mirabegron doses of 100 mg or less (2.4 to 3.1%) and tolterodine (3.1%) and was highest in mirabegron 200 mg (6.6%). In the EU/NA Long-term Controlled Population, the occurrence of TEAE in the cardiac arrhythmia SMQ was comparable between mirabegron 50 and 100 mg (3.9 and 4.1%, respectively) and was less than tolterodine (6.0%). The overall occurrence of tachycardia events either based on TEAE or observations

of pulse rate ≥ 100 bpm captured by patient diary, was 28/812 (3.4%) mirabegron 50 mg, 50/820 (6.1%) mirabegron 100 mg and 55/812 (6.8%) tolterodine patients.

Cardiac Failure

In the Global OAB 12-week Phase 2/3 Population, TEAE of CHF based on the SMQ of cardiac failure occurred in 14/2142 (0.7%), 4/811 (0.5%), 14/2131 (0.7%), 15/1305 (1.1%), and 5/958 (0.5%) patients in the placebo, mirabegron 25, mirabegron 50 mg, mirabegron 100 mg and tolterodine treatment groups, respectively; no events were observed for mirabegron 200 mg. The majority of cardiac failure TEAE were from the higher level term (HLT) of oedema not elsewhere classified (NEC) (29/33 patients in the total mirabegron group). In the EU/NA Long-term Controlled Population, TEAE of CHF based on the SMQ of cardiac failure occurred in 10/812 (1.2%), 6/820 (0.7%) and 9/812 (1.1%) patients for mirabegron 50 mg, mirabegron 100 mg and tolterodine, respectively. The majority of cardiac failure TEAE were from the HLT of oedema NEC (12/16 patients in the total mirabegron group).

Syncope, Postural Hypotension and falls

In the Global OAB 12-week Phase 2/3 Population, one or more syncope, postural hypotension and falls events were reported by 90/4414 (2.0%) mirabegron, 35/2142 (1.6%) placebo and 14/958 (1.5%) tolterodine patients, with no apparent mirabegron dose response. The majority of events were under the category of falls; one or more syncope or postural hypotension events was reported by ≤ 0.1% of patients for both total mirabegron and placebo; there were no events reported with tolterodine. One or more events of falls was reported by 86/4414 (1.9%) mirabegron, 32/2142 (1.5%) placebo and 14/958 (1.5%) tolterodine patients, with no apparent mirabegron dose response. The most common TEAE (by PT) in the total mirabegron group under the category of falls was contusion (mirabegron: 13/4414 [0.3%]); placebo: 8/2142 [0.4%]; tolterodine: 4/958

Serious adverse event / deaths / other significant events

Serious adverse events

In the Global OAB 12-week Phase 2/3 Population, one or more SAE was reported for 77/4414 (1.7%) mirabegron, 38/2142 (1.8%) placebo and 16/958 (1.7%) tolterodine patients, with no apparent mirabegron dose response. The most common SAE in the total mirabegron group were atrial fibrillation (mirabegron: 5/4414 [0.1%]; placebo: 1/2142 [< 0.1%]; tolterodine: 0/958), chest pain (mirabegron: 4/4414 [0.1%]; placebo: 2/2142 [0.1%]; tolterodine: 0/958) and pneumonia (mirabegron: 4/4414 [0.1%]; placebo: 1/2142 [< 0.1%]; tolterodine: 0/958). One or more drug-related SAE was reported by 17/4414 (0.4%) mirabegron, 8/2142 (0.4%) placebo and 7/958 (0.7%) tolterodine patients, with no apparent mirabegron dose response. The most common drug-related SAE in the total mirabegron group was atrial fibrillation (mirabegron: 3/4414 [0.1%]); there were no SAE of atrial fibrillation for placebo or tolterodine patients In the EU/NA Long-term Controlled Population, one or more SAE was reported by 93/1632 (5.7%) mirabegron patients (mirabegron 50 mg: 42/812 [5.2%]; mirabegron 100 mg: 51/820 [6.2%]) and 44/812 (5.4%) tolterodine patients. The most common SAE in the total mirabegron group were osteoarthritis (mirabegron: 3/1632 [0.2%]; tolterodine: 1/812 [0.1%]) and cerebrovascular accident (mirabegron: 3/1632 [0.2%]; tolterodine: 1/812 [0.1%]). A total of 11/820 (1.3%) patients in the mirabegron 100 mg group had one or more SAE in the neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC; 1/812 (0.1%) in the mirabegron 50 mg group and 4/812 (0.5%) in the tolterodine group had SAE in that SOC.

Deaths

There were 11 deaths in the mirabegron program, including 2 deaths in the ongoing 178-CL-090 study (one death on blinded treatment and one death that occurred prior to randomization). Nine deaths occurred in patients participating in completed trials (5 patients treated with mirabegron, one treated with placebo and 3 treated with tolterodine). All deaths were adjudicated for potential inclusion as a cardiovascular death by the Cardiovascular Adjudication Committee. The following is a brief listing of all 11 deaths presented by assigned dose group.

Table 26 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					
[178-CL-047, U00016176141] 66/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
[178-CL-049, 1530-6120] 64/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	
[178-CL-049, 3034-2380] 72/Female Mirabegron 50 mg	Cardiac failure (cardiac failure)	190/190 (190)	190	Not related	CV death
[178-CL-049, 3063-3438]† 27/Female Mirabegron 50 mg	Completed suicide (suicide patient)	359/359 (267 E)	359	Possible	Non-CV event
[178-CL-051, S01503] 59/Female Mirabegron 50 mg/100 mg	Aortic dissection (aortic dissection)	237/237 (224)	237	Not related‡	CV death
Placebo					
[178-CL-047, U00015976697] 76/Female	Cardiac arrest (Cardiac arrest)	142/142 (86)	142	Not related	CV death
Tolterodine ER 4 mg					
[178-CL-046, 3105-1598] 74/Male	Ruptured cerebral aneurysm (rupture of brain aneurysm / cerebral aneurysm)	68/70 (60)	70	Possible	CV death
[178-CL-049, 1838-6486] 57/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
[178-CL-049, 2190-6983] 68/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) 178-CL-090, 90724 55/Female	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
Treatment Group Blinded					
(ongoing study) 178-CL-090, 90701 57/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

Overall, mortality per 1000 patients years of mirabegron exposure was comparable to placebo and tolterodine, except the mirabegron/tolterodine group in the EU/NA Long-term Controlled Population was higher than mirabegron alone (6.4 vs 2.5, mortality per 1000 patient-years of exposure). Of the 5 deaths that occurred in the EU/NA Long-term Controlled Population, 3 patients received mirabegron and 2 patients received tolterodine at the time of death. The 2 patients who received tolterodine had prior exposure to mirabegron in a previous study.

Laboratory findings

Haematology

Across populations, there were 3/5863 (0.1%) mirabegron patients with a SAE from the SOC of Blood and Lymphatic System Disorders.

Safety analyses showed a reduction in the number of lymphocytes and neutrophils, and a positive correlation with mirabegron dose was observed.

In the EU/NA Long-term Controlled Population, the frequency of patients with clinical threshold of grade 2 lymphocytes was higher for the mirabegron 100 mg group (25/800 [3.1%]) compared with the mirabegron 50 mg group (14/792 [1.8%]) and the tolterodine group (11/790 [1.4%]), summarized in the table below [Module 5.3.5.3 ISS, End-of-Text Table 7.7.2].

Patients with Clinical Thresholds for Lymphocytes, EU/NA Long-term Controlled Population

Laboratory Test (Unit)/Criteria n/n (%) of Patients	Mirabegron		Tolterodine ER 4 mg (n = 812)
	50 mg (n = 812)	100 mg (n = 820)	
Lymphocytes (10^6/L)			
Grade 2 (≥ 500 to < 800)	14/792 (1.8%)	25/800 (3.1%)	11/790 (1.4%)
Grade 3 (≥ 200 to < 500)	2/792 (0.3%)	1/800 (0.1%)	2/790 (0.3%)

Study included: 178-CL-049

Patients with at least 1 post-baseline measurement within 10 days of the last dose of study drug are included.

ER: extended release; EU/NA: Europe, North America and Australia (for Study 178-CL-049, also includes New Zealand and South Africa)

Source: Module 5.3.5.3 Integrated Summary of Safety, Table 7.7.2.

Changes in haematological counts in the Phase 2/3 OAB population view were modest and transient and even being more apparent with 100 mg dose, these changes were quantitatively limited. Admittedly, the fact that a group of patients receiving 100 mg (two times the proposed dose) achieved the clinical threshold of grade 2 lymphocytes still represents an object of concern. The Applicant has attributed this fact to presence of decreased (or borderline) values at baseline for a number of patients. This justification dose not rule out a real relationship, mainly when this feature is also detected in the long term safety population.

In summary, whereas data for mirabegron 50 mg do not suggest being object of concern for lymphocytes a potential effect (at least with higher doses) cannot be considered totally discarded.

Chemistry

Liver

Overall, 1/5860 (< 0.1%) one mirabegron patient experienced a PCS hepatic chemistry laboratory abnormality of ALT and/or AST > 3 x ULN and total bilirubin > 2 x ULN and ALP < 2 x ULN on the same date; the results are the same when values within 3 days are considered. Two patients were identified as having 3 fold or more transaminase elevation combined with 2 fold or more bilirubin elevation. One patient in the EU/NA Long-term Controlled Population had 3 fold or more transaminase elevation combined with 2 fold or more bilirubin elevation Study 178-CL-049].

