Local Risk Management Plan

EUROPEAN UNION (EU) LOCAL RISK MANAGEMENT PLAN

MIRABEGRON (BETMIGA™)

The Astellas Group

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European Union Local Risk Management Plan for Betmiga (mirabegron)

RMP version to be assessed as part of this application:

RMP Version number:	8
Data lock point for this RMP:	30-Jun-2020
Date of final sign-off:	Date of final signature on the electronic signature page

Rationale for submitting an updated RMP: To update Module 3, Pharmacovigilance Plan (including post-authorization safety studies). Changes to the safety concerns (reviewed in compliance with the requirements of GVP Module V Rev. 2)

Summary of significant changes in this RMP:

- The data lock point of the previous RMP version was dated 2 years ago. The current RMP was updated with the most recent data through 30-Jun-2020
- Changes to the safety concerns (reviewed and reclassified in compliance with the requirements of GVP Module V Rev. 2): Increased heart rate and tachycardia and Increased blood pressure were removed from the list of important identified risks. UTI and Concomitant treatment with CYP2D6 substrates with narrow therapeutic indices or individually dose-titrated were removed from the list of important potential risks. End-stage renal disease and Severe hepatic impairment were removed from missing information.
- Safety specification includes more recent data for the Epidemiology of the indication and target population, updated Clinical trial exposure and updated Post-authorization exposure.
- Pharmacovigilance Plan: updates to Additional pharmacovigilance activities for mirabegron due to completion of 2 studies (Drug Utilization Study 178-PV-002 and Post-Authorization Study 178-CL-114) and editorial changes related to this in the document.
- Revision: implementation of an approved PIP was removed from Section 3.1, Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and instated in Section 3.2, Additional pharmacovigilance activities.

Other RMP versions under evaluation:

RMP Version Number(s)	Submitted on	Procedure Number(s)
Not applicable		

Details of the currently approved RMP:

Version number:	6.1
Approved with procedure:	EMEA/H/C/002388/IB/0029
Date of approval (opinion date)	20-Jun-2018

QPPV approval/oversight:

QPPV name: Ralph Nies

QPPV signature: Electronic signature appended at the end of the document

List of Abbreviations

Abbreviation	Definition
AE	adverse event
AMI	acute myocardial infarction
APTC	antiplatelet trialists' collaboration
AR	adrenal receptor (adrenoceptor)
ARB	angiotensin receptor blocker
AUC	area under the plasma concentration-time curve
BOO	bladder outlet obstruction
BPH	benign prostatic hyperplasia
bpm	beats per minute
CI	confidence interval
CNS	central nervous system
CL_{cr}	creatinine clearance
C_{max}	maximum (peak) serum concentration
CPRD	Clinical Practice Research Datalink
CTD	common technical document
CV	cardiovascular
CVA	cerebrovascular accident
CYP	cytochrome P450
DBP	diastolic blood pressure
DHPC	direct healthcare professional communication
DLP	data-lock point
DUS	drug utilization study
ECG	electrocardiogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ER	extended release
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FDC	fixed dose combination
GLP	good laboratory practice
hERG	human ether-a-go-go-related gene
HIRD	Healthcore Integrated Research Database
HF	heart failure
ICH	International council for harmonization of technical requirements for pharmaceuticals for human use

List of Abbreviations

ICS	International Continence Society
IMS	Intercontinental Medical Statistics
IR	immediate release
IV	intravenous
JNC7	Joint national committee on prevention, detection, evaluation, and treatment of high blood pressure seventh report
LUTS	lower urinary tract symptoms
MA	marketing authorization
MAA	marketing authorization application
MACE	major adverse cardiovascular event
MAH	marketing authorization holder
MI	myocardial infarction
MRHD	maximum recommended human dose
mRNA	messenger ribonucleic acid
NDA	new drug application
NDO	neurogenic detrusor overactivity
NOAEL	no-observed-adverse-effect level
NYHA	New York Heart Association
OAB	overactive bladder
OCAS	oral controlled absorption system
OCT	organic cation transporters
OR	odds ratio
PASS	post-authorization safety study
P-gp	P-glycoprotein
PIP	pediatric investigation plan
PL	Package Leaflet
PND	post-natal day
p.o.	per os (orally; i.e., by mouth)
PRA	plasma renin activity
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
PT	preferred term (MedDRA)
PVR	post-void residual (volume)
PY	person year
qd	once daily
QPPV	Qualified Person for Pharmacovigilance
QT	interval from start of Q to end of T waves on electrocardiogram

List of Abbreviations

QTc	QT interval corrected for heart rate
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
QTcI	QT interval corrected for heart rate using individual-specific correction formula
RAS	randomized analysis set
RMP	Risk Management Plan
RR	relative risk
SAF	safety analysis set
SBP	systolic blood pressure
SmPC	Summary of Product Characteristics
SMQ	standardized MedDRA query
SV	stroke volume
TdP	torsade de pointes
TEAE	treatment emergent adverse event
TME	targeted medical event
UK	United Kingdom
US	United States
UTI	urinary tract infection

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1 PRODUCT(S) OVERVIEW

Data-lock point for this Module	30-Jun-2020
Version when Module last updated	8.0

Table Part I.1 Product Overview	
Active substance(s) (International Nonproprietary Name [INN] or common name)	Mirabegron
Pharmacotherapeutic group(s) (ATC Code)	Urologicals, Urinary antispasmodics Beta 3-adrenoceptor (AR) agonist ATC code: G04BD12
Marketing Authorization Holder	Astellas Pharma Europe B.V.
Medicinal products to which this RMP refers	Mirabegron 25 mg/50mg tablets
Invented name(s) in the European Economic Area (EEA)	Betmiga
Marketing authorization procedure	Centralised procedure
Brief description of the product	Chemical class: Mirabegron is a potent and selective agonist for human beta$_3$-AR, as demonstrated in experiments using cloned human beta$_3$-AR.
	Summary of mode of action: Mirabegron relaxes the detrusor smooth muscle during the urinary bladder fill-void cycle by activation of beta$_3$-AR without interfering with the voiding contraction.
	Important information about its composition: Mirabegron showed very low intrinsic activity for cloned human beta$_1$-AR and beta$_2$-AR. Studies in OAB animal models have shown that mirabegron increases bladder capacity.
Hyperlink to the product information	Please reference to the CTD Module 1.3.1
Indication(s) in the EEA	Current: Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with OAB (overactive bladder) syndrome.
	Proposed: Not applicable
Dosage in the EEA	Current: 50 mg once daily

Table Part I.1 Product Overview	
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Prolonged release tablets 25 mg, 50 mg 25 mg: oval, brown tablet, debossed with company logo and "325" on the same side 50 mg: oval, yellow tablet, debossed with the company logo and "355" on the same side
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

2 SAFETY SPECIFICATION

Module SI. Epidemiology of the indication(s) and target population(s)

Data-lock point for this Module	30-Jun-2020
Version when Module last updated	8.0

Indication(s)

Mirabegron is indicated for symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence, as may occur in adult patients with OAB syndrome.

Epidemiology of the disease:

Lower urinary tract symptoms (LUTS) are categorized into 3 main groups – storage, voiding and post-micturition – based on the International Continence Society (ICS) criteria [Abrams et al, 2003]. OAB is a storage subset of LUTS that is characterized by symptoms of urinary urgency with or without urgency incontinence, and is usually associated with increased daytime frequency and nocturia [Abrams et al, 2006]. Despite efforts by the ICS to standardize the terminology and definitions for LUTS, including OAB (overactive bladder), many investigators use different definitions or criteria to survey participants in epidemiological studies [Irwin et al, 2008]. OAB is a common and bothersome symptom complex, which significantly affects patients' quality of life. Approximately 400 million people worldwide suffer from symptoms of urgency and frequency (dry OAB) and a proportion will have associated urgency incontinence (wet OAB) [Warren et al, 2016].

Incidence:

Estimates for the annual incidence of OAB range from 2.6 to 143 cases per thousand in Europe [Hartmann et al, 2009]. The lowest estimates come from a population-based estimate using the National Health Services Database of the United Kingdom (UK) [Dallosso et al, 2004]. In this study, by decade beginning at 40, the annual incidence of OAB was reported 78, 65, 100, 117 and 143 per 1000; additionally, there was an estimate of 54 new cases of OAB per 1,000 women per year [Dallosso et al, 2004]. More recently in Europe, the EPIC study, 1 of the largest population-based surveys studied the incidence and the prevalence of LUTS and OAB. It can be seen from the EPIC study that the incidence of LUTS in general was similar to what has been previously published, and slightly more common in women than in men (66.6% vs 62.5%) [Eapen et al, 2016].

In a 16-year follow-up (1991 to 2007) of 1081 Swedish women randomly selected from the general population, changes in the prevalence of urinary incontinence (UI), OAB, and other LUTS were assessed over time. The cumulative incidence of 20% (with a 43% remission rate) was reported for OAB in this prospective, population-based study [Wennberg et al, 2009]. Potential biases in reported OAB incidence and prevalence include the under-reporting of symptoms in some populations [Coyne et al, 2009; Milsom et al, 2001], and differences across studies in definitions of OAB. Sampling may also account for some differences [Irwin et al, 2006].

Prevalence:

OAB is a prevalent condition in both men and women. It may have a significant impact on overall quality of life, sexual function, sleep, and mental health. Numerous publications have studied the prevalence of OAB in developed countries and assessed the impact it has on quality of life with various results. [Eapen et al, 2016]. LUTS and OAB are highly prevalent in the adult population, and the prevalence of OAB increases with age with approximately 30 to 40% of the population over 75 being affected [Warren et al, 2016]. Until recently, however, the true prevalence of OAB was difficult to estimate, because most studies focused on specific symptom, gender and age group, examining incontinence in women and LUTS in men, and each study used different definitions [Lee et al, 2011]. Overall, the estimated prevalence of OAB is approximately 17% in both men and women [Wennberg et al, 2009]. In 5 European countries and by 2020, a number of 25.5 million individuals was projected to be affected by OAB [Reeves et al, 2006].

The National Overactive Bladder Evaluation (NOBLE) program was developed to estimate the prevalence of OAB and its burden in the United States (US) [Eapen et al, 2016]. Their study showed an overall OAB prevalence of approximately 16% with no significant differences between the 2 sexes (16.9% among women and 16.0% among men) [Stewart et al, 2003; Eapen et al, 2016]. The epidemiology of lower urinary tract symptoms (Epi-LUTS) survey was a population-based, cross-national survey assessing the prevalence of LUTS in men and women over 40 years of age in the US, UK, and Sweden. Overall, 72.3% of men and 76.3% of women reported at least 1 LUTS occurring at least "sometimes" [Coyne et al, 2009; Eapen et al, 2016]. The prevalence of OAB

depended on how OAB was defined. When symptoms were defined as "sometimes", the overall prevalence was 35.6%. When defined as "often", the overall prevalence decreased to 24.7% [Eapen et al, 2016].

In Europe, OAB prevalence has been estimated to range from 11.8% to 16.6% (12.8% to 17.4% in women, and 10.8% to 15.6% men) based on results from the EPIC study [Milsom et al, 2001] and from the Sifo/Gallup network [Eapen et al, 2016]. In addition, the overall prevalence of OAB increased from 17% to 26% during a 16-year observational period, between 1991 and 2007 [Wennberg et al, 2009]. A more recent extension of the EPIC study conducted among subjects in Czech Republic, Russia and Turkey found an overall OAB prevalence of 18% in men and 28% in women, with those 60+ years old having a notably greater prevalence [Kogan et al, 2014].

One Finnish study reported even lower rates of 8% to 11.8% with the suggestion that differences in estimates across studies may be due to differences in survey methodology [Tikkinen et al, 2007]. As with incidence rates, prevalence estimates may also be biased by patients' under-reporting of symptoms and the use of non-standard definitions of OAB in their studies [Irwin et al, 2006].

The prevalence of OAB increases with age, and varies by gender. In Europe, women report a higher prevalence before the age of 60, but men report a higher rate after the age of 60. Prevalence in men increases steadily with age however, prevalence in women tends to plateau from age 55 to 69, but increases again at age 70 (Table 1) [Milsom et al, 2001].