In the Global OAB 12-week Phase 2/3 Population, one or more hepatotoxicity TEAE was reported by 242/4414 (5.5%) mirabegron, 121/2142 (5.6%) placebo and 78/958 (8.1%) tolterodine patients. A total of 3 patients (one each in the mirabegron 25 mg, mirabegron 50 mg and tolterodine groups)

experienced hepatotoxicity SAE. The mirabegron 25 mg patient experienced an SAE of liver function test abnormal, the mirabegron 50 mg patient experienced an SAE of hepatic enzyme increased and the tolterodine patient experienced an SAE of hepatitis. In the EU/NA Long-term Controlled Population, hepatotoxicity was reported as a TEAE for 36/1632 (2.2%) mirabegron patients (tolterodine: 15/812 [1.8%]), from laboratory data for 37/1632 (2.3%) mirabegron patients (tolterodine: 14/812 [1.7%]) and both as a TEAE and from laboratory data for 19/1632 (1.2%) mirabegron patients (tolterodine: 7/812 [0.9%]).

Renal

A total of 3 mirabegron 25 mg patients and one mirabegron 200 mg patient had a potentially clinically significant increase in serum creatinine (> 177 mcmol/L) on at least one measurement. For all 3 patients, the potentially clinically significant value for creatinine occurred on a single occasion. These patients had serum creatinine levels above the ULN at baseline and throughout the study. None of the 3 patients experienced a TEAE related to abnormal renal function. For BUN, the frequency of patients with potentially clinically significant increase in BUN (> 12.5 mmol/L) was comparable across treatment groups

Glucose and HbA1c (Endocrine and Metabolic Disorders)

Endocrine and metabolic disorders were assessed separately as AE of interest in the mirabegron development program primarily because of the theoretical potential for beta 3-AR to influence metabolic function, inclusive of glucose regulation. The early clinical development of mirabegron included 2 randomized, placebo-controlled, 12-week phase 2a POC studies evaluating mirabegron in the treatment of diabetes mellitus. Study 178-CL-003 examined the effect of placebo and mirabegron administered in addition to diet and exercise for 12 weeks in the treatment of 59 patients with type 2 diabetes mellitus. Mirabegron was administered as an IR formulation given once daily in the morning with 3 escalating dose levels (60 mg, 130 mg and 200 mg). The primary endpoint of the study was the change from baseline in HbA1c. Fasting blood glucose values were measured throughout the study and showed no difference between the change from baseline to final visit in the mirabegron (0.34 mmol/L) and placebo (0.32 mmol/L) treatment groups. There were no reports of hypoglycaemia in this study.

Study 178-CL-004 examined the effect of placebo and mirabegron administered in addition to metformin, diet and exercise for 12 weeks in the treatment of 60 patients with type 2 diabetes mellitus. Mirabegron was administered as an IR formulation given once daily in the AM with 3 escalating dose levels (60 mg, 130 mg and 200 mg). The primary endpoint of the study was the change from baseline in HbA1c. Fasting blood glucose values were measured throughout the study and showed no difference between the change from baseline to final visit in the mirabegron + metformin (0.88 mmol/L) and placebo + metformin (0.87 mmol/L) treatment groups. There were no observations of hypoglycaemic events in this study.

The frequency of hypoglycaemia and hyperglycaemia TEAE and laboratory measurements of blood glucose and HbA1c in the Global OAB 12-week Phase 2/3 Population and in the EU/NA Long-term Controlled Population were similar across treatment groups. In the Global OAB 12-week Phase 2/3 Population, the frequency of hypoglycaemia was reported by 31/4414 (0.7%) mirabegron, 19/2142 (0.9%) placebo and 10/958 (1.0%) tolterodine patients. No patients in the EU/NA Long-term Controlled Population reported a hypoglycaemia TEAE. In the Global OAB 12-week Phase 2/3 Population, one or more hyperglycaemia TEAE was reported by 249/4414 (5.6%) mirabegron, 134/2142 (6.3%) placebo and 85/958 (8.9%) tolterodine patients. In the EU/NA Long-term Controlled Population, one or more hyperglycaemia TEAE was reported by 30/1632 (1.8%) mirabegron patients (mirabegron 50 mg: 16/812 [2.0%]; mirabegron 100 mg: 14/820 [1.7%]) and 13/812 (1.6%)

tolterodine patients. No patient reported a hypoglycaemia SAE, hyperglycaemia SAE or hypoglycaemia TEAE leading to permanent discontinuation of study drug. In the Global OAB 12-week Phase 2/3 Population, one patient in the mirabegron 25 mg group reported a hyperglycaemia TEAE (blood glucose increased) that led to permanent discontinuation of study drug.

Thyroid function

Two thyroid function-related serious adverse events were reported in the mirabegron clinical program (one with mirabegron 100 mg and one with tolterodine).

Vital signs

Pulse rate

- Mirabegron administered at the proposed therapeutic dose of 50 mg once daily in the 12-week studies was associated with an approximately 1 bpm increased adjusted mean change from baseline pulse rate compared with placebo. The adjusted mean difference vs placebo for change from baseline pulse rate in the EU/NA OAB 12-week Phase 3 Population receiving mirabegron 25, 50 and 100 mg and tolterodine was 0.9, 1.0, 1.9 and 1.0 bpm for AM measurements and 0.6, 1.0, 2.3 and 2.1 bpm for PM measurements.
- In the EU/NA OAB Phase 3 Population, the adjusted mean change from baseline pulse rate following mirabegron at doses of 50 to 100 mg once daily was similar to or less than the adjusted mean change from baseline pulse rate following tolterodine in the long term study. The adjusted mean change from baseline pulse rate in the EU/NA Long-term Controlled Population for the mirabegron 50 mg, 100 mg and tolterodine groups was 0.9, 1.6 and 1.5 bpm for AM measurements and 0.4, 1.3 and 1.9 bpm for PM measurements.
- Categorical increases in pulse rate in the EU/NA OAB 12-week Phase 3 Population were noted more frequently at various cut-points with mirabegron than with placebo. Mirabegron 25 and 50 mg were roughly comparable to tolterodine while mirabegron 100 mg demonstrated more outliers at various cut-points than tolterodine. In the EU/NA Long-term Controlled Population, the proposed therapeutic dose of 50 mg showed fewer outliers at the various cut-points than either tolterodine or mirabegron 100 mg.
- TEAE related to rapid pulse rate (cardiac arrhythmia, mostly tachycardia) were more frequently observed in all active treatments (2.4 to 6.6%) than placebo (1.8%) in the Global OAB 12-week Phase 2/3 Population. The frequency of such events was roughly comparable for all mirabegron doses of 100 mg or less (2.4 to 3.1%) and tolterodine (3.1%). In the EU/NA Long-term Controlled Population, the occurrence of such events was comparable between mirabegron 50 and 100 mg (3.9 and 4.1%, respectively) and was less than tolterodine (6.0%).
- The overall frequency of atrial fibrillation TEAE was low (0.2%, 0.2%, 0.4%, 0.5%, 0.6% and 0.6% for placebo, mirabegron 25, 50, 100 and 200 mg, and tolterodine, respectively) and comparable for mirabegron and tolterodine in the Global OAB 12-week Phase 2/3 Population. In the EU/NA Long-term Controlled Population, the overall frequency of atrial fibrillation TEAE was low (0.7%, 0.5% and 0.9% for mirabegron 50 and 100 mg and tolterodine, respectively) and comparable for the mirabegron and tolterodine groups.
- Female patients demonstrated a generally higher increase in pulse rate compared with male patients, consistent with the approximately 40 to 50% increased exposure in female patients, although this finding was inconsistent across treatment groups and AM/PM measurements. In patients who received the proposed mirabegron therapeutic dose of 50 mg, pulse rate changes from baseline compared with placebo were approximately 1 bpm or less and pulse rate changes

from baseline were similar to those in patients who received tolterodine, in both the 12-week studies and the long-term study, in both genders.

- Overall data suggest a greater effect of mirabegron on pulse rate in younger compared with older patients, although this finding was inconsistent. For the 12-week studies, there were no clear trends observed in change from baseline to final visit in pulse rate for patients < 65 years vs. ≥ 65 years in any treatment group, while in the long-term study, changes from baseline AM and PM pulse rate were greater in patients < 65 years of age than in patients ≥ 65 years of age. Pulse rate changes in the mirabegron 50 mg and 100 mg groups were similar or less than the changes in the tolterodine group in both age groups. In an additional analysis, stratifying patients into < 45 years, ≥ 45 to < 65 years and ≥ 65 years of age, change from baseline and difference vs placebo in change from baseline were generally smaller in older compared with younger patients receiving mirabegron, with the greatest change generally seen in patients < 45 years of age in the 12-week studies, while in the long-term study, change from baseline for pulse rate was small and similar in older and younger patients. Patients who received mirabegron 50 mg, the proposed therapeutic dose, had a difference vs placebo in change from baseline pulse rate of approximately 1 bpm or less in all 3 age categories, except for a 3 bpm increase in PM but not AM pulse rate for patients < 45 years of age in the 12-week studies. Pulse rate changes in patients who received mirabegron 50 mg were similar to those in patients who received tolterodine, in both the 12-week studies and the long-term study in all 3 age categories. This included greater increases in the placebo-difference change from baseline in PM but not AM pulse rate for patients < 45 years of age in the 12-week studies.
- Overall, the increase in pulse rate in the OAB population associated with the proposed therapeutic mirabegron dose of mirabegron 50 mg was approximately 1 bpm, similar to tolterodine, and did not result in more outliers or tachycardia-related AE than observed with tolterodine.

Blood Pressure

- Mirabegron administered at the proposed therapeutic dose of 50 mg once daily was associated with an approximately 1 mm Hg or less adjusted mean difference for change from baseline SBP/DBP compared with placebo. The adjusted mean difference vs placebo for change from baseline SBP in the EU/NA OAB 12-week Phase 3 Population in mirabegron 25, 50 and 100 mg and tolterodine was -0.5, 0.6, 0.4 and -0.1 mm Hg for AM measurements and -1.0, 0.5, 0.9 and -0.0 mm Hg for PM measurements. The adjusted mean difference vs placebo for change from baseline DBP in the EU/NA OAB 12-week Phase 3 Population in mirabegron 25, 50 and 100 mg and tolterodine was -0.1, 0.4, 0.2 and 0.7 mm Hg for AM measurements and -0.3, 0.4, 0.5 and 1.0 mm Hg for PM measurements.
- In the EU/NA Long-term Controlled Population, the adjusted mean changes from baseline SBP and DBP following mirabegron 50 mg, mirabegron 100 mg and tolterodine were generally similar. The adjusted mean change from baseline for SBP in mirabegron 50 and 100 mg and tolterodine was 0.2, 0.4 and -0.5 mm Hg for AM measurements and -0.3, 0.1 and -0.0 mm Hg for PM measurements, respectively. The adjusted mean change from baseline for DBP in mirabegron 50 and 100 mg and tolterodine was -0.3, 0.4 and 0.1 mm Hg for AM measurements and -0.0, 0.1 and 0.6 mm Hg for PM measurements, respectively.
- Categorical increases from baseline in SBP and DBP for the EU/NA OAB 12-week Phase 3 and the EU/NA Long-term Controlled populations were generally comparable across all treatment groups.
- TEAE related to hypertension were similar for the total mirabegron (230/2736 [8.4%]), placebo (117/1380 [8.5%]) and tolterodine (48/495 [9.7%]) groups in the EU/NA OAB 12-week Phase 3

Population. The frequency of such events was comparable for mirabegron 50 mg (120/1375 [8.7%]) or 100 mg (58/929 [6.2%]) and was highest in mirabegron 25 mg (52/432 [12.0%]). In the EU/NA Long-term Controlled Population, the occurrence of such events was comparable between mirabegron 50 and 100 mg (89/812 [11.0%] and 83/820 [10.1%]) and tolterodine (86/812 [10.6%]).

- Male patients had generally larger changes from baseline in adjusted mean difference vs placebo in SBP/DBP in the 12-week studies and the adjusted mean changes in SBP/DBP in the long-term study, although this finding was inconsistent across treatment groups and AM/PM measurements.
- Overall data suggested a greater effect of mirabegron on SBP/DBP in younger compared with older patients, although this finding was inconsistent. No consistent trend of SBP/DBP change was evident in patients < 65 years of age compared with patients ≥ 65 years of age. In the 12-week studies, changes in adjusted mean difference vs placebo were generally similar in both age groups. In the long-term study, adjusted mean changes in AM/PM SBP were larger in patients ≥ 65 years, while changes in AM/PM DBP were larger in patients < 65 years of age. This trend in the long-term study was seen in both the mirabegron and tolterodine treatment groups. In an additional analysis, stratifying patients into < 45 years, ≥ 45 to < 65 years and ≥ 65 years of age, change from baseline and adjusted mean difference vs placebo in change from baseline SBP/DBP was generally smaller in older compared with younger patients who received mirabegron, with the greatest change generally seen in patients < 45 years of age. This trend was also seen in the adjusted mean change from baseline SBP/DBP measurements in the long-term study. Patients who received mirabegron 50 mg, the proposed therapeutic dose, had an adjusted mean difference vs placebo and an adjusted mean change from baseline SBP/DBP of approximately 1 mm Hg or less in the 12-week studies and the long-term study, respectively, comparable to tolterodine in both younger and older patients.
- Objective blood pressure decreases and/or hypotension were similar across treatment groups

ECGs

A brief summary of both the first and second TQT studies [Study 178-CL-037 and Study 178-CL-077, respectively] and events potentially suggestive of QTc interval prolongation in the integrated safety database are presented below. Excluding intervals related to rate (HR, RR interval) and QT, there are generally no trends observed in the remaining ECG intervals (QRS and PR) across treatments and subgroups in either the EU/NA OAB 12-week Phase 3 Population or the EU/NA Long-term Controlled Population. The only exceptions are small and inconsistent baseline to end point changes of the PR interval (3.8 msec or less) observed for the mirabegron 100 mg treatment group. These trends were more apparent in the EU/NA OAB 12-week Phase Population than in the EU/NA Long-term Controlled Population and were more apparent in male than female patients and patients ≥ 65 years of age vs. those < 65 years of age. This mean baseline to end point change generally did not manifest itself in more outliers based on maximum PR interval for the mirabegron 100 mg dosage group. A slightly higher frequency of 1st degree atrio-ventricular (AV) block was observed among ECG treatment-emergent abnormalities for the mirabegron 100 mg treatment group (2.9% vs. 0.2% to 2.4% for the other treatment groups) in the EU/NA OAB 12-week Phase 3 Population, but this tendency was not replicated in the EU/NA Long-term Controlled Population.

Study 178-CL-037 evaluated the effects of 100 mg once daily and 200 mg once daily oral doses of mirabegron OCAS at steady state on the individually corrected QT interval (QTcI) compared with placebo. A single 400 mg dose of moxifloxacin or matching moxifloxacin placebo was incorporated into the study design to evaluate assay sensitivity. The study included 25 healthy male and 23 healthy female volunteers.

Overall, the pharmacodynamic results demonstrated that mirabegron prolongs QT interval dose dependently, with a differential effect in males and females. Reanalysis of QT data revealed the following:

- Reduced variability, increased effect size relative to the original analysis, and larger effects overall and by gender (although the dose-dependency and gender differences remained consistent)
- Confirmation of the effect of mirabegron on QT interval with mirabegron 200 mg
- A statistically significant effect of mirabegron 100 and 200 mg on QT interval in females

Study 178-CL-077 was a double-blind, randomized, placebo- and active-controlled, parallel crossover, phase 1 TQT study. Healthy volunteers who were randomized to 8 treatment sequences (10 days of mirabegron 50 mg, mirabegron 100 mg or mirabegron 200 mg, or 9 days of placebo followed by a single dose moxifloxacin 400 mg).

- The upper bound of the 1-sided 95% CI was less than 10 msec at all evaluated time points for all subjects receiving the therapeutic dose of *mirabegron 50 mg*. In the mirabegron 50 mg group, the largest treatment effect occurred at 3 to 4 hours with a mean (upper bound of the 1-sided 95% CI) treatment difference of 3.66 (5.16) msec in all volunteers, 4.49 (6.81) msec in females and 2.96 (5.00) msec in males.
- The upper bound of the 1-sided 95% CI was also less than 10 msec at all evaluated time points for all subjects receiving the supratherapeutic dose of *mirabegron 100 mg* that is associated with an approximately 2.9- and 2.6-fold increase in Cmax and AUCtau relative to mirabegron 50 mg. In the mirabegron 100 mg group, the largest treatment effect occurred at 4-5 hours with a mean (upper bound of the 1-sided 95% CI) treatment difference of 6.19 (7.65) msec in all volunteers, 7.70 (9.72) msec in females and 4.63 (6.45) msec in males.

Mirabegron prolonged the QTc interval at the supratherapeutic dose of 200 mg, a dose which increased Cmax and AUCtau by approximately 8.4- and 6.5-fold relative to mirabegron 50 mg. In the mirabegron 200 mg group, the largest QTcI treatment effect occurred at 4 to 5 hours with a mean (upper bound of the 1-sided 95% CI) treatment difference of 8.21 (9.99) msec in all volunteers, 10.42 (13.44) msec in females and 7.33 (9.42) msec in males. The increased QTc in female volunteers was consistent with their approximately 30% to 60% higher mean Cmax and 40% to 50% higher mean AUCtau of mirabegron compared to male volunteers.

Phase 2/3 results in OAB patients

The following key conclusions were noted for QTc in a subset of phase 2/3 studies in OAB patients:

- All mirabegron treatment groups had a decrease in mean QTcF from baseline to 12 weeks of approximately 2 msec; the decrease observed for mirabegron 200 mg was slightly larger at 4.4 msec.
- There was a higher occurrence of maximum QTcF measurements > 450 msec in the mirabegron 200 mg group compared with placebo and compared with the lower mirabegron dose groups; the same trends were not observed for mirabegron 200 mg for maximum changes in baseline QTcF ≥ 30 msec. QTc measurements exceeding these thresholds occurred with similar frequency in patients receiving mirabegron 25, 50 and 100 mg and placebo.
- Maximum QTcF values > 450 msec occurred more often in female than male patients with a comparable frequency in all treatment groups except for mirabegron 200 mg. No differences were

observed between male and female patients in the frequency of maximum change from baseline in QTcF of ≥ 30 msec.