Table 1 Prevalence of OAB by Age and Sex in Europe

Prevalence by Age and Sex	Men	Women
Age 40-44	3.4%	8.7%
Age 45-49	6.0%	10.6%
Age 50-54	9.8%	11.9%
Age 55-59	13.2%	16.9%
Age 60-64	18.9%	16.9%
Age 65-69	23.7%	17.5%
Age 70-74	22.3%	22.1%
Age > 75	41.9%	31.3%

Source: [Milsom et al, 2001]

Demographics of the population in the authorized indication and risk factors for the disease:

Previously, the difference in overall prevalence rates for men and women have been reported to be less than 2% [Milsom et al, 2001; Stewart et al, 2003; Irwin et al, 2006]. More recently, studies in Europe and the US have reported symptoms characteristic of OAB to occur with a 4 to 16% greater prevalence in women than in men [Coyne et al, 2009; Coyne et al, 2011]. Overall, the OAB prevalence in the US appears to increase steadily with increasing age, with women more likely to report OAB with urge incontinence and men more likely to report OAB without urge incontinence [Stewart et al, 2003; Coyne et al, 2011]. In women, OAB prevalence with and without urge

incontinence is similar at 9.3% and 7.6%, respectively. In men, the prevalence of OAB without urge incontinence is higher than that of OAB with urge incontinence (13.4% and 2.6%, respectively) [Stewart et al, 2003].

The most common risk factor for OAB is increasing age [Irwin et al, 2006; Stewart et al, 2003]. Other common risk factors include obesity, diabetes mellitus, neurological disorders (e.g., multiple sclerosis, Parkinson's disease) and stroke [Teleman et al, 2004; Jo et al, 2012; Wen et al, 2014]. Pregnancy and menopause may also increase the risk of developing OAB symptoms in women [Brown, 2002; Lugo Salcedo et al, 2013].

Main existing treatment options:

The main treatment options for OAB are conservative management (e.g., bladder training, lifestyle modification and pelvic floor exercises) and pharmacotherapy, or a combination of both. The Fourth International Consultation on Incontinence divides the management of urinary incontinence into initial treatment and specialized therapy. Initial management strategies for OAB should be offered to symptomatic patients who are bothered by the condition [Gulur et al, 2010]. Behavioral treatment for OAB comprises a number of interventions including bladder re-training (timed toileting), dietary modifications (reducing fluid intake and caffeine consumption) and pelvic floor muscle training (PFMT). Behavioral training has been shown to be effective in the treatment of OAB [Van Kerrebroeck, 2012], however, the benefits tend to be short-lived outside the clinical trial setting due to non-compliance. Behavioral treatment is commonly used alone or as an adjunct to pharmacotherapy with the evidence showing that behavioral treatment in addition to pharmacotherapy was better than pharmacotherapy alone.

Pharmacotherapy for OAB consists mainly of muscarinic receptor antagonists (antimuscarinics). Branded antimuscarinic agents include solifenacin succinate, fesoterodine, and darifenacin. Generic agents include oxybutynin, tolterodine and trospium.

Antimuscarinics provide partial relief of the symptoms of OAB. In controlled clinical studies, urgency incontinence is reduced by 30 to 80% and urgency episodes are reduced by 20 to 55% [Novara et al, 2008]. Daytime micturition frequency is reduced by approximately 2 to 3 episodes per day which represents an improvement of approximately 70% (where 100 % improvement represents reduction to eight episodes per day). Dry mouth and constipation are common side effects of antimuscarinics.

Neurotoxins, such as botulinum toxin, are approved for OAB in some European countries such as the UK. A study that has followed new users of darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium in 3 European countries reported that by 2012, solifenacin was the preferred drug for OAB treatment and that persistence with antimuscarinic drugs was low in the studied cohort [Margulis et al, 2018].

The first-in-class β_3-adrenoceptor agonist mirabegron is indicated in the EU (Betmiga™), Japan (Betanis™) and several other countries for the management of overactive bladder (OAB) syndrome [Deeks, 2018].

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

OAB is generally not associated with mortality [Bhosle et al, 2005], but a relationship was found with nocturia in elderly men and women with 3 or more nocturnal voiding episodes per night [Asplund, 1999]. When compared to patients with 2 or less voiding episodes per night, mortality following a 54-month observation period was significantly greater among men with 3 or more nocturnal voiding episodes (3.4% vs 1.9% per 6 months; P<0.001) but only slightly elevated among women (1.4% vs 1.1% per 6 months; P=0.07). However, the excess mortality was independent of age, health status, cardiac disease, stroke and diabetes and could not be attributed to any specific cause of death. The within-gender causes of death distributions between excessive- and moderate-voiding patients were found not to be different; coronary diseases (26.3% to 32.8%), neoplasms (22.0% to29.4%) and cerebrovascular diseases (7.3% to 13.4%) comprised the top 3 causes.

OAB also has a significant impact on health-related quality of life, particularly emotional symptoms, sexual health, and overall well-being [Rogers et al, 2009; Warren et al, 2016]. The negative impact of OAB on quality of life, work productivity, sexuality and the emotional well-being has been reported in a study of both men and women in Sweden, Italy, Canada, Germany, and the UK [Coyne et al, 2008]. Problems with sleep are common due to nocturia [Kemmer et al, 2009; Sexton et al, 2009; Irwin et al, 2008]. Patients with OAB have been found to suffer a higher prevalence of sleep disturbance due to nocturia [Brown et al, 2000], and the prevalence of depression and skin infections in this population may be directly attributable to OAB [Klotz et al, 2007]. Overall, patients with OAB generally exhibit poor health, impaired quality of life, social isolation, and depression [Holroyd-Leduc et al, 2004].

Important co-morbidities:

The following important co-morbidities were selected based on disease prevalence, severity and public health impact relative to the target population with the indication of OAB:

- Stroke
- Diabetes mellitus
- Bladder cancer
- Prostate cancer
- Urinary tract infection (UTI)
- Skin infections
- Hypertension and cardiovascular disease
- Benign prostatic hyperplasia (BPH)

Module SII. Nonclinical part of the safety specification

Data-lock point for this Module	30-Jun-2020
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A comprehensive safety evaluation of mirabegron was performed including safety pharmacology, genotoxicity, carcinogenicity, local tolerance, single- and repeat-dose toxicity, fertility, embryonic development, as well as prenatal and postnatal development studies. The following potential safety concerns were identified in pharmacology and toxicology studies:

- Cardiovascular effects
- Skin sensitization effects
- Male fertility
- Female fertility
- Embryo fetal toxicity
- Juvenile animal toxicity
- Hepatic effects
- Central nervous system (CNS) effects

Table 2 Key safety data from non-clinical studies

Key safety findings (from non-clinical studies)	Relevance to human usage
Cardiovascular effects (QT interval prolongation)	
Mirabegron or its metabolites at concentrations markedly higher than the non-protein bound human C_{max} at MRHD did not inhibit the hERG potassium conductance, IKs, IK to, INa, or ICaL in vitro. In the dog ventricular wedge model, neither mirabegron nor its metabolites prolonged the QT interval, altered transmural dispersion of repolarization, induced premature ventricular contractions or induced ventricular tachycardia. *Dog:* Increased QTcB interval in non-GLP studies, at doses ≥ 3 mg/kg. However, QTc prolongation (Matsunaga's formula) was not observed (doses up to 100 mg/kg) in a follow-up study. *Monkey*: Oral administration of mirabegron at doses up to 100 mg/kg had no effect on QT or QTc intervals.	Non-clinical data do not suggest risk in humans. Prolonged QTc interval was not observed in the test species. The mechanism for QTc prolongation observed in humans at supratherapeutic doses is unknown.
Cardiovascular effects (Increased heart rate and blood pressure)	
Rat: Increased heart rate blocked by metoprolol, indicating a beta1-AR-mediated response. *Dog*: Decreased systolic and mean blood pressure and increased heart rate were noted in conscious dogs at doses ≥ 0.3 mg/kg, p.o. Tachycardia in 1 male and 2 female animal within 2 hours of dosing on the first day of a 2-week repeated dose study at a lethal dose of 20 mg/kg. *Rabbit (anesthetized):* Oral administration of mirabegron at doses of 10 or 30 mg/kg increased heart rate 1 to 8 hours post dose, returning to baseline by 24 hours.	The observed increases in heart rate and blood pressure in the human studies were less pronounced than those seen in rats, dogs and monkeys. These observations concur with the more pronounced beta1-AR agonistic effect of mirabegron seen in laboratory animals compared to that in humans.
Table continued on next page	

Key safety findings (from non-clinical studies)	Relevance to human usage
Monkey (conscious): Increased heart rate at a dose of 100 mg/kg p.o. No observed changes in blood pressure. Oral administration of mirabegron (30 mg/kg) daily for 13 weeks resulted in 1 male animal at the highest dose (30 mg/kg) having an abnormal ECG wave form indicative of ventricular tachycardia only at 2 hours after dosing in week 13. This observation was not repeated in this animal even with continued dosing.	
Skin sensitization effect	
Mirabegron has been shown to have moderate skin sensitization potential in guinea pigs. Mirabegron showed no irritation reactions in rabbits topically exposed to mirabegron. Histopathological assessment of lymph nodes in the pivotal repeat-dose toxicity study in rats revealed the presence of microgranuloma. The frequency was close to that observed for controls and the overall weight of evidence indicated no discernible immunotoxic potential for mirabegron.	Relevant for dermal exposure, but the study is not predictive of risk for human hypersensitivity. It was concluded that proper protective clothing should be used during the manufacturing process.
Male Fertility	
Rat: Effects on male fertility were observed only in rodents at the lethal dose of 300 mg/kg per day. No effect on male fertility was observed at a dose of 100 mg/kg per day (47.8-fold the non-protein bound systemic exposure seen at MRHD; 77.0-fold total systemic exposure at MRHD). In the 2-week repeated dose study in rats, hyposecretion by the seminal vesicle was noted at the 300 mg/kg per day dose level (non-protein bound systemic exposure was 129.4-fold the non-protein bound AUC seen in young males at MRHD; 168.2-fold the total AUC in young males at MRHD) and the safety margin for this finding, based on a NOAEL of 100 mg/kg per day, and the non-protein bound fraction in rat and human plasma, was 43.1-fold (56.0-fold the total AUC in young males at MRHD). This finding was not confirmed over the same dose range in the 13-week repeated dose study (non-protein bound systemic exposure 152.1-fold the non-protein bound young male AUC at MRHD; 197.7-fold the total young male AUC at MRHD). Finally, in the 26-week repeated dose rat study, at a maximum dose of 100 mg/kg per day, there was also no seminal vesicle hyposecretion reported (non-protein bound systemic exposure 52.8-fold higher than the non-protein bound male human AUC at MRHD; 68.7-fold higher than the total young male AUC at MRHD). Therefore, despite the decrease in seminal vesicle secretion seen at the 300 mg/kg per day dose level in the 2-week repeated dose study, the absence of similar findings at the 100 and 300 mg/kg per day dose levels in the 13- and 26-week repeated dose studies leads to the conclusion that mirabegron has no long term effects on the seminal vesicle function. This conclusion was confirmed by the fact that male rats administered mirabegron at doses up to 100 mg/kg per day for 14 days before mating showed no decrease in fertility while at the lethal dose of 300 mg/kg per day a significant decrease in male fertility was noted.	These data show that 1) mirabegron at nonlethal doses had no effect on male fertility; 2) mirabegron reduced seminal vesicle weight in rodents, but had no effect on reproductive organ weights in non-rodent species; and 3) mirabegron had limited effect on the seminal vesicle histology in rats, but had no effect on male reproductive histology in non-rodent species. These data indicate that mirabegron at the MRHD is unlikely to affect male fertility.
Table continued on next page	