- Elderly OAB patients (≥ 65 years) had a higher frequency of maximum QTcF values > 450 msec; the frequency of maximum changes from baseline > 30 msec were similar for patients < 65 years and ≥ 65 years.
- There were few SAE, TEAE and CV adjudicated events that involved QT prolongation or ventricular arrhythmias and there was no difference between the frequency of these events in the mirabegron, placebo, and tolterodine groups. No events of torsades de pointes were reported in any patient in the mirabegron clinical program.

Summary of ECG Data

- At the proposed therapeutic dose, mirabegron 50 mg did not have a clinically meaningful treatment effect on QTc interval in females or males.
- Prolongation of the QT interval was seen for mirabegron in females at a supratherapeutic dose of 200 mg and this treatment effect could be attributed to higher mirabegron exposure in females. A 200 mg dose of mirabegron is associated with an 8.4- and 6.5-fold increased Cmax and AUCtau compared with a therapeutic 50 mg dose.
- In OAB patients, there was a higher frequency of maximum QTcF measurements > 450 msec in the mirabegron 200 mg group compared with placebo and compared with the lower mirabegron dose groups. Female patients had higher frequency of maximum QTcF values > 450 msec than male patients; however, the frequency in mirabegron dose groups lower than 200 mg was similar to that observed in placebo.

Post-void residual Volume (PVR)

There were no clinically meaningful differences between treatments groups in mean changes from baseline to any post-baseline visit in PVR volume or in overall categorical shifts from baseline to post-baseline PVR volume. Few patients had shifts from a baseline PVR volume < 150 mL to a PVR volume ≥ 150 mL to < 300 mL post-baseline (54/4482 [1.2%] for total mirabegron in the subset of the Global Phase 2/3 Population (all studies except Studies 178-CL-003, 178-CL-004 and 178-CL-049; 0.4% to 1.1% across all treatment groups for the Global OAB 12-week Phase 2/3 Population) or from any baseline value to a PVR volume of ≥ 300 mL post-baseline, with a comparable frequency across treatment groups. In a urodynamic study in male patients with LUTS/BOO, mirabegron 50 mg and 100 mg did not affect detrusor pressure at maximum urinary flow rate or urinary flow rate in men with LUTS and BOO. Two TEAE of urinary retention were reported in this study; one in the placebo group and one in the mirabegron 100 mg dose group. While the urinary retention event in the placebo-treated patient required catheterization and the event resolved without invasive intervention in the mirabegron 100 mg-treated patient, neither event was reported as an SAE. These events are expected in the patient population with documented BOO, as was evaluated in this study. A statistically significant increase in PVR volume was observed at week 12 with mirabegron 100 mg treatment that is considered not clinically meaningful; no changes in PVR volume were observed with mirabegron 50 mg; this increase was < 30 mL.

Immunological events

A total of 34 plausible hypersensitivity reactions were reported in mirabegron patients during the clinical development (23 in the short-term trials and 11 during the long term trials). Nonimmediate, primarily cutaneous hypersensitivity reactions of urticaria, leukocytoclastic vasculitis, rash, pruritus,

purpura, and lip and eyelid edema were reported including SAE of cutaneous vasculitis (1 patient) and urticaria (2 patients). An association of mirabegron, particularly at doses > 100 mg, with nonimmediate, primarily cutaneous reactions cannot be ruled out.

Safety in special populations

Gender

The overall frequency of TEAE was generally higher in female patients compared with male patients across treatment groups. In the Global OAB 12-week Phase 2/3 Population and the EU/NA Long-term Controlled Population, although TEAE were generally reported more frequently in female patients compared with male patients across treatment groups, the difference from placebo or from tolterodine was generally similar between genders. Hypertension was the most frequently occurring TEAE in males and females in the total mirabegron group and reported with a greater frequency in males compared with females. The frequency of SAE and TEAE leading to permanent discontinuation of study drug was similar in male and female patients across treatment groups. Female patients had generally larger changes in pulse rate consistent with their higher exposure following oral administration of mirabegron in the 12-week phase 3 studies, although this finding was inconsistent across treatment groups and AM/PM measurements.

Age Group 1 (< 65 years, ≥ 65 years)

In the 12-week and long-term studies, the overall frequency of TEAE was generally higher in patients ≥ 65 years of age compared with patients < 65 years of age across treatment groups. The frequency of SAE and TEAE leading to permanent discontinuation of study drug was lower in patients < 65 years of age compared with patients ≥ 65 years of age across treatment groups. No consistent trend of SBP/DBP change was evident in patients < 65 years of age compared with patients ≥ 65 years of age. In the 12-week studies, mean changes were generally similar in both age groups. In the long-term study, changes in morning and evening SBP were larger in patients ≥ 65 years and changes in AM and PM DBP were larger in patients < 65 years of age. This trend in the long-term study was seen in both the mirabegron and tolterodine treatment groups.

Age Group 2 (< 75 years, ≥75 years)

In the Global OAB 12-week Phase 2/3 Population, the frequency of TEAE was similar in patients < 75 years of age and patients 75 years of age for the total mirabegron treatment group, but was numerically higher for patients ≥75 years in the tolterodine group. In the EU/NA Long-term Controlled Population, the frequency of TEAE was numerically higher in patients ≥ 75 years of age compared with patients < 75 years of age across treatment groups. In the 12-week and long-term studies, the frequency of SAE and TEAE leading to permanent discontinuation of study drug was generally higher in patients ≥ 75 years of age compared with patients < 75 years of age for the total mirabegron group.

Safety related to drug-drug interactions and other interactions

Tamsulosin

The cardiovascular results from Study 178-CL-080 do not suggest a clinically relevant pharmacodynamic interaction between tamsulosin and mirabegron. In addition, combination treatment of mirabegron and tamsulosin did not appear to affect the safety profiles of either of these drugs. The higher exposure to tamsulosin following combination treatment of mirabegron and tamsulosin HCl 0.4 mg is not reflected by an overt change in safety profile of tamsulosin. Similarly, the reduction of

exposure to mirabegron with combination administration of tamsulosin and mirabegron is not reflected by a change in safety profile in mirabegron. This is supported by the number of AE related to orthostasis showing a numerically similar frequency across treatments. There were also no SAE and no syncope events in either treatment arm during this study.

CYP3A4 and/or P-gp Inhibitors [Study 178-CL-036]

Administration of mirabegron (100 mg single dose) with the potent cytochrome P450 (CYP) 3A4 and P glycoprotein (P-gp) inhibitor ketoconazole (400 mg daily) in healthy volunteers resulted in higher mirabegron exposure (45% higher Cmax and 81% higher AUCinf).

CYP3A4 and/or P-gp Inducers [Study 178-CL-070]

The effects of rifampin 600 mg once daily on the pharmacokinetics of a single 100 mg dose of mirabegron were investigated. A 35% decrease in Cmax and a 44% decrease in AUCinf of mirabegron were observed. No dose adjustment is needed for mirabegron when administered with therapeutic doses of rifampin or other potent CYP3A4 or P-gp inducers.

CYP2D6 Substrates [Study 178-CL-005 and 178-CL-058]

In healthy volunteers, the inhibitory potency of mirabegron towards CYP2D6 is moderate and the CYP2D6 activity recovers over a period of 15 days. Multiple once daily dosing of 160 mg mirabegron IR resulted in a 90% increase in Cmax and a 229% increase in AUCinf of a single 100 mg dose of metoprolol. Multiple once daily dosing of mirabegron 100 mg resulted in a 79% increase in Cmax and a 241% increase in AUCinf of a single 50 mg dose of desipramine. At 15 days after the last mirabegron dose, no relevant effect on the pharmacokinetics of desipramine was measured. Drugs that are CYP2D6 substrates are not expected to require dose adjustment when co-administered with mirabegron. Caution is advised if mirabegron is co-administered with medication with a narrow therapeutic index and significantly metabolized by CYP2D6.

Digoxin [Study 178-CL-059]

With multiple dosing of mirabegron 100 mg once daily the Cmax of a single 0.25 mg dose of digoxin increased 29%, while AUClast increased 27%. For patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should initially be prescribed. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect.

Solifenacin [Study 178-CL-069]

Co-administration of solifenacin (10 mg) with mirabegron (100 mg once daily) was evaluated in healthy volunteers. Mean mirabegron Cmax was not impacted by concomitant solifenacin; however, mean solifenacin Cmax and AUCinf were increased by 23% and 26%, respectively with concomitant mirabegron. No dose adjustment is necessary for mirabegron when administered with solifenacin.

Oral Contraceptives [Study 178-CL-068]

With multiple dosing of mirabegron 100 mg once daily, no changes in the plasma concentrations of combined oral contraceptives (ethinyl estradiol/levonorgestrel; both CYP3A4 substrates) were observed.