Key safety findings (from non-clinical studies)	Relevance to human usage
In the 2-week repeated dose rat study, the seminal vesicle weights at the 100 mg/kg dose level (non-protein bound systemic exposure was 43.1-fold the non-protein bound AUC seen in at MRHD; 56.0-fold the total AUC in young males at MRHD) were significantly lower than that observed in control animals. These findings were reversible by the end of a 2-week recovery period. The decrease in seminal vesicle weight observed in the 2-week repeated dose study was not confirmed in the 13-week repeated dose rat study at the same dose level. Similarly, extending the daily exposure to 26 weeks at the 100 mg/kg per day dose level also showed no reduced seminal vesicle weight compared to vehicle-treated controls. This absence of effect on the seminal vesicle at the same dose with increasing duration of administration argues against a toxic effect of mirabegron on the seminal vesicle. The prostate weights in rats administered mirabegron for 2 or 13 weeks were significantly lower than that of vehicle treated control animals at a lethal dose and with non-protein bound systemic exposures that were 129.4- and 152.1-fold higher, respectively, than the non-protein bound AUC for young human male subjects at MRHD (total systemic exposures that were 168.2- and 197.7-fold higher, respectively, than the total AUC for young human male subjects at MRHD). However, in rats administered mirabegron at a dose of 100 mg/kg (non-protein bound systemic exposures up to 52.8-fold the human non-protein bound AUC at MHRD; total systemic exposure up to 68.7-fold the young male human systemic exposure at MRHD) for 26 weeks, no decrease in prostate weights were recorded. In addition, no histological findings were noted in the prostate in any of the rat studies. *Monkey*: Cynomolgus monkeys administered mirabegron for 52 weeks (non-protein bound systemic exposures up to 17.2-fold the young male human non-protein bound AUC at MHRD; total systemic exposures up to 10.4-fold the young male human total AUC at MHRD), showed no significant effect on seminal vesicle weights. In addition, no histological findings were noted in the seminal vesicles of cynomolgus monkeys administered mirabegron for 52 weeks at non-protein bound systemic exposures up to 17.2-fold above the human non-protein bound AUC at MRHD (10.4-fold the young male human total AUC at MHRD). Monkeys administered mirabegron for 52 weeks (non-protein bound systemic exposures up to 17.2-fold the young male human non-protein bound AUC at MHRD; total systemic exposures up to 10.4-fold the young male human total AUC at MHRD) showed no effects on prostate weights and no histological findings.	
Table continued on next page	

Key safety findings (from non-clinical studies)	Relevance to human usage
Female Fertility	
Rat: Mirabegron, at the lethal dose of 300 mg/kg, reduced female fertility when administered to female rats for 14 days before mating and continuing through gestation day 7. This decrease in fertility was related to a decrease in ovulation (reduced number of corpora lutea) resulting in lower number of implantations; there was no increased preimplantation or postimplantation loss. It is likely that these findings are due to the compromised health of the dams. Administration of mirabegron at the non-lethal dose of 100 mg/kg per day had no effect on female fertility (human equivalent dose 19.2-fold the MRHD).	Given that the findings were only seen at lethal doses, and the safety margin at the NOAEL is 19.2 fold above the MHRD, it is concluded that mirabegron, at the MRHD is unlikely to affect female fertility.
Embryo-fetal toxicity	
Rat: No embryo-fetal toxicity was observed in rats at non-protein bound systemic exposures that were 4.8-fold higher than the human systemic exposure at the MRHD (total systemic exposures that were 6.2-fold higher than the total human systemic exposure at the MRHD). An increased incidence of a skeletal anomaly and variation (wavy rib) was observed at non-protein bound systemic exposures that were equal to or greater than 16.5-fold the human systemic exposure at MRHD (21.5-fold the total human systemic exposure at MRHD). These findings were reversible. Transient developmental changes were observed in pups of dams, repeatedly treated with toxic doses of mirabegron during pregnancy. *Rabbit*: No embryo-fetal toxicity was observed in rabbits at non-protein bound systemic exposures that were 0.3-fold the human systemic exposure at the MRHD (0.7- fold the total human systemic exposure at MRHD). The embryo-fetal NOAEL in this species was based on reduced fetal body weight observed at systemic exposures that were 6.2-fold higher than the human non-protein bound systemic exposure at MRHD (14.1- fold the total human systemic exposure at MRHD). At still higher doses, where the non-protein bound systemic exposures were 15.7-fold higher than the human exposure at MRHD (35.7- fold the total human systemic exposure at MRHD), 1 of 17 pregnant rabbits died, and fetal findings of dilated aorta and cardiomegaly were reported. The frequency of these findings was reduced by co-administration the beta1-AR antagonist, metoprolol. *Monkey*: There were no significant changes in reproductive organs of cynomolgus monkeys following repeated administration of mirabegron for up to 52 weeks. *Urogenital*: There were no urogenital findings in the rat fetuses and similarly, there were no uro-genital findings in rabbit fetuses.	At higher doses (non-protein bound systemic exposure 15.7-fold higher than the MRHD), fetal findings of dilated aorta and cardiomegaly were reported in rabbits. As a precautionary measure, it is preferable to avoid the use of mirabegron during pregnancy or if proper contraception is missing. Mirabegron should not be used by breastfeeding women.
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Key safety findings (from non-clinical studies)	Relevance to human usage
Juvenile animal toxicity	
Rat In the 13-week oral repeated-dose toxicity study in juvenile rats (PND10 to PND100) with a 4-week recovery period, decreased activity, salivation and decrease in body weight gain were observed in the juvenile rats treated with 10 and 30 mg/kg mirabegron. There were minimal to mild changes in clinical chemistry (increases in aspartate aminotransferase and alanine aminotransferase) and urinalysis parameters (increases in the urine volume and decrease in the specific gravity) in male and female pups at 30 mg/kg/day. Gross pathology in the 30 mg/kg group showed reversible decreases in thymus weights in males and females, reversible increases in relative weights of the submandibular gland and heart in males, and reversible increases in relative liver weights in females. Also observed at the 30 mg/kg dose level was an increase in ovary weights that was not reversible in the 4-week recovery period. In the histopathology, decreased lipid droplets due to the β_3-adrenoceptor agonistic activity were observed in the brown adipose tissues and white adipose tissues in males and females in the 10 and 30 mg/kg groups. No adverse effects on development of any organ system evaluated, passive avoidance behavior, motor activity, performance in an open field, fertility or mating performance were observed following administration of mirabegron for 13 weeks at doses up to 30 mg/kg/day. These data showed that the no-observable adverse-effect level (NOAEL) of mirabegron was 3 mg/kg per day and that the findings observed in the juvenile rats were similar to that seen in adult animals.	The safety and efficacy of mirabegron in children below 18 years of age have not yet been established. Therefore, mirabegron should not be used in children. The target organs of toxicity in juvenile animals were the same as previously identified in adult animal toxicity studies and these findings occurred at comparable systemic exposures. In addition, doses of mirabegron up to 30 mg/kg/day had no discernible adverse effects on the post-natal development of any organ system evaluated and had no adverse effects on the central nervous system and reproductive system.
Hepatic effects	
Distribution studies using radiolabelled mirabegron showed higher levels of radioactivity in the liver than in plasma in rodents and non-rodents. *Mice*: A higher incidence of hepatocelluar adenoma was determined in mirabegron-treated mice in the 2-year carcinogenicity study. Incidence was significant in low-dose animals only and showed a hormetic dose-response. Similar findings were not present in either the 2-year rat carcinogenicity study (34.6-fold the non-protein bound human AUC at MRHD; 35.2-fold the total human AUC at MRHD) nor were neoplastic findings noted in the liver of monkeys repeatedly treated with mirabegron for up to 52 weeks (13.5-fold the non-protein bound human AUC at MRHD; 8.1-fold the total human AUC at MRHD).	Hepatic findings were observed in non-clinical studies at systemic exposures >3.7-fold non-protein bound human systemic exposure at MRHD. As such, mirabegron at the recommended dose appears to pose a minimal risk to humans. In patients with mild hepatic impairment concomitantly receiving strong CYP3A4 inhibitors, the recommended dose of mirabegron is 25 mg once daily.
Table continued on next page	

Key safety findings (from non-clinical studies)	Relevance to human usage
Rat: Increases in liver enzymes were noted in the 2-week repeated dose study without histopathological findings at a dose of 30 mg/kg (3.7-fold the non-protein bound human AUC at MRHD; 4.8-fold the total human AUC at MRHD). Increased liver enzymes and hepatocellular necrosis were observed in males in the 13-week rat repeated dose study at doses ≥ 30 mg/kg (7.8-fold the non-protein bound human AUC at MRHD; 15.2-fold the total bound human AUC at MRHD). Transient increase in liver enzymes with accompanying eosinophilic changes (eosinophilic liposomes in hepatocytes and/or Kupffer cells) attributable to decreased glycogen particles were reported in the 26-week repeated dose study at doses >30 mg/kg (10.9-fold the non- protein bound human AUC at MRHD; 14.2-fold the total human AUC at MRHD). The eosinophilic changes were considered to be reflections of altered lipid metabolism, which is known to occur only in rodents that were administered mirabegron. Hepatocellular necrosis not confirmed in the 26-week study. *Dog* In a 3-day repeated dose study, slight increases in transaminases and alkaline phosphatase were observed at a dose of 20 mg/kg (35.9-fold the non-protein bound human AUC at MRHD; 25.1-fold the total human AUC at MRHD). Hepatocellular hypertrophy/deposition of lipid droplets was also recorded. Neither of these findings was confirmed by a 14-day repeated dose dog study. *Monkey*: Clinically relevant changes in liver transaminases were not observed.	
Central nervous system effects	
Penetration of mirabegron into the CNS is poor. The compound is a substrate of the P-gp transporter; the concentration at which transport changes occurred (1000 μM) was 21907-fold higher than the non-protein bound human C_{max} and mirabegron did not inhibit P-gp. *Mice*: Prone position and increased body temperature were observed at doses ≥10 mg/kg. At 100 mg/kg observations included decreased alertness, limb tone, abdominal muscle tone, and suspension force. *Rat*: At 30, 100, and 300 mg/kg, p.o., decrease in spontaneous activity was observed. At 100 mg/kg, side positioning, moderate decreased grip strength, slight palpebral closure and deep respiration were noted. At 300 mg/kg, decreased muscle tone, loss of righting reflex, abnormal body position, palpebral closure and deep respiration were observed. Although mirabegron leads to an increase in body temperature in rodents, this response is not indicative of a CNS effect but rather mediated by uncoupling electron transport in brown fat.	Non-clinical data suggest that mirabegron is unlikely to have significant CNS effects in humans at the recommended therapeutic dose.
Table continued on next page	

Key safety findings (from non-clinical studies)	Relevance to human usage
Monkey: Neurobehavioral effects were observed at doses of ≥60 mg/kg (51.7-fold the non-protein bound human systemic exposure at MRHD; 31.3-fold the total human AUC at MRHD). Ptosis occurred in this species at non-protein bound plasma concentrations 15.9- to 51.7-fold higher than observed in humans at the MRHD (9.7 to 31.3-fold the total human systemic exposure at MRHD), but these levels would be present in humans only at toxic doses.	

AUC: area under the plasma concentration-time curve; AR: adrenoceptor; Cmax: maximum (or peak) serum concentration; CNS: central nervous system; ECG: electrocardiography; GLP: Good Laboratory Practice; hERG: human ether-a-go-go-related gene; ICaL: L-type calcium current; IKs: outward currents in heart muscle cells; IKto: rapidly activating transient outward current; INa: rapidly activating sodium current; MRHD: maximum recommended human dose; PND: post-natal day; p.o.: per os (orally); NOAEL: no-observed-adverse-effect level; QTc: QT interval corrected for heart rate; QTcB: QT interval corrected for heart rate using Bazett's formula.

Module SIII. Clinical trial exposure

Data-lock point for this Module	30-Jun-2020
Version when Module last updated	8.0

SIII.1 Brief overview of development

SIII.1.1 Mirabegron monotherapy clinical development program

Until the data-lock point (DLP) of 30-Jun-2020, the mirabegron monotherapy clinical development program consists of 53 completed studies in volunteers, patients with OAB, patients with lower urinary tract symptoms/bladder outlet obstruction (LUTS/BOO) or patients with type 2 diabetes mellitus. There is a total of 35 phase 1 studies in volunteers, 14 phase 2/3 studies (11 in patients with OAB, 1 in patients with LUTS/BOO and 2 in patients with type 2 diabetes mellitus) and 4 phase 4 studies which have been conducted globally in Europe, the US, Canada, Japan, Australia/New Zealand, South Africa, China, India, Korea, and Taiwan.

Of the 53 completed studies in the mirabegron monotherapy clinical development program, 4 phase 1 studies in healthy volunteers and 2 phase 3 studies in patients with OAB conducted in Asia were completed after the new drug application (NDA) submission to the Food and Drug Administration (FDA) and the Marketing authorization application (MAA) submission to the European Medicines Agency (EMA), and after obtaining Marketing Authorization (MA).

Clinical trial exposure is presented based on the 53 completed studies. Additional information and analyses in this RMP are presented on 5 safety populations which are based on the 12 phase 2 and 3 completed studies at the time of the NDA submission to the FDA and MAA submission to EMA. A description of each safety population is given below and in [Table 3].

Randomized, blinded trial populations

- Global OAB 12-week Phase 2/3: This population consists of the 6 placebo-controlled, double-blind, 12-week phase 2/3 studies conducted globally in Europe, North America, Japan, and Australia in patients with OAB. Three of the 6 studies also included tolterodine extended release (ER) 4 mg as an active comparator group. These studies all used the same formulation (oral controlled absorption system [OCAS]), and had the same duration (12 weeks), design (double-blind, placebo-controlled) and indication (OAB).
- Europe/North America OAB 12-week Phase 3: This population is a subset of the Global OAB 12-week Phase 2/3 Population and includes data from 3 placebo-controlled, double-blind, 12-week phase 3 studies conducted in Europe, North America and Australia in patients with OAB. One of the 3 studies also included tolterodine ER 4 mg as an active comparator group.
- Europe/North America Long-term Controlled: This population consists of study 178-CL-049, a 12-month, double-blind phase 3 study with an active-controlled tolterodine ER 4 mg comparator arm conducted in Europe, North America, Australia/New Zealand and South Africa in patients with OAB. Patients who completed studies 178-CL-046 or 178-CL-047 and met inclusion and exclusion criteria could be re-randomized in study 178-CL-049 after a 30-day washout period; mirabegron-naïve patients could also enter study 178-CL-049.

Global phase 2/3 clinical trial populations (including open extension)

- Global Phase 2/3: This population includes all patients who received at least 1 dose of mirabegron in a phase 2/3 study. The 12 studies included in this population were of varying durations (4 weeks, 12 weeks, 52 weeks), indications (OAB, LUTS/BOO, type 2 diabetes mellitus), mirabegron formulations (immediate release [IR] or OCAS), study designs (double-blind, open-label) and geographic locations (Europe, North America, Japan, Australia/New Zealand, South Africa).

Japanese uncontrolled phase 3 trial population

- Japanese Long-term Uncontrolled: This population consists of study 178-CL-051, a Japanese long-term study (52 weeks) to study the safety and efficacy of treatment with YM178. The total duration of the study was 53 weeks, consisting of a 1-week run-in and 52-week treatment period.

Table 3 Overview of mirabegron monotherapy global phase 2/3 completed studies and populations at the time of NDA submission to FDA and MAA submission to EMA

Study	Phase	Randomized blinded	Treatment groups	Mirabegron formulation	Population	Treatment duration	Global Phase 2/3	Global OAB 12-week Phase 2/ 3	Europe/North America OAB 12-week Phase 3	Europe/North America Long-term Controlled	Japan Long-term Uncontrolled
178-CL-044	2	X	Placebo, Mirabegron, Tolterodine	OCAS	OAB	12 weeks	X	X			
178-CL-045	2	X	Placebo, Mirabegron	OCAS	OAB	12 weeks	X	X			
178-CL-046	3	X	Placebo, Mirabegron, Tolterodine	OCAS	OAB	12 weeks	X	X	X		
178-CL-047	3	X	Placebo, Mirabegron	OCAS	OAB	12 weeks	X	X	X		
178-CL-048	3	X	Placebo, Mirabegron, Tolterodine	OCAS	OAB	12 weeks	X	X			
178-CL-074	3	X	Placebo, Mirabegron	OCAS	OAB	12 weeks	X	X	X		
178-CL-049	3	X	Mirabegron, Tolterodine	OCAS	OAB	52 weeks	X			X	
178-CL-051	3		Mirabegron	OCAS	OAB	52 weeks	X				X
178-CL-008	2	X	Placebo, Mirabegron, Tolterodine	IR	OAB	4 weeks	X				
178-CL-060	2	X	Placebo, Mirabegron	OCAS	LUTS/BOO	12 weeks	X				
178-CL-003	2	X	Placebo, Mirabegron	IR	Type 2 diabetes mellitus	12 weeks	X				
178-CL-004	2	X	Placebo + Metformin, Mirabegron + Metformin	IR	Type 2 diabetes mellitus	12 weeks	X				

BOO: bladder outlet obstruction; EMA: European Medicines Agency; FDA: Food and Drug Agency; IR: immediate release; LUTS: lower urinary tract symptoms; MAA: marketing authorization application; NDA: new drug application; OAB: overactive bladder; OCAS: oral controlled absorption system.

Since the mirabegron NDA submission to the FDA and the mirabegron MAA submission to the EMA and after obtaining MA, until the DLP of 30-Jun-2020, 1 post-marketing phase 1 study (178-CL-111) in healthy volunteers in Japan, 2 post-marketing phase 3b studies (178-CL-090 and 178-EC-001) and 4 phase 4 studies (178-MA-1001, 178-MA-1005, 178-MA-1008 and 178-MA-3016) have been conducted.

Table 4 Overview of mirabegron monotherapy post-marketing studies

Study	Phase	Randomized	Treatment groups	Treatment duration	Countries	Status
178-CL-111	1	N/A	Mirabegron as add-on to Tolterodine	2 weeks	Japan	Completed
178-CL-090	3	X	Placebo, Mirabegron, Tolterodine	12 weeks	China, India, Korea, Taiwan	Completed
178-EC-001	3b	X	Mirabegron, Solifenacin succinate	12 weeks	Australia, Canada, Europe, Latin America, Middle East	Completed
178-MA-1001	4	X	Mirabegron, Tolterodine	14 weeks	Canada, USA	Completed
178-MA-1005	4	X	Mirabegron, Placebo	20 weeks	Canada, USA	Completed
178-MA-1008	4	X	Mirabegron, Placebo	20 weeks	North America and Europe	Completed
178-MA-3016	4	X	Mirabegron, Placebo	16 weeks	Japan, Korea	Completed

SIII.1.2 Mirabegron and solifenacin combination therapy clinical development program

A clinical development program for the combination of mirabegron and solifenacin succinate (antimuscarinic) for the indication of OAB is currently ongoing (project code EB178). The individual compounds, mirabegron and solifenacin succinate, are approved marketed drugs. Until the DLP of 30-Jun-2020 and since the mirabegron NDA submission to the FDA and the mirabegron MAA submission to the EMA, 4 phase 1 studies (178-CL-103, 178-CL-107, 178-CL-109 and 178-CL-121) in healthy volunteers conducted in Europe, 1 phase 2 study (178-CL-100) in patients with OAB conducted in Europe, 3 phase 3 studies (905-EC-012, 178-CL-101, and 178-CL-102) conducted globally, and 2 post-marketing studies conducted in Japan (178-CL-110 and 178-CL-112) were completed in the mirabegron and solifenacin succinate combination program.

SIII.1.3 Mirabegron pediatric clinical development program

A clinical development program for use of mirabegron in pediatric patients with OAB and neurogenic detrusor overactivity (NDO) is currently ongoing (project code ED178, study 178-CL-204 [planned phase 3 study with prolonged-release microgranula - based suspension in pediatric OAB patients aged 5 to < 18 years] and 178-CL-207 [planned phase 3 study with prolonged-release microgranula - based suspension in pediatric NDO patients aged 6 months to < 5 years]).

Until the DLP of 30-Jun-2020, 4 phase 1 studies have been completed: studies 178-CL-201 and 178-CL-208 in young healthy volunteers conducted in Europe; study 178-CL-202 in pediatric subjects from 5 to less than 18 years of age with NDO or OAB conducted in several European countries; study 178-CL-203 in pediatric subjects from 3 to less than 12 years of age with NDO or OAB conducted in Europe. In addition, 1 phase 3 study has been completed: study 178-CL-206A in pediatric subjects from 3 to less than 18 years of age with NDO was conducted globally (excluding the US).

SIII.2 Clinical trial exposure

SIII.2.1 Mirabegron Clinical Development Program

Overall, until the DLP of 30-Jun-2020, 1933 volunteers and 14266 patients have been enrolled into the mirabegron monotherapy program, of which approximately 1595 volunteers and 8566 patients have received mirabegron.

In the mirabegron monotherapy clinical development program, patients and volunteers were treated with mirabegron in doses ranging from 0.1 to 400 mg per day. Except for 2 phase 2 studies in a small number of patients with type II diabetes mellitus (119 patients in total of which 80 received mirabegron) and 1 phase 2 study in patients with LUTS/BOO (200 patients in total of which 135 received mirabegron), no patients other than the target population with OAB were included in the clinical investigations. In the ongoing clinical development program for mirabegron monotherapy in the pediatric population, the target population consists of patients with OAB and NDO. In the overview on exposure for the mirabegron monotherapy phase 2 through phase 4 studies, no specific distinction is made by indication, though additional tables for OAB were added (Table 5, Table 7 and Table 9). Therefore, exposure tables are presented for the combined phase 2 through phase 4 randomized open-label clinical studies. The completed studies (178-CL-201, 178-CL-208) are part of the development program in the pediatric population, but were conducted in adult volunteers and are therefore summarized in this section.

Exposure is presented based on the Safety Analysis Set (SAF) which consists of all randomized/enrolled subjects who took at least 1 dose of study drug where study drug can refer to double-blind or open-label study drug depending on the study.

The mirabegron monotherapy phase 2 through phase 4 exposure tables display total exposure to any dose of mirabegron, except for exposure by dose level table. Patients who took mirabegron in both studies 178-CL-046/047 and 178 CL-049 will be presented such that the

exposure duration from studies 178-CL-046/047 and 178-CL-049 are added together for 1 measure of cumulative exposure (similarly for the titration studies). The exposure by dose level table presents patients under the treatment dose group to which the patient was exposed to the longest. In studies which include dose titrations of mirabegron (178-CL-003, 178-CL-004, 178-CL-051, and 178-MA-1005), a patient is counted once under the mirabegron total daily dose treatment group with the longest exposure.

The exposure by duration is not presented for the mirabegron monotherapy phase 1 clinical studies since mirabegron was taken for a short duration except for an intraocular pressure study in 320 subjects who could have taken mirabegron for up to 8 weeks.

The exposure by duration for the mirabegron monotherapy phase 2 through phase 4 clinical studies is presented in the table below:

Table 5 Exposure by duration, mirabegron monotherapy phase 2 through 4 clinical studies†

Cumulative for all indications (person time)		
Duration of exposure (days)	**Patients**	**Person time (year)**
≥ 1	8549	NA
≥ 7	8469	NA
≥ 14	8395	NA
≥ 28	8236	NA
≥ 56	7725	NA
≥ 84	5896	NA
≥ 182	1621	NA
≥ 274	1508	NA
≥ 365	964	1108.7
Missing	17	NA
Total person time	**8566*****	**3181.9†††**
Indication: OAB		
Duration of exposure (days)	**Patients**	**Person time (year)**
≥ 1	8335	NA
≥ 7	8255	NA
≥ 14	8184	NA
≥ 28	8026	NA
≥ 56	7520	NA
≥ 84	5736	NA
≥ 182	1621	NA
≥ 274	1508	NA
≥ 365	964	1108.7
Missing	16	NA
Total person time for indication	**8351*****	**3133.9†††**

Studies included: 178-CL-003, 178- CL-004, 178-CL-008, 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048, 178-CL-049, 178-CL-051, 178-CL-060, 178-CL-074, 178-CL-090, 178-EC-001 and 178-MA-1001, 178-MA-1005*** 178-MA-3016* and 178-MA-1008**.

NA: not applicable.

† Includes subjects from completed studies until 30-Jun-2020.

Footnotes continued on next page

Exposure is presented for any exposure to mirabegron such that duration is summed across doses of mirabegron within a study or between studies.