Warfarin [Study 178-CL-040]

With multiple dosing of mirabegron 100 mg once daily, no effects on the pharmacokinetics of R-warfarin (substrate for CYP3A4) or S-warfarin (substrate for CYP2C9) or on prothrombin time were observed. No dose adjustment is necessary for warfarin when co-administered with mirabegron.

CYP2D6 Inhibitors [Study 178-CL-005]

In poor metabolisers for CYP2D6, used as a surrogate for CYP2D6 inhibition, mean Cmax and AUCinf of a single 160 mg dose of mirabegron IR were 14% and 19% higher than in extensive metabolizers, indicating that CYP2D6 genetic polymorphism has minimal impact on the mean plasma exposure to mirabegron. The interaction of mirabegron with a known CYP2D6 inhibitor was not studied. No dose adjustment is needed for mirabegron when administered with CYP2D6 inhibitors or in patients who are CYP2D6 poor metabolisers.

Metformin [Study 178-CL-006 and 178-CL-004]

Co-administration of metformin (500 mg twice daily) with mirabegron IR (160 mg once daily) resulted in an approximate 20% decrease in mean Cmax and AUC of mirabegron. Multiple doses of mirabegron IR had no relevant effect on AUCtau and Cmax of metformin. No dose adjustment is needed when mirabegron is coadministered with therapeutic doses of metformin. In a 12-week study, in patients with diabetes mellitus, daily doses of mirabegron IR (up to 200 mg) in combination with metformin therapy had no effect on fasting plasma glucose levels or HbA1c in this patient population.

Discontinuation due to adverse events

In the Global Phase 2/3 Population, one or more TEAE leading to permanent discontinuation of study drug was reported in 285/5863 (4.9%) mirabegron patients. The most common TEAE (by preferred term) leading to permanent discontinuation of study drug were headache (20/5863 0.3%]), constipation (17/5863 [0.3%]) and hypertension (16/5863 [0.3%]). One or more drug-related TEAE leading to permanent discontinuation of study drug was reported in 183/5863 (3.1%) mirabegron patients. The most common drug-related TEAE (by PT) leading to permanent discontinuation of study drug were headache (18/5863 [0.3%]), constipation (14/5863 [0.2%]) and hypertension (14/5863 [0.2%]) One or more SAE leading to permanent discontinuation of study drug was reported in 61/5863 (1.0%) mirabegron patients. The most common SAE leading to permanent discontinuation of study drug were atrial fibrillation (3/5863 [0.1%]), liver function test abnormal (3/5863 [0.1%]) and prostate cancer (3/5863 [0.1%]).

In the EU/NA Long-term Controlled Population, one or more TEAE leading to permanent discontinuation of study drug was reported in 98/1632 (6.0%) mirabegron patients (mirabegron 50 mg: 48/812 [5.9%]; mirabegron 100 mg: 50/820 [6.1%]) and 46/812 (5.7%) tolterodine patients. The most common TEAE (by preferred term) leading to permanent discontinuation of study drug in the total mirabegron group were constipation (mirabegron: 9/1632 [0.6%]; tolterodine: 0/812), headache (mirabegron: 9/1632 [0.6%]; tolterodine: 3/812 [0.4%]), dizziness (mirabegron: 6/1632 [0.4%]; tolterodine: 0/812) and hypertension (mirabegron: 6/1632 [0.4%]; tolterodine: 3/812 [0.4%]). One or more drug-related TEAE leading to permanent discontinuation of study drug was reported in 64/1632 (3.9%) mirabegron patients (mirabegron 50 mg: 35/812 [4.3%]; mirabegron 100 mg: 29/820 [3.5%]) and 31/812 (3.8%) tolterodine patients. The most common drug-related TEAE (by preferred term) leading to permanent discontinuation of study drug in the total mirabegron group were constipation (mirabegron: 8/1632 [0.5%]; tolterodine: 0/812) and headache (mirabegron: 8/1632 [0.5%]; tolterodine: 3/812 [0.4%]).

Post marketing experience

No post marketing data has been submitted for evaluation within this MAA.

2.6.1. Discussion on clinical safety

The OAB safety database size is considered sufficiently self-standing for a proper safety evaluation. It is mainly based on exposure in 2858 OAB patients treated ≥ 12 weeks with mirabegron (1254 with the proposed 50 mg dosage) and 564 patients treated ≥12 months (294 with 50 mg). Additional data from a number of patients (n=345) from trials conducted in other indications (diabetes, LUTS) also offer further information to the general safety profile of the drug.

Although middle-aged women constitute the preferential group of patients represented in the clinical development of mirabegron the database size allows the characterisation of most of the population.

During the short term exposure, 53.4% of mirabegron patients reported TEAEs (55.2% placebo, 60.2% of tolterodine). The most frequently reported were nasopharyngitis, hypertension and blood glucose increase that were similar for mirabegron, tolterodine and placebo. No dose dependent pattern was observed.

For the intended 50 mg the reported incidences were naspharyngitis 7.4%, hypertension 5.2% and blood glucose increase 5.7%. Urinary sedment abnormal, (3.5%), CPK increased (3.3%), headache (3.1%), GGT increased (3%), constipation (2.1%), protein urine present (2.1%) and urinary tract infection (2%) were reported with lower frequency.

Regarding the severe TEAEs the most frequent were supraventricular extrasystoles, headache and nasopharyngitis without relevant differences among treatments (included placebo). Hypertension, dry mouth (much more frequent with tolterodine) and constipation were the most frequently drug-related TEAEs, with a similar incidence among the groups.

When looking at the long-term exposure, the percentage of patients with one or more TEAEs was 60.5% for mirabegron and 62.6% for tolterodine patients. The adverse event pattern (TEAEs, severe TEAEs and drug-related TEAEs) was similar.

There was an increase in the number of neoplasms in the mirabegron 100 mg group mainly due to subjects from study 178-CL-047, however the rates of the most frequent malignancies was similar to the age-adjusted population and it is considered biological implausible that the malignancies are linked to mirabegron as they were varied and no specific malignancy dominated. This explanation is considered acceptable by the CHMP.

The overall incidence of AEs leading to discontinuation of study drug was similar among treatment groups (including placebo). No qualitative differences both in short- and long-term exposed populations were observed.

Overall 11 deaths occurred in the mirabegron development program. From the 5 patients treated with mirabegron 2 deaths were considered to be possibly due to mirabegron according to the investigator. Further, two of the deaths are noted to have occurred because of bladder cancer and cardiac failure. The narratives for these deaths were carefully assessed and don't appear to be related to mirabegron.

A total of 77 mirabegron-treated patients experienced at least 1 SAE in the OAB 12-week studies. No remarkable differences were observed among treatments (mirabegron 1.7%, tolterodine 1.7%, and placebo 1.8%). Similar incidences were reported for all mirabegron doses. More SAEs were reported after long-term treatment: Mirabegron 5.7% vs tolterodine 5.4%.

Beta-3 agonists were initially developed for the treatment of diabetes and beta 3-adrenoceptors (AR) are known to be present in adipose tissue. Mirabegron does not appear to have any relevant effect on blood glucose levels or body weight. Results from non clinical studies also show an effect of mirabegron on lipid metabolism. Results from studies in which mirabegron was administered to diabetic patients at doses of 60, 130 and 200 mg (much higher than those intended in OAB condition) did not show any significant change in the lipid parameters. During OAB clinical development blood glucose increase was reported for mirabegron (4.7%) with similar or higher incidences reported for tolterodine (7.6%) and placebo (5.4%). Therefore, a relevant effect on the lipid profile of OAB patients is not expected.

A total of 34 plausible hypersensitivity reactions were reported in mirabegron patients during the clinical development (23 in the shor-term trials and 11 during the long term trials). Given that incidences of these events were 2-3 times higher with doses of mirabegron ≥ 100 mg than for tolterodine or placebo a potential relationship cannot be excluded. Hypersensitivity to the active substance or any of the excipients has been made contraindication in the SmPC and has been included as important identified risk into the RMP.

Cardiovascular safety

Clinical pharmacology studies carried out in healthy volunteers (CL-037, CL-072, CL-031) showed an increase of the heart rate and the blood pressure. Females and younger subjects were more susceptible to pulse increases whereas male had larger changes in blood pressure. These effects were influenced by the dose, being maximal at 200 mg.

These findings were also observed in Phase II studies and partially determined the selection of doses to be tested in Phase 3 (where mirabegron 200 mg dose was discarded).

During the Phase 3 development, cardiac arrhythmia events, mostly tachycardia, were more frequently reported with mirabegron than with placebo (1.8%). Mirabegron at doses up to 100 mg reported frequencies from 2.1% to 3.1%, being the highest for mirabegron 200 mg (6.6%). For the proposed 50 mg dose only a modest not clinically significant, increment of pulse rate (1 bpm compared with placebo) and blood pressure (≤ 1 mm Hg compared to placebo) were reported. This effect was not translated into clinical adverse events (cardiac arrhythmia, tachycardia, and hypertension) distinct from those reported for tolterodine or in most of cases for placebo. Therefore the primary safety concern arising from these findings is a risk of increased heart rate in patients who are exposed to doses that are greater than or equal to the supratherapeutic dose of mirabegron 100 mg.