‡ Person Time (year) at final duration category (≥ 365 days) is the sum of exposure to study drug expressed in years for the subset of patients with ≥ 365 days of study drug exposure; where patient exposure at final duration category is the last dosing date – first dosing date + 1.

††Total Person time (year) is the sum of exposure to study drug expressed in years for all patients from day 1 of dosing through last day of dosing; where duration of exposure is the last dosing date - first dosing date + 1.

*All subjects in clinical trial 178-MA-3016 started in a 4-week screening period on tamsulosin 0.2 mg; 162 subjects did not complete this run-in period and 2 more subjects were randomized after completion of the run-in period but not treated in the double-blind study period.

**All subjects in clinical trial 178-MA-1008 started in a 4-week screening period on tamsulosin 0.4 mg; 293 subjects did not complete this run-in period and 9 more subjects were randomized after completion of the run-in period but not treated in the double-blind study period.

***The data in Table 5 excluded patients in study 178-MA-1005 based on major GCP violations at 1 site which are described below.

Twenty-two patients randomized in study 178-MA-1005 at 1 specific study site are excluded in this table due to concerns with the data because protocol noncompliance study misconduct and GCP violations were observed at this site.

The exposure by dose level for mirabegron monotherapy phase 1 clinical studies is presented in [Table 6] and for phase 2 through phase 4 clinical studies in [Table 7].

Table 6 Exposure by dose level, mirabegron monotherapy phase 1 clinical studies†

Mirabegron treatment category	Total daily dose of mirabegron (mg)	Persons‡
Overall mirabegron		**1595**
Mirabegron IR/OCAS single dose	< 25	29
	≥ 25 to < 50	47
	≥ 50 to < 100	187
	≥ 100 to < 200	308
	≥ 200	42
	Total	**589**
Mirabegron IR/OCAS multiple dose	< 25	0
	≥ 25 to < 50	78
	≥ 50 to < 100	208
	≥ 100 to < 200	580
	≥ 200	223
	Total	**975**
Mirabegron IV	**Total**	**103**
Mirabegron Suspension	**Total**	**49**

Studies included: 178-CL-001, 178-CL-002, 178-CL-005, 178-CL-006, 178-CL-007, 178-CL-030, 178-CL-031, 178-CL-033, 178-CL-034, 178-CL-036, 178-CL-037, 178-CL-038, 178-CL-039, 178-CL-040, 178-CL-041, 178-CL-053, 178-CL-058, 178-CL-059, 178-CL-064, 178-CL-066, 178-CL-068, 178-CL-069, 178-CL-070, 178-CL-072, 178-CL-076, 178-CL-077, 178-CL-078, 178-CL-080, 178-CL-081, 178-CL-091, 178-CL-092, 178-CL-093, 178-CL-111, 178-CL-201 and 178-CL-208.

IR: immediate release; OCAS: oral controlled absorption system; IV: intravenous.

† Includes subjects from completed studies until 30-Jun-2020.

‡ A subject may be counted in more than 1 treatment category, but will be counted once in the overall mirabegron group.

Table 7 Exposure by dose level, mirabegron monotherapy phase 2 through 4 clinical studies†

Total daily dose of mirabegron (mg)	Persons§	Person time (year) ‡
< 25	0	0
≥ 25 to < 50	1184	239.8
≥ 50 to < 100	5144	1680.3
≥ 100 to < 200	1847	957.5
≥ 200	374	62.0
Missing	17	0
Total	**8566**	**2939.6††**
Indication: OAB		
< 25	0	0
≥ 25 to < 50	1114	239.8
≥ 50 to < 100	5074	1664.7
≥ 100 to < 200	1780	943.1
≥ 200	297	47.3
Missing	16	0
Total	**8351**	**2895††**

Studies included: 178-CL-003, 178- CL-004, 178-CL-008, 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048, 178-CL-049, 178-CL-051, 178-CL-060, 178-CL-074, 178-CL-090, 178-EC-001 and 178-MA-1001, 178-MA-1005***, 178-MA-3016* and 178-MA-1008**.

† Includes subjects from completed studies until 30-Jun-2020.

§ A patient is counted only once under the mirabegron total daily dose with the longest exposure.

‡ Person time (year) is the sum of exposure to study drug expressed in years for all patients within a category; where duration of exposure is the last dosing date - first dosing date + 1.

††Total Person time (year) is the sum of exposure to study drug expressed in years for all patients; where duration of exposure is the last dosing date - first dosing date + 1.

*All subjects in clinical trial 178-MA-3016 started in a 4-week screening period on tamsulosin 0.2 mg; 162 subjects did not complete this run-in period and 2 more subjects were randomized after completion of the run-in period but not treated in the double-blind study period.

**All subjects in clinical trial 178-MA-1008 started in a 4-week screening period on tamsulosin 0.4 mg; 293 subjects did not complete this run-in period and 9 more subjects were randomized after completion of the run-in period but not treated in the double-blind study period.

***The data in Table 7 excluded patients in study 178-MA-1005 based on major GCP violations at 1 site see description above in Table 5.

The exposure by age group and gender for mirabegron monotherapy phase 1 clinical studies is presented in [Table 8] and for phase 2 through phase 4 clinical studies in [Table 9].

Table 8 Exposure by age group and gender, mirabegron monotherapy phase 1 clinical studies†

Mirabegron treatment category	Age range (years)	Persons‡	
		Male	Female
Overall mirabegron	< 45	733	455
	≥ 45 to < 65	206	131
	≥ 65 to < 75	34	28
	≥ 75	3	5
	Total	**976**	**619**
Mirabegron IR/OCAS single dose	< 45	328	143
	≥ 45 to < 65	58	41
	≥ 65 to < 75	10	4
	≥ 75	2	3
	Total	**398**	**191**
Mirabegron IR/OCAS multiple dose	< 45	389	299
	≥ 45 to < 65	146	90
	≥ 65 to < 75	24	24
	≥ 75	1	2
	Total	**560**	**415**
Mirabegron IV	< 45	53	32
	≥ 45 to < 65	12	6
	≥ 65 to < 75	0	0
	≥ 75	0	0
	Total	**65**	**38**
Mirabegron Suspension	< 45	23	25
	≥ 45 to < 65	1	0
	≥ 65 to < 75	0	0
	≥ 75	0	0
	Total	**24**	**25**

Studies included: 178-CL-001, 178-CL-002, 178-CL-005, 178-CL-006, 178-CL-007, 178-CL-030, 178-CL-031, 178-CL-033, 178-CL-034, 178-CL-036, 178-CL-037, 178-CL-038, 178-CL-039, 178-CL-040, 178-CL-041, 178-CL-053, 178-CL-058, 178-CL-059, 178-CL-064, 178-CL-066, 178-CL-068, 178-CL-069, 178-CL-070, 178-CL-072, 178-CL-076, 178-CL-077, 178-CL-078, 178-CL-080, 178-CL-081, 178-CL-091, 178-CL-092, 178-CL-093, 178-CL-111, 178-CL-201 and 178-CL-208.

IR: immediate release; OCAS: oral controlled absorption system; IV: intravenous.

† Includes subjects from completed studies until 30-Jun-2020.

‡ Subjects may be counted in more than 1 mirabegron treatment category, but will be counted once in the overall mirabegron group.

Table 9 Exposure by age group and gender, mirabegron monotherapy phase 2 through phase 4 clinical studies†

Age range (years)	Male		Female	
	Persons	Person time (year)‡	Persons	Person time (year)‡
≥ 18 to < 65	1349	487.4	3835	1487.31
≥ 65 to < 75	949	309.3	1536	587.6
≥ 75 to < 85	339	113.1	513	185.5
≥ 85	18	4.8	27	6.9
Total	**2655**	**914.6††**	**5911**	**2267.3††**
Indication: OAB				
≥ 18 to < 65	1235	462	3802	1479.8
≥ 65 to < 75	908	300.3	1529	586.0
≥ 75	320	108.9	513	185.5
	17	4.8	27	6.9
Total	**2480**	**875.8††**	**5871**	**2258.2††**

Studies included: 178-CL-003, 178- CL-004, 178-CL-008, 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048, 178-CL-049, 178-CL-051, 178-CL-060, 178-CL-074, 178-CL-090, 178-EC-001, 178-MA-1001, 178-MA-1005***, 178-MA-3016* and 178-MA-1008**.

† Includes subjects from completed studies until 30-Jun-2020.

Exposure is presented for any exposure to mirabegron such that duration is summed across doses of mirabegron within a study or between studies.

‡ Person time (year) is the sum of exposure to study drug expressed in years for all patients within a category; where duration of exposure is the last dosing date - first dosing date + 1.

††Total Person time (year) is the sum of exposure to study drug expressed in years for all patients within a gender; where duration of exposure is the last dosing date - first dosing date + 1.

*All subjects in clinical trial 178-MA-3016 started in a 4-week screening period on tamsulosin 0.2 mg; 162 subjects did not complete this run-in period and 2 more subjects were randomized after completion of the run-in period but not treated in the double-blind study period.

**All subjects in clinical trial 178-MA-1008 started in a 4-week screening period on tamsulosin 0.4 mg; 293 subjects did not complete this run-in period and 9 more subjects were randomized after completion of the run-in period but not treated in the double-blind study period.

***The data in Table 9 excluded patients in study 178-MA-1005 based on major GCP violations at 1 site, see description above in Table 5.

The exposure by racial origin for mirabegron monotherapy phase 1 clinical studies is presented in [Table 10] and for phase 2 through phase 4 clinical studies in [Table 11].

Table 10 Exposure by racial origin, mirabegron monotherapy phase 1 clinical studies†

Mirabegron treatment category	Racial origin	Subjects‡
Overall mirabegron	Caucasian	1034
	Black	238
	Asian	262
	Other	61
	Total	**1595**
Mirabegron IR/OCAS single dose	Caucasian	345
	Black	57
	Asian	161
	Other	26
	Total	**589**
Mirabegron IR/OCAS multiple dose	Caucasian	658
	Black	181
	Asian	101
	Other	35
	Total	**975**
Mirabegron IV	Caucasian	74
	Black	18
	Asian	2
	Other	9
	Total	**103**
Mirabegron Suspension	Caucasian	47
	Black	0
	Asian	1
	Other	1
	Total	**49**

Studies included: 178-CL-001, 178-CL-002, 178-CL-005, 178-CL-006, 178-CL-007, 178-CL-030, 178-CL-031, 178-CL-033, 178-CL-034, 178-CL-036, 178-CL-037, 178-CL-038, 178-CL-039, 178-CL-040, 178-CL-041, 178-CL-053, 178-CL-058, 178-CL-059, 178-CL-064, 178-CL-066, 178-CL-068, 178-CL-069, 178-CL-070, 178-CL-072, 178-CL-076, 178-CL-077, 178-CL-078, 178-CL-080, 178-CL-081, 178-CL-091, 178-CL-092, 178-CL-093, 178-CL-111, 178-CL-201, and 178-CL-208.

IR: immediate release; OCAS: oral controlled absorption system; IV: intravenous.

† Includes subjects from completed studies until 30-Jun-2020.

‡ A subject may be counted in more than 1 mirabegron treatment category, but will be counted once in the overall mirabegron group.

Table 11 Exposure by racial origin, mirabegron monotherapy phase 2 through phase 4 clinical studies†

Racial origin	Subjects	Person time (year)†,‡
White	6247	2494.1
Black or African American	284	87.1
Asian	1983	582.2
Other	45	17.3
Unknown	7	1.2
Total	**8566**	**3181.9**

Clinical trials included: 178-CL-003, 178- CL-004, 178-CL-008, 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048, 178-CL-049, 178-CL-051, 178-CL-060, 178-CL-074, 178-CL-090, 178-EC-001, 178-MA-1001, 178-MA-1005***, 178-MA-1008** and 178-MA-3016*. In study 178-MA-3016, race was not collected, but the study was conducted in Japanese and Korean subjects.

†Includes patients from completed clinical trials until 30-Jun-2020. Exposure is presented for any exposure to mirabegron such that duration is summed across doses of mirabegron within a study or between studies.

‡Person time (year) is the sum of exposure to study drug expressed in years for all patients within a category; where duration of exposure is the last dosing date - first dosing date + 1. Total Person Time (year) is the sum of exposure to study drug expressed in years for all patients; where duration of exposure is the last dosing date - first dosing date + 1.

*All subjects in clinical trial 178-MA-3016 started in a 4-week screening period on tamsulosin 0.2 mg; 162 subjects did not complete this run-in period and 2 more subjects were randomized after completion of the run-in period but not treated in the double-blind study period.

**All subjects in clinical trial 178-MA-1008 started in a 4-week screening period on tamsulosin 0.4 mg; 293 subjects did not complete this run-in period and 9 more subjects were randomized after completion of the run-in period but not treated in the double-blind study period.

***The data in Table 11 excluded patients in study 178-MA-1005 based on major GCP violations at 1 site, see description above in Table 5.

Patient populations described in this section include exposure by baseline renal status and baseline hypertension status.

Baseline renal status was determined for 3 mirabegron monotherapy phase 2 and 3 populations (Global OAB 12-week Phase 2/3, Europe/North America OAB 12-week Phase 3, and Europe/North America Long-term Controlled) as shown in [Table 12], [Table 13] and [Table 14]. Baseline hypertension status was determined in 2 mirabegron monotherapy phase 2 and 3 populations (Europe/North America OAB 12-week Phase 3 and Europe/North America Long-term Controlled) in which blood pressure measurements were collected in patient diaries, as shown in [Table 13] and [Table 14].

Baseline Creatinine Clearance refers to renal status based on estimated calculated creatinine clearance by the Cockcroft Gault method measured in mL/min.

Baseline Hypertension Status is defined according to criteria in the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure seventh report (JNC7), from baseline systolic and diastolic blood pressure measurements collected in the patient diary. A patient is categorized in the most severe category of hypertension based on the greater of 2 parameters - systolic blood pressure [SBP] or diastolic blood pressure [DBP]) relative to the given thresholds: Normal – SBP < 120 mmHg and DBP < 80 mmHg;

Prehypertension – SBP 120 to 139 mmHg or DBP 80 to 89 mmHg; Stage 1 Hypertension – SBP 140 to 159 mmHg or DBP 90 to 99 mmHg; Stage 2 Hypertension – SBP ≥ 160 mmHg or DBP ≥ 100 mmHg.

Table 12 Exposure by patient populations, mirabegron monotherapy Global OAB 12-week Phase 2/3 Population

Baseline creatinine clearance (mL/min)†	Total mirabegron (n=4414)	
	Persons	Person time (year)‡
≥ 90 (normal)	2296	503.0
60 to < 90 (mild)	1726	380.7
30 to < 60 (moderate)	384	81.7
< 30 (severe)	6	0.8
Not reported	2	0.5

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

OAB: overactive bladder.

† Baseline Creatinine Clearance refers to renal status based on estimated calculated creatinine clearance by Cockcroft Gault (CG) measured in mL/min.

‡ Person time (year) is the sum of exposure to study drug expressed in years for all patients within a category; where duration of exposure is the last dosing date - first dosing date + 1.

Table 13 Exposure by patient populations, mirabegron monotherapy Europe/North America OAB 12-week Phase 3 Population

Parameter category	Total mirabegron (n=2736)	
	Persons	Person time (year)‡
Baseline creatinine clearance (mL/min)†		
≥ 90 (normal)	1483	321.6
60 to < 90 (mild)	1026	225.7
30 to < 60 (moderate)	222	47.3
< 30 (severe)	3	0.3
Not reported	2	0.5
Baseline hypertension status (JNC7 Criteria)§		
SBP < 120 mmHg AND DBP < 80 mmHg	850	185.5
SBP 120 to 139 mmHg OR DBP 80 to 89 mmHg	1329	291.4
SBP 140 to 159 mmHg OR DBP 90 to 99 mmHg	466	99.1
SBP ≥ 160 mmHg OR DBP ≥ 100 mmHg	91	19.4

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

DBP: diastolic blood pressure; JNC7: Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure seventh report; OAB: overactive bladder; SBP: systolic blood pressure.

‡ Baseline Creatinine Clearance refers to renal status based on estimated calculated creatinine clearance by Cockcroft Gault (CG) measured in mL/min.

§ Baseline Hypertension Status is defined according to criteria in JNC7 from baseline systolic and diastolic blood pressure measurements collected in the patient diary; a patient is categorized in the most severe category of hypertension based on the greater of 2 parameters (SBP or DBP) relative to the given thresholds.

‡ Person time (year) is the sum of exposure to study drug expressed in years for all patients within a category; where duration of exposure is the last dosing date - first dosing date + 1.

Table 14 Exposure by patient populations, mirabegron monotherapy Europe/North America Long-term Controlled Population

Parameter category	Total mirabegron (n=1632)	
	Persons	Person time (year)‡
Baseline creatinine clearance (mL/min)†		
≥ 90 (normal)	869	739.8
60 to < 90 (mild)	605	521.2
30 to < 60 (moderate)	154	130.9
< 30 (severe)	0	0
Not Reported	4	4.0
Baseline hypertension status (JNC7 Criteria)§		
SBP < 120 mmHg AND DBP < 80 mmHg	462	390.7
SBP 120 to 139 mmHg OR DBP 80 to 89 mmHg	857	738.3
SBP 140 to 159 mmHg OR DBP 90 to 99 mmHg	271	230.8
SBP ≥ 160 mmHg OR DBP ≥ 100 mmHg	41	35.2
Not Reported	1	1.0

Study included: 178-CL-049.

DBP: diastolic blood pressure; JNC7: Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure seventh report; SBP: systolic blood pressure.

† Baseline Creatinine Clearance refers to renal status based on estimated calculated creatinine clearance by Cockcroft Gault (CG) measured in mL/min.

§ Baseline Hypertension Status is defined according to criteria in JNC7 from baseline systolic and diastolic blood pressure measurements collected in the patient diary; a patient is categorized in the most severe category of hypertension based on the greater of 2 parameters (SBP or DBP) relative to the given thresholds.

‡ Person time (year) is the sum of exposure to study drug expressed in years for all patients within a category; where duration of exposure is the last dosing date - first dosing date + 1.

Exposure in the ongoing mirabegron monotherapy clinical study is presented in the table below:

Table 15 Estimated Exposure in Ongoing Mirabegron Monotherapy Clinical Trials

Study number	Phase	Number of persons randomized†, all treatments
178-MA-2294	4	0

†Includes subjects randomized until 30-Jun-2020.

SIII.2.2 Mirabegron and solifenacin combination therapy clinical development program

Overall, until the DLP of 30-Jun-2020, 166 healthy volunteers and 7629 patients have received at least 1 dose of study drug in the mirabegron and solifenacin succinate combination therapy program, of which approximately 166 healthy volunteers received combination therapy and 4189 patients received combination therapy, 1265 patients received mirabegron only, and 2411 patients received solifenacin succinate only.

The mirabegron and solifenacin succinate combination therapy phase 1 through phase 3 studies were conducted using oral formulations for both mirabegron and solifenacin succinate. The phase 1 studies 178-CL-103 and 178-CL-121 had both a fixed dose combination (FDC) tablet of mirabegron and solifenacin succinate and co-administration of single entity tablets (SET) of mirabegron and solifenacin succinate. The other 2 phase 1 studies and the phase 2 and 3 studies were conducted using co-administration of SET of mirabegron and solifenacin succinate.

Exposure is presented based on the SAF which consists of all randomized subjects who took at least 1 dose of study drug. Patients who took mirabegron or solifenacin, or combination treatment in both studies 178-CL-101/905-EC-012 and 178 CL-102 will be presented such that the exposure duration from studies 178-CL-101/905-EC-012 and 178-CL-102 are added together for one measure of cumulative exposure.

The exposure by duration is not presented for the mirabegron and solifenacin succinate combination phase 1 clinical studies since only a single dose of combination therapy was taken within each treatment period.

The exposure by duration for the mirabegron and solifenacin succinate combination phase 2 and 3 clinical studies is presented in [Table 16].

Table 16 Exposure by duration, mirabegron and solifenacin succinate combination therapy phase 2 and 3 clinical studies†

Treatment group	Duration of exposure (days)	Persons	Person time (year)‡
Mirabegron + Solifenacin succinate	≥ 1	4189	NA
	≥ 7	4169	NA
	≥ 14	4147	NA
	≥ 28	4088	NA
	≥ 56	3988	NA
	≥ 84	3485	1944.2
	≥ 112	1490	1473.5
	≥ 182	1295	1406.3
	≥ 273	1253	1379.2
	≥ 365	823	955.2
	Total	**4189**	**2067.7††**
Mirabegron only	≥ 1	1265	NA
	≥ 7	1255	NA
	≥ 14	1245	NA
	≥ 28	1231	NA
	≥ 56	1192	NA
	≥ 84	994	457.6
	≥ 112	291	293.0
	≥ 182	277	287.6
	≥ 273	272	284.8
	≥ 365	146	160.3
	Total	**1265**	**505.6††**

Table continued on next page

Treatment group	Duration of exposure (days)	Persons	Person time (year)‡
Solifenacin succinate only	≥ 1	2411	NA
	≥ 7	2400	NA
	≥ 14	2386	NA
	≥ 28	2362	NA
	≥ 56	2305	NA
	≥ 84	1879	670.2
	≥ 112	314	305.0
	≥ 182	285	292.2
	≥ 273	271	283.9
	≥ 365	154	167.9
	Total	**2411**	**771.4††**
Mirabegron + Imidafenacin	≥ 1	161	NA
	≥ 7	160	NA
	≥ 14	158	NA
	≥ 28	157	NA
	≥ 56	153	NA
	≥ 84	146	137.7
	≥ 112	145	137.4
	≥ 182	140	135.8
	≥ 273	134	131.9
	≥ 365	37	37.4
	Total	**161**	**139.4††**
Mirabegron + Propiverine	≥ 1	161	NA
	≥ 7	160	NA
	≥ 14	159	NA
	≥ 28	155	NA
	≥ 56	146	NA
	≥ 84	146	135.2
	≥ 112	141	133.9
	≥ 182	135	131.8
	≥ 273	130	128.8
	≥ 365	38	38.3
	Total	**161**	**136.3††**
Mirabegron + Tolterodine	≥ 1	159	NA
	≥ 7	159	NA
	≥ 14	158	NA
	≥ 28	154	NA
	≥ 56	146	NA
	≥ 84	142	131.7
	≥ 112	137	130.5
	≥ 182	133	128.9
	≥ 273	127	125.3
	≥ 365	29	29.2
	Total	**159**	**133.4††**

Clinical trials included: 178-CL-100, 178-CL-110, 178-CL-101**, 178-CL-102**, 178-CL-112, and 905-EC-012**.

NA: not applicable.

† Includes subjects from completed studies until 30-Jun-2020.

‡ Person time (year) at final duration category (≥ 84 days) is the sum of exposure to study drug within a treatment group expressed in years for the subset of patients with ≥ 84 days of study drug exposure; where patient exposure at final duration category is the last dosing date – first dosing date + 1.

Footnotes continued on next page

††Total Person time (year) is the sum of exposure to study drug for all patients within a treatment group expressed in years from day 1 of dosing through last day of dosing; where duration of exposure is the last dosing date - first dosing date + 1.

*All patients in clinical trial 905-EC-012 started in a 4-week run-in period on solifenacin succinate 5 mg; 227 subjects did not complete this run-in period and 2 more patients were randomized after completion of the run-in period but not treated in the double-blind study period.

**The data in Table 13 included patients in 178-CL-101, 905-EC-012, and 178-CL-102 otherwise excluded based on major GCP violations at 1 site which are described below.