The SmPC indicates to reduce the dose to 25 mg daily in patients with renal or hepatic impairment who are at risk for higher exposure at the therapeutic dose of 50 mg. Furthermore it is clearly labeled that increases in mirabegron exposure due to drug interactions may be associated with increases in pulse rate. Post marketing data on increased heart rate and tachycardia among initiators of mirabegron and comparator drugs indicated for OAB will be generated within a PASS, as detailed in the RMP.

In the TQT studies the effect of repeat oral dosing of mirabegron at 50 mg and two supra-therapeutic doses (100 and 200 mg) on the QTcI interval was evaluated. The supra-therapeutic doses represent approximately 2.6- and 6.5-fold the exposure of the therapeutic dose, respectively. At a mirabegron dose of 200 mg, the QTcI interval did not exceed 10 msec at any time point in males, while in females exceeded the upper bound of the one-sided 95% confidence interval did exceed 10 msec between 0.5–6 hours, with a maximum difference from placebo at 5 hours where the mean effect was 10.42 msec (upper bound of the one-sided 95% CI 13.44 msec). At the mirabegron 100 mg dose QTc interval changes were below 10 msec, although females showed greater mean change differences than males. Mirabegron 50 mg dose did have no remarkable effect on QTc interval (males and females).

Results from a PK/PD analysis indicate a small effect of age on mirabegron exposure (about 11%). When the simulations considered the additive effect of moderate renal impairment, mild hepatic impairment or the concomitant treatment with a strong CYP3A4 inhibitor (ketoconazole) changes in mirabegron exposure remained being relatively small. In any case, plasma concentrations for mirabegron 50 mg do not reach the exposure observed with the 100 mg dose. However data from an ad hoc Pk/PD analysis conducted by the Applicant showed maximal ddQTc values of 500.4 msec (95th percentile) in the simulation group of 75 year old females with mild renal impairment, mild hepatic impairment and taking ketoconazole). Therefore circumstances of mild and moderate renal impairment or mild hepatic impairment, each combined with the intake of a strong CYP3A4inhibitor, are taken into account in the SmPC recommending a dose reduction to 25 mg. The use of mirabegron concomitantly with a strong CYP3A4 inhibitor in patients with severe renal impairment or moderate hepatic impairment is not recommended.

Clinical trials in OAB population were mainly composed by females (> 70%) with a median age about 60 years (35% ≥ 65 years). Analysis of the effect of mirabegron on QTc in Phase 2/3 studies did not show any signal of concern on QT for 50 mg or 100 mg dose. Changes observed (and also when gender or age were considered) were similar to those reported for placebo.

In conclusion mirabegron 50 mg dose does not appear to raise safety concerns related to the potential QT prolongation when factors such as gender or age (which may influence the exposure to mirabegron) are considered. However, in patients receiving the therapeutic dose of mirabegron 50 mg once daily who have a known history of QT prolongation or who are concurrently taking medications known to prolong QT interval a safety concern arises. Adequate warnings have been included into the SmPC. Furthermore, the planned post authorisation safety study will generate further data on the cardiovascular safety particularly in the elderly, as specified in the risk management plan.

A decrease of lymphocytes and/or neutrophils counts was reported (greater with higher doses) after both short and long- term exposure to mirabegron. It is acknowledged by the CHMP that these changes were modest and transient however a group of patients receiving 100 mg (two times the proposed dose) achieved the clinical threshold of grade 2. This may be due to the presence of decreased (or borderline) values at baseline for a number of patients and whereas it is acknowledged that data for mirabegron 50 mg are not object of concern for the decrease of lymphocytes a potential effect (at least with higher doses) cannot be considered totally discarded. In order to properly address this issue it was included into the RMP as important missing information.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The available safety data is adequate to characterise the safety profile of mirabegron for the intended indication and the proposed patient population. Overall, the beta 3-adrenoceptor agonist mirabegron show a favourable safety profile comparable to that commonly reported with antimuscarinic agents. The potential for hypersensitivity reactions with mirabegron and exipients is adequately reflected in the SmPC.

For the 50 mg dose small increments in pulse rate and blood pressure have been observed within the clinical development programme. This effect was not translated into clinical adverse events (cardiac arrhythmia, tachycardia, and hypertension) distinct from those reported for tolterodine or in most of cases for placebo. Further mirabegron 50 mg dose does not appear to raise safety concerns related to

the potential QT prolongation when factors such as gender or age (which may influence the exposure to mirabegron) are considered. To prevent increases in mirabegron exposure and subsequent prolongation of the QTc interval due to drug interactions appropriate warnings have been included into the SmPC. Furthermore, the risk management plan specifies specific pharmacovigilance activites to further characterise the cardiovascular safety profile. This includes the conduct of a Post-authorisation Safety Study focusing on CV safety, especially in elederly patients. The protocol for this study will be provided for agreement and follow-up reporting will be performed, as specified in the Risk Management Plan.

The CHMP agrees to calculate the PSUR cycle based on the IBD. Therefore the first DLP for the PSUR submission will be 30 June 2013.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan

Summary of the risk management planSafety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimization activities**
Important identified risks		
Increased heart rate and tachycardia	Routine pharmacovigilance to assure continuous monitoring; Targeted Data Questionnaire to enhance collection of relevant data for individual reports. Post-authorization safety study focused on CV safety, especially in elderly patients.	SmPC • Section 4.5: Interaction with other medicinal products and other forms of interaction Increases in mirabegron exposure due to drug interactions may be associated with increases in pulse rate. • Section 5.1: Pharmacodynamic properties *Effects on Pulse Rate and Blood Pressure in Patients with OAB* In OAB patients (mean age of 59 years) across three 12-week phase 3 double-blind, placebo-controlled studies receiving mirabegron 50 mg once daily, an increase in mean difference from placebo of approximately 1 bpm for pulse rate and approximately 1 mm Hg or less in SBP/DBP was observed. Changes in pulse rate and blood pressure are reversible upon discontinuation of treatment. • Section 4.8: Undesirable effects list tachycardia, palpitation. PL • Section 4: Possible side effects Common side effects include increased heart rate (tachycardia) and uncommon side effects include feeling your heartbeat (palpitations).

Summary of the risk management planSafety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimization activities**
Hypersensitivity reactions	Routine pharmacovigilance to assure continuous monitoring; Targeted Data Questionnaire to enhance collection of relevant data for individual reports.	SmPC • Section 4.3: Contraindications Hypersensitivity to the active substance or to any of the excipients. • Section 4.8: Undesirable effects include eyelid oedema, lip oedema, urticaria, leukocytoclastic vasculitis, rash, rash macular, rash papular, pruritus, purpura. PL • Section 2: Do not use mirabegron Patients are instructed to not use mirabegron if allergic (hypersensitive) to mirabegron or any of the other ingredients of mirabegron. • Section 4: Possible side effects Uncommon side effects include itching, rash or hives (urticaria, rash, rash macular, rash papular, pruritus); Rare side effects include swelling of the eyelid (eyelid oedema), swelling of the lip (lip oedema), small purple spots on the skin (purpura), and inflammation of small blood vessels mainly affecting the skin (leukocytoclastic vasculitis).
Important potential risks		
QT prolongation	Routine pharmacovigilance to assure continuous monitoring; Targeted Data Questionnaire to enhance collection of relevant data for individual reports. Post-authorization safety study focused on CV safety, especially in elderly patients.	SmPC • Section 4.4: Special Warnings and Precautions for Use *Patients with Congenital or Acquired QT Prolongation* Before deciding to prescribe mirabegron to patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval, the clinician should consider the observations from the QTc study (see SmPC Section 5.1). PL • Section 2: Warnings and precautions Special care instructions are provided for patients who have an ECG (heart tracing) abnormality known as QT prolongation or who are taking any medicine known to cause this. Medicines that can prolong the QT interval include some medicines used for abnormal heart rhythm such as quinidine, sotalol, procainamide, ibutilide, flecainide, dofetilide, and amiodarone; or used for allergic rhinitis such as terfenadine and astemizole; or used as antipsychotic medicines (medicines for mental illness) such as thioridazine, mesoridazine, haloperidol, and chlorpromazine; or used as anti-infective such as pentamidine, moxifloxacin, erythromycin, and clarithromycin.

Summary of the risk management planSafety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimization activities**
Increased blood pressure	Routine pharmacovigilance to assure continuous monitoring; Targeted Data Questionnaire to enhance collection of relevant data for individual reports. Post-authorization safety study focused on CV safety, especially in elderly patients.	SmPC • Section 4.4: Special Warnings and Precautions for Use *Hypertension* Mirabegron has not been evaluated in severe uncontrolled hypertensive patients (systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg); therefore it is not recommended for use in this patient population. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg. • Section 5.1: Pharmacodynamic properties *Effects on Pulse Rate and Blood Pressure in Patients with OAB* In OAB patients (mean age of 59 years) across three 12-week phase 3 double-blind, placebo-controlled studies receiving mirabegron 50 mg once daily, an increase in mean difference from placebo of approximately 1 bpm for pulse rate and approximately 1 mm Hg or less in SBP/DBP was observed. Changes in pulse rate and blood pressure are reversible upon discontinuation of treatment. PL • Section 2: Warnings and precautions Patients with very high uncontrolled blood pressure are instructed to talk to their doctor or pharmacist before using mirabegron. • Section 4: Possible side effects Uncommon side effects include increased blood pressure.
Urinary tract infection	Routine pharmacovigilance to assure continuous monitoring.	SmPC • Section 4.8: Undesirable effects include urinary tract infection and cystitis. PL • Section 4: Possible side effects Common side effects include infection of the structures that carry urine (urinary tract infections). Uncommon side effects include bladder infection (cystitis).