178-CL-101: Protocol noncompliance, study misconduct and GCP violations were identified at 1 of the participating sites. Gross protocol noncompliance in terms of OAB diagnosis and type of incontinence (stress or urgency incontinence) for all patients screened and randomized at this site were observed. All efficacy data including micturition diary data and patient reported health outcomes appeared to be questionable. In addition, a blinded interim bioanalytical summary report indicated that about 30% of the patients randomized to active treatment had no quantifiable drug concentrations suggesting that these patients may not have taken study drug. Hence the decision was made to exclude patients from this site from the Safety Analysis Set (SAF), Full Analysis Set (FAS), Per Protocol Set and Pharmacokinetic Analysis Set. A modified SAF was generated to facilitate inclusion of all randomized patients who received at least 1 dose of double-blind treatment from all sites including patients from this site in listings. In addition, a separate overview table of treatment emergent adverse events (TEAEs) and a separate table of TEAEs for this site were created. At this site 2 pregnancies occurred and were also summarized separately. Critical findings were observed during a GCP audit of another site. After further data review and follow-up with the site, it became clear that for some patients, data entry into the electronic diary was performed by the investigator for patients who were not able to record the data into the diaries themselves. Since it was not possible to identify the patients who could not adequately record data into the electronic diaries themselves, the decision was made to exclude all randomized patients from the Per Protocol Set analysis set and to conduct a sensitivity analysis for the coprimary and key secondary efficacy variables excluding this site from the FAS.

905-EC-012: During the final blinded data review meeting for this study, some unusual patterns of matching and repetitive data patterns were observed in the patient reported electronic diary data for 52 of 58 patients randomized at 1 of the participating sites. Of specific concern was a high number of voiding events reported within 1 minute of each other for several different patients, unusual patterns in the mean volume voided reported by patients, a very high percentage of patients becoming continent at week 12, and the low number of adverse events (AEs) reported by patients enrolled at this site. Because of these unusual patterns, Astellas Global Clinical and Research Quality Assurance conducted a directed for-cause audit at this site, the main purpose of which was to investigate the unusual electronic diary (e-diary) data. During the audit, review of the patients' addresses revealed that many of the patients lived close to each other and it was thought that they could have completed their e-diary data together. While no fraud or misconduct was identified confirmed by the auditors, they confirmed that they had concerns about the integrity and quality of the patient-reported diary data, which was the basis for the primary and key secondary endpoints of the study. The primary analysis included all patients from the FAS, including all appropriate patients from this site. In addition, a sensitivity analysis was conducted in which all patients from this site were excluded.

No difference in the overall results and conclusions of the study was detected following this analysis.

Note that the patient data from this site were excluded only retrospectively during integration for the Integrated Safety Summary as more definitive evidence about the findings at this site surfaced after the study was finalized.

178-CL-102: Protocol noncompliance, study misconduct and GCP violations were identified at this site. Gross protocol noncompliance in terms of OAB diagnosis and type of incontinence (stress or urgency incontinence) for all patients screened and randomized at this site were observed. All efficacy data including micturition eDiary data and patient reported health outcomes appeared to be questionable. Therefore, all 5 randomized patients from this site were discontinued and excluded from the SAF and the FAS. As a result, the listings are based on the modified SAF, which includes all RAS (randomized analysis set) patients (including patients from site 10153) who took ≥ 1 dose of double-blind treatment.

The exposure by dose level for the mirabegron and solifenacin succinate combination therapy phase 1 clinical studies is presented in [Table 17] and for phase 2 through phase 4 clinical studies in [Table 18].

Table 17 Exposure by dose level, mirabegron and solifenacin succinate combination therapy phase 1 clinical studies†

Treatment group and formulation	Mirabegron dose (mg)	Solifenacin dose (mg)	Persons‡
Overall mirabegron + solifenacin succinate			**166**
Mirabegron + Solifenacin FDC single dose	25	2.5	23
	25	5	24
	50	5	47
	50	10	24
	Total		**118**
Mirabegron + Solifenacin coadministration of SET single dose	25	2.5	24
	25	5	24
	50	5	47
	50	10	24
	Total		**119**
Mirabegron + Solifenacin coadministration of SET multiple dose	50	5	46
	Total		**46**

Studies included: 178-CL-103, 178-CL-107, 178-CL-109, and 178-CL-121.

FDC: fixed dose combination; SET; single entity tablets.

† Includes subjects from completed studies until 30-Jun-2020.

‡ Subjects who received more than 1 formulation are counted in all formulations they received. For the overall mirabegron + solifenacin succinate group, a subject is counted once regardless of formulation.

Table 18 Exposure by dose level, mirabegron and solifenacin succinate combination therapy phase 2 through 4 clinical studies†

Treatment group	Mirabegron dose (mg)	Solifenacin dose (mg)	Persons	Person time (year)‡
Mirabegron + Solifenacin	25	2.5	184	43.7
	25	5	1080	241.4
	25	10	81	18.7
	50	2.5	186	45.0
	50	5	2862	1700.6
	50	10	81	18.3
	Total		**4189**	**2067.7††**
Mirabegron only	25	NA	513	112.7
	50	NA	789	392.9
	Total		**1265**	**505.6††**
Solifenacin only	NA	2.5	79	17.9
	NA	5	1563	575.4
	NA	10	797	178.1
	Total		**2411**	**771.4††**
Mirabegron + Imidafenacin	**Mirabegron dose (mg)**	**Imidafenacin dose (mg)**		
	50	0.2	161	139.4
	Total		**161**	**139.4††**

Table continued on next page

Footnotes

Treatment group	Mirabegron dose (mg)	Solifenacin dose (mg)	Persons	Person time (year)‡
Mirabegron + Propiverine	**Mirabegron dose (mg)**	**Propiverine dose (mg)**		
	50	20	161	136.3
	Total		**161**	**136.3††**
Mirabegron + Tolterodine	**Mirabegron dose (mg)**	**Tolterodine dose (mg)**		
	50	4	159	133.4
	Total		**159**	**133.4††**

NA: not applicable.

The Safety analysis set was used.

Studies included: 178-CL-100, 178-CL-110, 905-EC-012, 178-CL-101, 178-CL-102, and 178-CL-112.

† Includes subjects from completed studies until 30-Jun-2020.

‡ Person time (year) is the sum of exposure to study drug expressed in years for all patients within a combination dose level or monotherapy dose level; where duration of exposure is the last dosing date – first dosing date + 1.

††Total Person time (year) is the sum of exposure to study drug for all patients within a treatment group expressed in years from day 1 of dosing through last day of dosing; where total patient exposure is the last dosing date - first dosing date + 1.

*Data for studies 178-CL-101, 178-CL-102, and 905-EC-012 is based on a modified safety set, which includes data from 1 site otherwise excluded based on major GCP violations.

The exposure by age group and gender for the mirabegron and solifenacin succinate combination therapy phase 1 clinical studies is presented in [Table 19] and for the phase 2 and 3 clinical studies in [Table 20].

Table 19 Exposure by age group and gender, mirabegron and solifenacin succinate combination therapy phase 1 clinical studies†

Treatment group and formulation	Age range (years)	Persons‡	
		Male	Female
Overall Mirabegron + Solifenacin	< 45	44	40
	≥ 45 to < 65	49	31
	≥ 65 to < 75	2	0
	≥ 75	0	0
	Total	**95**	**71**
Mirabegron + Solifenacin FDC single dose	< 45	35	30
	≥ 45 to < 65	24	29
	≥ 65 to < 75	0	0
	≥ 75	0	0
	Total	**59**	**59**
Mirabegron + Solifenacin coadministration of SET single dose	< 45	35	30
	≥ 45 to < 65	25	29
	≥ 65 to < 75	0	0
	≥ 75	0	0
	Total	**60**	**59**
Mirabegron + Solifenacin coadministration of SET multiple dose	< 45	8	10
	≥ 45 to < 65	24	2
	≥ 65 to < 75	2	0
	≥ 75	0	0
	Total	**34**	**12**

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Studies included: 178-CL-103, 178-CL-107, 178-CL-109 and 178-CL-121.

FDC: fixed dose combination; SET; single entity tablets.

† Includes subjects from completed studies until 30-Jun-2020.

‡ Subjects who received more than 1 formulation are counted in all formulations they received. For the overall mirabegron plus solifenacin succinate group, a subject is counted once regardless of formulation.

Table 20 Exposure by age group and gender, mirabegron and solifenacin succinate combination therapy phase 2 and 3 clinical studies†

Treatment group	Age range (years)	Male		Female	
		Person	Person time (years)‡	Person	Person time (years)‡
Mirabegron + Solifenacin	≥ 18 to < 65	563	261.2	2205	1097.3
	≥ 65 to < 75	280	124.9	762	399.1
	≥ 75 to < 85	95	45.2	269	134.5
	≥ 85	5	1.9	10	3.6
	Total	**943**	**433.1**	**3,246**	**1634.6††**
Mirabegron only	≥ 18 to < 65	181	70.1	684	273.1
	≥ 65 to < 75	95	37.2	209	83.9
	≥ 75 to < 85	24	8.0	70	32.8
	≥ 85	0	NA	2	0.5
	Total	**300**	**115.3**	**965**	**390.3††**
Solifenacin only	≥ 18 to < 65	291	92.5	1369	433.4
	≥ 65 to < 75	136	42.6	419	133.8
	≥ 75 to < 85	52	17.9	133	46.4
	≥ 85	4	1.71	7	3.0
	Total	**483**	**154.8**	**1,928**	**616.6††**
Mirabegron + Imidafenacin	≥ 18 to < 65	6	5.9	59	56.8
	≥ 65 to < 75	8	6.9	61	49.8
	≥ 75 to < 85	1	1.0	25	18.9
	≥ 85	0	NA	1	0.1
	Total	**15**	**13.8**	**146**	**125.6††**
Mirabegron + Propiverine	≥ 18 to < 65	11	10.9	71	67.8
	≥ 65 to < 75	2	1.8	55	41.5
	≥ 75 to < 85	4	2.9	18	11.5
	≥ 85	0	NA	0	NA
	Total	**17**	**15.6**	**144**	**120.7††**
Mirabegron + Tolterodine	≥ 18 to < 65	11	9.4	54	48.8
	≥ 65 to < 75	10	7.5	53	44.3
	≥ 75 to < 85	4	4.0	26	18.5
	≥ 85	0	NA	1	1.0
	Total	**25**	**20.9**	**134**	**112.5††**

Clinical trials included: 178-CL-100, 178-CL-110, 178-CL-101*, 178-CL-102*, 178-CL-112, and 905-EC-012*.

†Includes subjects from completed clinical trials until 30-Jun-2020.

‡Person time (year) is the sum of exposure to study drug expressed in years for all patients within an age and sex category for a treatment group; where duration of exposure is the last dosing date – first dosing date + 1.

*Data for studies 178-CL-101, 178-CL-102, and 905-EC-012 is based on a modified safety set, which includes data from 1 site otherwise excluded based on major GCP violations.

††Total Person time (year) is the sum of exposure to study drug for all patients within a sex category for a treatment group expressed in years from day 1 of dosing through last day of dosing; where total patient exposure is the last dosing date - first dosing date + 1.

Age range is ≥18years.

The exposure by racial origin for the mirabegron and solifenacin succinate combination therapy phase 1 clinical studies is presented in [Table 21] and for phase 2 through phase 4 clinical studies in [Table 22].

Table 21 Exposure by racial origin, mirabegron and solifenacin succinate combination therapy phase 1 clinical studies†

Treatment group and formulation	Racial group	Person‡
Overall Mirabegron + Solifenacin	Caucasian	163
	Black	0
	Asian	1
	Other	2
	Total	**166**
Mirabegron + Solifenacin FDC single dose	Caucasian	115
	Black	0
	Asian	1
	Other	2
	Total	**118**
Mirabegron + Solifenacin Coadministration of SET single dose	Caucasian	116
	Black	0
	Asian	1
	Other	2
	Total	**119**
Mirabegron + Solifenacin Coadministration of SET multiple dose	Caucasian	46
	Black	0
	Asian	0
	Other	0
	Total	**46**

Studies included: 178-CL-103, 178-CL-107, 178-CL-109 and 178-CL-121.

FDC: fixed dose combination; SET; single entity tablets.

† Includes subjects from completed studies until 30-Jun-2020.

‡ Some subjects received more than 1 formulation and are counted in all formulations they received. For the overall mirabegron plus solifenacin succinate group, a subject is counted once regardless of formulation.