Summary of the risk management planSafety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimization activities**
Embryo-fetal toxicity	Routine pharmacovigilance to assure continuous monitoring; Targeted Data Questionnaire to enhance collection of relevant data for individual reports.	SmPC • Section 4.6: Fertility, pregnancy and lactation *Pregnancy* There are limited amount of data from the use of mirabegron in pregnant women. Studies in animals have shown reproductive toxicity (see SmPC Section 5.3). Mirabegron is not recommended during pregnancy and in women of childbearing potential not using contraception. PL • Section 2: Pregnancy and breast-feeding Patients who are pregnant, may be pregnant, or planning to have a baby should not use mirabegron. Patients who are breast feeding are instructed to ask their doctor or pharmacist for advice before using mirabegron
Concomitant treatment with CYP2D6 substrates with narrow therapeutic indices or individually dose-titrated	Routine pharmacovigilance to assure continuous monitoring.	SmPC • Section 4.5 Interaction with other medicinal products and other forms of interaction In healthy volunteers, the inhibitory potency of mirabegron towards CYP2D6 is moderate and the CYP2D6 activity recovers within 15 days after discontinuation of mirabegron. Multiple once daily dosing of mirabegron IR resulted in a 90% increase in C_{max} and a 229% increase in AUC of a single dose of metoprolol. Multiple once daily dosing of mirabegron resulted in a 79% increase in C_{max} and a 241% increase in AUC of a single dose of desipramine. Caution is advised if mirabegron is co-administered with medicinal products with a narrow therapeutic index and significantly metabolized by CYP2D6, such as thioridazine, Type 1C antiarrhythmics (e.g., flecainide, propafenone), and tricyclic antidepressants (e.g., imipramine, desipramine). Caution is also advised if mirabegron is co-administered with CYP2D6 substrates that are individually dose titrated. PL • Section 2: Other medications and <Trade Name> Patients are instructed to tell their doctor if they use thioridizine (a medicine for mental illness), propafenone or flecainide (medicines for abnormal heart rhythm), imipramine or desipramine (medicines used for depression). These specific medicines may require dose adjustment by their doctor.

Summary of the risk management planSafety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities
Important missing information		

<table>
<tr><th>Summary of the risk management planSafety concern</th><th>Proposed pharmacovigilance activities</th><th>Proposed risk minimization activities</th></tr>
<tr><td>End-stage renal disease</td><td>Routine pharmacovigilance to assure continuous monitoring.</td><td>SmPC
• Section 4.2: Posology and Method of Administration
Renal and hepatic impairment
The following table provides the daily dosing recommendations for subjects with renal or hepatic impairment in the absence and presence of strong CYP3A inhibitors (see SmPC Sections 4.4, 4.5 and 5.2).
<table>
<tr><td></td><td></td><td colspan="2">Strong CYP3A inhibitors(3)</td></tr>
<tr><td></td><td></td><td>Without inhibitor</td><td>With inhibitor</td></tr>
<tr><td rowspan="3">Renal Impairment(1)</td><td>Mild</td><td>50 mg</td><td>25 mg</td></tr>
<tr><td>Moderate</td><td>50 mg</td><td>25 mg</td></tr>
<tr><td>Severe</td><td>25 mg</td><td>Not recommended</td></tr>
<tr><td rowspan="2">Hepatic Impairment(2)</td><td>Mild</td><td>50 mg</td><td>25 mg</td></tr>
<tr><td>Moderate</td><td>25 mg</td><td>Not recommended</td></tr>
</table>
1. Mild: GFR 60 to 89 mL/min/1.73 m^2; moderate: GFR 30 to 59 mL/min/1.73 m^2; severe: GFR 15 to 29 mL/min/1.73 m^2.
2. Mild: Child-Pugh Class A; Moderate: Child-Pugh Class B.
3. Strong CYP3A inhibitors see SmPC Section 4.5
Mirabegron has not been studied in patients with End Stage Renal Disease (GFR < 15 ml/min/1.73 m^2 or patients requiring haemodialysis) or severe hepatic impairment (Child-Pugh Class C) and it is therefore not recommended for use in these patient populations (see SmPC Sections 4.4 and 5.2).
Patients with Renal Impairment
No dose adjustment is necessary in patients with mild or moderate renal impairment (GFR 30 to 89 mL/min/1.73 m^2. In patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2), the recommended dose of mirabegron is 25 mg once daily with or without food. Mirabegron has not been studied in patients with End Stage Renal Disease (GFR < 15 mL/min/1.73 m^2 or patients requiring haemodialysis) (see SmPC Section 5.2).
• Section 4.4: Special Warnings and Precautions for Use
Renal Impairment
Mirabegron has not been studied in patients with End Stage Renal Disease (GFR <15 mL/min/1.73 m^2 or patients requiring haemodialysis) and, therefore, it is not recommended for use in these patient populations. Data are limited in patients with severe renal impairment (GFR 15 to 29 ml/min/1.73 m^2); based on a pharmacokinetic study (see Section 5.2) a dose reduction to 25 mg is recommended in this population. Mirabegron is not recommended for use in patients with severe renal impairment (GFR 15 to 29 ml/min/1.73 m^2) concomitantly receiving strong CYP3A inhibitors (see SmPC Section 4.5).</td></tr>
</table>

<table>
<tr><th>Summary of the risk management planSafety concern</th><th>Proposed pharmacovigilance activities</th><th>Proposed risk minimization activities</th></tr>
<tr><td>End-stage renal disease (continued)</td><td></td><td>PL
• Section 2: Warnings and precautions
Patients with kidney problems are instructed to talk to their doctor or pharmacist before taking mirabegron (the patient's doctor may need to reduce the dose).
• Section 3: Instructions for proper use
Instructions are provided for patients with kidney problems (the patient's doctor may need to reduce the dose to one 25 mg mirabegron tablet by mouth once daily).</td></tr>
<tr><td>Severe hepatic impairment</td><td>Routine pharmacovigilance to assure continuous monitoring.</td><td>SmPC
• Section 4.2: Posology and Method of Administration
Renal and hepatic impairment
The following table provides the daily dosing recommendations for subjects with renal or hepatic impairment in the absence and presence of strong CYP3A inhibitors (see SmPC Sections 4.4, 4.5 and 5.2).
<table>
<tr><td></td><td></td><td colspan="2">Strong CYP3A inhibitors(3)</td></tr>
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<tr><td rowspan="2">Hepatic Impairment(2)</td><td>Mild</td><td>50 mg</td><td>25 mg</td></tr>
<tr><td>Moderate</td><td>25 mg</td><td>Not recommended</td></tr>
</table>
1. Mild: GFR 60 to 89 mL/min/1.73 m^2; moderate: GFR 30 to 59 mL/min/1.73 m^2; severe: GFR 15 to 29 mL/min/1.73 m^2.
2. Mild: Child-Pugh Class A; Moderate: Child-Pugh Class B.
3. Strong CYP3A inhibitors see SmPC Section 4.5
Mirabegron has not been studied in patients with End Stage Renal Disease (GFR <15 ml/min/1.73 m^2 or patients requiring haemodialysis) or severe hepatic impairment (Child-Pugh Class C) and it is therefore not recommended for use in these patient populations (see SmPC Sections 4.4 and 5.2).</td></tr>
</table>

Summary of the risk management planSafety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimization activities**
Severe hepatic impairment (continued)		*Patients with Hepatic Impairment* No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh Class A). In patients with moderate hepatic impairment (Child-Pugh Class B), the recommended dose of mirabegron is 25 mg once daily with or without food. Mirabegron has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) (see SmPC Section 5.2). • Section 4.4: Special Warnings and Precautions for Use *Hepatic Impairment* Mirabegron 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. Mirabegron is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors (see SmPC Section 4.5). PL • Section 2: Warnings and precautions Patients with liver problems are instructed to talk to their doctor or pharmacist before using mirabegron (the patient's doctor may need to reduce the dose). • Section 3: Instructions for proper use Instructions are provided for patients with liver problems (the patient's doctor may need to reduce the dose to one 25 mg mirabegron tablet by mouth once daily).
Severe uncontrolled hypertension	Routine pharmacovigilance to assure continuous monitoring. Post-authorization safety study focused on CV safety, especially in elderly patients.	SmPC • Section 4.4: Special Warnings and Precautions for Use *Hypertension* Mirabegron has not been evaluated in severe uncontrolled hypertensive patients (systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg); therefore it is not recommended for use in this patient population. PL • Section 2: Warnings and precautions Patients with very high uncontrolled blood pressure are instructed to talk to their doctor or pharmacist before using mirabegron.

Summary of the risk management planSafety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimization activities**
Cardiovascular disease in patients at particular risk of developing heart failure if they experience increased blood pressure, tachycardia, and/or arrhythmia secondary to QT prolongation	Routine pharmacovigilance to assure continuous monitoring. Post-authorization safety study focused on CV safety, especially in elderly patients.	SmPC • Section 4.4: Special Warnings and Precautions for Use *Patients with Congenital or Acquired QT Prolongation* Before deciding to prescribe mirabegron to patients with a known history of QT prolongation or patients who are using medicinal products known to prolong the QT interval, the clinician should consider the observations from the QTc study (see SmPC Section 5.1). • Section 4.4 Special Warnings and Precautions for Use *Hypertension* Mirabegron has not been evaluated in severe uncontrolled hypertensive patients (systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg); therefore it is not recommended for use in this patient population. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥ 100 mm Hg. • Section 5.1: Pharmacodynamic properties *Effects on Pulse Rate and Blood Pressure in Patients with OAB* In OAB patients (mean age of 59 years) across three 12 week phase 3 double-blind placebo-controlled studies receiving mirabegron 50 mg once daily, an increase in mean difference from placebo of approximately 1 bpm for pulse rate and approximately 1 mm Hg or less in SBP/DBP was observed. Changes in pulse rate and blood pressure are reversible upon discontinuation of treatment. • Section 4.8: Undesirable effects include tachycardia, palpitation. Serious adverse drug reactions include atrial fibrillation.

Summary of the risk management planSafety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimization activities**
Cardiovascular disease in patients at particular risk of developing heart failure if they experience increased blood pressure, tachycardia, and/or arrhythmia secondary to QT prolongation (continued)		PL • Section 2: Warnings and precautions Special care instructions are provided for patients who have an ECG (heart tracing) abnormality known as QT prolongation or who are taking any medicine known to cause this. Such patients are instructed to talk to their doctor or pharmacist before using mirabegron. Patients with very high uncontrolled blood pressure are instructed to talk to their doctor or pharmacist before using mirabegron. • Section 4: Possible side effects The most serious side effects include irregular heart beat (atrial fibrillation). This is an uncommon side effect (may affect up to 1 in 100 people), but if it occurs, patients are instructed to immediately stop taking the medicine and seek urgent medical advice. Common side effects include increased heart rate (tachycardia) and uncommon side effects include feeling your heartbeat (palpitations) and increased blood pressure.
Pediatric use	Routine pharmacovigilance to assure continuous monitoring. Applicant will implement the PIP.	SmPC • Section 4.2: Posology and Method of Administration *Paediatric population* The safety and efficacy of mirabegron in children below 18 years of age have not yet been established. No data are available. PL • Section 2: Children and adolescents Do not give this medicine to children and adolescents under the age of 18 years because the safety and efficacy of mirabegron in this age group has not been established.
Decreased lymphocytes	Routine pharmacovigilance to assure continuous monitoring; Targeted Data Questionnaire to enhance collection of relevant data for individual reports.	None

The below pharmacovigilance activity in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
PASS to specifically address the issue of cardiovascular safety, especially in elderly patients (RMP measure)	Draft final protocol to be submitted within 6 months after granting of the MA Study protocol, study status, and progress reports will be included in each PSUR after approval in line with EU requirements.

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

Benefits

Beneficial effects

In the main clinical studies a statistically superior effect in comparison to placebo was shown for the co-primary endpoints. The pooled data from the three main studies showed after 12 weeks of treatment that the effect in terms of urinary frequency was -1.75 micturitions for the 50 mg dose versus -1.20 micturitions for placebo. Likewise, the effect of mirabegron on incontinence (assessed in a subset of the recruited population) was -1.49 incontinence episodes for the 50 mg dose versus -1.10 for placebo. When the effect was expressed in responder analyses mirabegron achieves equal or less than 10% responders more than placebo. Data for most of the secondary endpoints support this efficacy.

Patient-reported outcomes reported a positive trend in most of the domains, even if the size effect is not impressive. It is noteworthy that the perception of the patients is especially significant in such a non-life threatening condition to provide reassurance of the clinical relevance of the changes measured in the quantitative outcomes.
Reassurance on the efficacy of mirabegron can also be obtained from the double and triple responder rate analyses based on predefined minimal important differences where mirabegron was significantly better than placebo. It is of special relevance, that this has also been observed when a more stringent definition of responder was used.
Indirect comparison of the effect observed with mirabegron 50 mg on the co-primary endpoint (incontinence and micturitions) with products licensed in this condition shows that the effect of mirabegron is within the range of the mean values for the other products.

Uncertainty in the knowledge about the beneficial effects.

Long-term efficacy data of mirabegron are limited. Available data have been measured as secondary endpoints and the main evidence comes from the non-formal comparison between mirabegron (50 mg and 100 mg) and tolterodine. Although the results obtained at 12 months do not suggest a loss of efficacy, these data do not allow for sound conclusions regarding the maintenance of the effect of mirabegron. However in the comparative review from publicly available sources mirabegron does not show a distinct behaviour from other medicinal products approved for that condition (i.e. antimuscarinic drugs). In this respect, comparative effects of mirabegron with tolterodine help to put in context the results as the comparison reveals an effect of similar magnitude both in short and long (52 weeks) term treatment. The uncertainty with regard to long-term data specific for mirabegron is therefore acceptable at this point in time.

Risks

Unfavourable effects

Overall mirabegron shows a comparable safety profile with respect to that commonly reported with antimuscarinics. The most frequently reported AEs with the intended 50 mg dosage were nasopharyngitis, hypertension, blood glucose increase, urinary sediment abnormal, CPK increased, headache, GGT increased, constipation, protein urine present, and urinary tract infection (2%). In general the incidences reported were similar to the ones for tolterodine and placebo.
Some cases of hypersensitivity reactions have been reported during the clinical development. Given that these events were 2-3 times higher with doses of mirabegron ≥ 100 mg than for tolterodine or placebo a potential relationship cannot be excluded. Therefore hypersensitivity to the active substance or any of the excipients has been added as a contraindication in the SmPC and has been included as important identified risk into the RMP.

With regard to cardiovascular safety, mirabegron at the proposed 50 mg dose shows a modest increment of pulse rate and blood pressure (1 bpm and ≤ 1 mm Hg compared with placebo). These effects appear to be dose dependant (up to 100 mg 2.1% to 3.1%, 200 mg 6.6%) and superior to placebo (1.8%). Adequate safety warnings with regards to arterial hypertension and tachycardia have been included into the SmPC. Concerning the potential effect on the QT interval the 50 mg dose was shown to be reasonably safe in the thorough QT studies and as well in the clinical development program. The SmPC contains adequate information regarding the observations related to cardiovascular safety. Furthermore, the RMP requires the conduct of a post-authorisation safety study to further explore the CV safety particularly in the elderly, as detailed in the RMP. The posology of the drug takes possible higher exposure due to impaired hepatic or renal impairment or due to the influence of relevant drug interactions into account and relevant safety warning for the use of mirabegron in these conditions and with regards to patients taking drugs with narrow therapeutic indices metabolized via CYP2D6 or P-gp have been included into the SmPC.

Uncertainty in the knowledge about the unfavourable effects

Based on findings during the development of mirabegron increased blood pressure and QT prolongation were considered important potential risks that merit further assessment of cardiovascular safety in a real-life setting, especially in elderly patients.

For the authorisation of this medicinal product these uncertainties are addressed by adequate risk management strategies and warnings in the Product Information. Further, as described above,

initiators of the treatment, especially elderly patients, with mirabegron will be monitored within a PASS for their cardiovascular parameters.

Benefit-risk balance

Importance of favourable and unfavourable effects

Overactive bladder is a chronic condition with an increased prevalence in advanced ages. It adversely impact on quality of life derived from the psychological and life-style consequences of the condition. Urinary tract infection, skin ulceration and a greater risk of fall and bone fractures in some reports have been described among the complications.
Mirabegron represents a new alternative in the treatment of this condition with a new mechanism of action. It has shown a significant effect in the main symptoms of overactive bladder.The reduction in the frequency of micturitions, in the number of episodes of incontinence, the volume voided per micturition or urgency episodes has been considered to be modest in terms of clinical relevance, although comparable to other agents approved for this indication. The results of the measures aimed at capturing the subjective perception of the benefit reflect also these findings.

Mirabegron appears to be well tolerated. In terms of cardiovascular safety a modest increment of pulse rate and blood pressure at the proposed 50 mg dose was shown. This risk is considered addressed with the relevant SmPC wordings and implemented RMP risk minimisation strategies.

Benefit-risk balance

The available data indicate that except for the fact that mirabegron belongs to a new therapeutic class it falls within what is expected from other products authorised for the treatment of overactive bladder symptoms (i.e. antimuscarinics) with an acceptable safety profile. The overall benefit-risk balance is considered positive.

Discussion on the benefit-risk balance

A consistent effect is observed in favour to mirabegron. The comparison with tolterodine (and indirectly, with other antimuscarinics) reveals an effect of similar magnitude in the quantitative measures and also when patients valued the subjective impact. The safety profile is comparable to that commonly reported with antimuscarinics and can be considered to be balanced through the relevant SmPC wordings and risk minimisation measures. Therefore, the effect, although modest, can be considered clinically relevant and sufficient to conclude on the positive benefit-risk balance of this medicinal product in the treatment of OAB.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Betmiga in the treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome is

favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1.5 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

The PSUR cycle for the product will follow the standard requirements until otherwise agreed by the CHMP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Obligation to complete post-authorisation measures

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that mirabegron is qualified as a new active substance.