Table 22 Exposure by racial origin, mirabegron and solifenacin succinate combination therapy phase 2 through 4 clinical studies†

Treatment group	Racial group	Persons‡	Person time (years)‡
Mirabegron + Solifenacin	Caucasian	3342	1642.1
	Black	98	43.3
	Asian	709	369.9
	Other	32	11.2
	Unknown	8	1.2
	Total	**4189**	**2067.7††**
Mirabegron only	Caucasian	1051	428.7
	Black	30	8.8
	Asian	161	59.8
	Other	17	6.9
	Unknown	6	1.4
	Total	**1265**	**505.6††**
Solifenacin only	Caucasian	2201	694.6
	Black	69	18.7
	Asian	123	51.7
	Other	15	5.8
	Unknown	3	0.5
	Total	**2411**	**771.4††**
Mirabegron + Imidafenacin	Caucasian	0	NA
	Black	0	NA
	Asian	161	139.4
	Other	0	NA
	Unknown	0	NA
	Total	**161**	**139.4††**
Mirabegron + Propiverine	Caucasian	0	NA
	Black	0	NA
	Asian	161	136.3
	Other	0	NA
	Unknown	0	NA
	Total	**161**	**136.3††**
Mirabegron + Tolterodine	Caucasian	0	NA
	Black	0	NA
	Asian	159	133.4
	Other	0	NA
	Unknown	0	NA
	Total	**159**	**133.4††**

Clinical trials included: 178-CL-100, 178-CL-110, 178 -CL-101*, 178-CL-102, 178-CL-112, and 905-EC-012*. In studies 178-CL-110 and 178-CL-112, race was not collected, but the studies were conducted in Japanese subjects.

†Includes subjects from completed clinical trials until 30-Jun-2020.

‡Person time (year) is the sum of exposure to study drug expressed in years for all patients within a racial origin category for a treatment group; where duration of exposure is the last dosing date – first dosing date + 1.

††Total Person time (year) is the sum of exposure to study drug for all patients within a treatment group expressed in years; where duration of exposure is the last dosing date first dosing date + 1.

*Data for studies 178-CL-101, 178-CL-102, and 905-EC-012 is based on a modified safety set, which includes data from 1 site otherwise excluded based on major GCP violations (see footnote under Table 23).

SIII.2.3 Mirabegron pediatric clinical development program

Overall, until the DLP of 30-Jun-2020, 129 pediatric patients have received at least 1 dose of study drug (mirabegron) in the completed clinical trials of the mirabegron monotherapy program in the pediatric population.

In the clinical development program, pediatric patients were treated with mirabegron in single doses ranging from 25 to 75 mg per day (study 178-CL-202) or with mirabegron as suspension ranging from 80 to 130 mg mirabegron as from 40 to 65 ml suspension (study 178-CL-203) or with multiple doses of 25 mg, titrated up to 50 mg, or suspension ranging from 24 to 48 mg mirabegron as from 3 to 6 ml suspension, titrated up to 48 to 88 mg mirabegron as from 6 to 11 ml suspension (depending on body weight, study 178-CL-206A). No patients other than the target population with OAB or NDO were included in the clinical investigations in pediatric patients. Therefore, in the overview on cumulative exposure, no specific distinction is made by indication. The completed studies 178-CL-201 and 178-CL-208 are part of the development program in the pediatric population, but were conducted in adult volunteers and are, therefore, summarized in Section SIII.2.1

Overall, cumulative subject exposure in the mirabegron monotherapy program in the pediatric population is provided in Table 23 (phase 1) and Table 24 (phase 3) based upon exposure data from completed clinical trials.

Table 23 Cumulative exposure, mirabegron monotherapy in the pediatric population (tablets and suspension) in phase 1 clinical trials†

Treatment	Number of persons		
	Tablets single dose	Suspension single dose	Total mirabegron
Mirabegron	34	9	43

Clinical trials included: 178-CL-202 and 178-CL-203.

† Includes subjects from completed clinical trials until 30-Jun-2020.

Table 24 Cumulative exposure, mirabegron monotherapy in the pediatric population (tablets and suspension) in phase 3 clinical trials†

Treatment	Number of persons		
	Tablets multiple dose	Suspension multiple dose	Total mirabegron
Mirabegron	47	39	86

Clinical trials included: 178-CL-206A.

† Includes subjects from completed clinical trials until 30-Jun-2020.

The exposure by age group and sex for the mirabegron monotherapy program in the pediatric population is provided in Table 25 (phase 1) and Table 26 (phase 3).

Table 25 Exposure by age group and sex, mirabegron monotherapy in the pediatric population phase 1 clinical trials†

Mirabegron treatment category	Age range(years)	Persons‡	
		Male	Female
Overall mirabegron	≥ 2 to < 5	0	1
	≥ 5 to < 12	11	16
	≥ 12 to < 18	4	11
	Total	**15**	**28**
Mirabegron tablets multiple dose	≥ 5 to < 12	7	12
	≥ 12 to < 18	4	11
	Total	**11**	**23**
Mirabegron suspension single dose	≥ 2 to < 5	0	1
	≥ 5 to < 12	4	4
	≥ 12 to < 18	0	0
	Total	**4**	**5**

Clinical trials included: 178-CL-202 and 178-CL-203.

† Includes subjects from completed clinical trials until 30-Jun-2020.

‡ Some subjects received more than 1 treatment and/or formulation and are counted in all treatment groups and formulations they received. For the total mirabegron column, a subject is counted once regardless of formulation.

Table 26 Exposure by age group and sex, mirabegron monotherapy in the pediatric population phase 3 clinical trials†

Mirabegron treatment category	Age range (years)	Persons‡	
		Male	Female
Overall mirabegron	≥ 2 to < 5	1	5
	≥ 2 to < 12	21	28
	≥ 12 to < 18	17	14
	Total	**39**	**47**
Mirabegron tablets multiple dose	≥ 2 to < 5	0	0
	≥ 5 to < 12	8	11
	≥ 12 to < 18	16	12
	Total	**24**	**23**
Mirabegron suspension multiple dose	≥ 2 to < 5	1	5
	≥ 5 to < 12	13	17
	≥ 12 to < 18	1	2
	Total	**15**	**24**

Clinical trials included: 178-CL-206A.

† Includes subjects from completed clinical trials until 30-Jun-2020.

‡ Some subjects received more than 1 treatment and/or formulation and are counted in all treatment groups and formulations they received. For the total mirabegron column, a subject is counted once regardless of formulation.

Exposures by racial origin for the mirabegron monotherapy program in the pediatric population study are presented in Table 27 (phase 1) and Table 28 (phase 3).

Table 27 Exposure by racial origin, mirabegron monotherapy in the pediatric population (tablets and suspension) in phase 1 clinical trials†

Mirabegron treatment category	Racial origin	Persons‡
Overall mirabegron	Caucasian	43
	Black	0
	Asian	0
	Other	0
	Total	**43**
Mirabegron tablets single dose	Caucasian	34
	Black	0
	Asian	0
	Other	0
	Total	**34**
Mirabegron suspension single dose	Caucasian	9
	Black	0
	Asian	0
	Other	0
	Total	**9**

Clinical trials included: 178-CL-202 and 178-CL-203.

† Includes subjects from completed clinical trials until 30-Jun-2020.

‡ A subject may be counted in more than 1 mirabegron treatment category, but will be counted once in the overall mirabegron group.

Table 28 Exposure by racial origin, mirabegron monotherapy in the pediatric population (tablets and suspension) in phase 3 clinical trials†

Mirabegron treatment category	Racial origin	Persons‡
Overall mirabegron	Caucasian	62
	Black	0
	Asian	20
	Other	4
	Total	**86**
Mirabegron tablets multiple dose	Caucasian	37
	Black	0
	Asian	8
	Other	2
	Total	**47**
Mirabegron suspension multiple dose	Caucasian	25
	Black	0
	Asian	12
	Other	2
	Total	**39**

Clinical trials included: 178-CL-206A.

† Includes subjects from completed clinical trials until 30-Jun-2020.

‡ A subject may be counted in more than 1 mirabegron treatment category, but will be counted once in the overall mirabegron group.

Estimated subject exposure for ongoing clinical trial in the mirabegron monotherapy program in the Pediatric Population is provided in Table 29.

Table 29 Estimated Exposure in Ongoing Mirabegron Monotherapy in the Pediatric Population Clinical Trials

Study number	Phase	Number of persons randomized†, all treatments
178-CL-204	3	0

† Includes subjects randomized until 30-Jun-2020.

Module SIV. Populations not studied in clinical trials

Data-lock point for this Module	30-Jun-2020
Version when Module last updated	8.0

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Hypersensitivity

Reason for exclusion: This is a general contraindication for all medicinal products.

Is it considered to be included as missing information? : No

Rationale:

These patients have been excluded in order to protect trial patients from potential safety risks associated with hypersensitivity to mirabegron or any of the excipients.

Severe uncontrolled hypertension defined as systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 110 mmHg

Reason for exclusion:

Patients with severe uncontrolled hypertension defined as SBP≥ 180 mmHg and/or DBP≥ 110 mmHg have been excluded from participation in clinical trials to protect trial patients from potential safety risks.

Is it considered to be included as missing information? : No

Rationale:

These patients have been excluded in order to protect trial patients from potential safety risks associated with mirabegron and/or to study an OAB population where the safety results are not confounded by severe uncontrolled hypertension which can be expected to lead to AEs not related to mirabegron.

The overall impact of exclusion criteria was considered for the phase 2/3 OAB studies. The majority of patients exposed to mirabegron were enrolled in ten studies from Phase 2 (178-CL-044; 178-CL-045) and Phase 3 (178-CL-046; 178-CL-047; 178-CL-074; 178-CL-048; 178-CL-049; 178-CL-051; 178-CL-090; 178-EC-001) that were considered most representative of patients with OAB and represented a high proportion of mirabegron patients studied in the overall clinical program.

Table 30 Comparison of key safety exclusion criteria for phase 2/3 studies

	Phase 2, 12-weeks		Phase 3, 12-weeks				Phase 3, 12-weeks			Phase 3, 12-weeks
Study number	**178-CL-044**	**178-CL-045**	**178-CL-046**	**178-CL-047**	**178-CL-074**	**178-CL-048**	**178-CL-049**	**178-CL-051**	**178-EC-001**	**178-CL-090**
Number of patients exposed to mirabegron	673	626	989	875	872	379	1632[†]	203	936	369
Age range	≥ 18 years	20-80 years	≥ 18 years	≥ 18 years	≥ 18 years	≥ 20 years	≥ 18 years	≥ 20 years	≥ 18	Legal minimum age requirement (country-specific) at the time of informed consent
Bladder outflow obstruction	Clinically significant	Significant lower urinary tract obstructive disease (BPH, etc.)	Clinically significant, at risk for urinary retention	None	None	Clinically significant lower urinary tract obstructive disease (BPH)	Clinically significant, at risk for urinary retention	Clinically significant lower urinary tract obstructive disease (BPH)	Clinically significant	None
PVR volume	> 200 mL	≥ 100 mL	None	None	None	≥ 100 mL	None	≥ 100 mL	> 200 ml	≥ 100 mL
Urinary diseases	Evidence of symptomatic UTI, chronic inflammation or previous or current malignant disease of the pelvic organs	Complication of UTI, urinary stones and/or interstitial cystitis or history of recurrent UTI (at least 3 episodes within 24 weeks before start of run-in period); bladder tumors or prostatic tumors	Evidence of symptomatic UTI, chronic inflammation or previous or current malignant disease of the pelvic organs	Evidence of symptomatic UTI, chronic inflammation or previous or current malignant disease of the pelvic organs	Evidence of symptomatic UTI, chronic inflammation or previous or current malignant disease of the pelvic organs	Complication of UTI, urinary calculus, and/or interstitial cystitis or history of recurrent UTI (at least 3 episodes within 24 weeks before consent); bladder tumors or prostatic tumors	Evidence of symptomatic UTI, chronic inflammation or previous or current malignant disease of the pelvic organs	Complication of UTI, urinary calculus, and/or interstitial cystitis or history of recurrent UTI (at least 3 episodes within 24 weeks before consent); bladder tumors or prostatic tumors	Evidence of symptomatic UTI, chronic inflammation or previous or current malignant disease of the pelvic organs	Complication of UTI, (prostatitis, cystitis, etc.), urinary stones (ureter stone, urethral stone, bladder stone, etc.), and/or interstitial cystitis or with a historical condition of recurrent urinary tract infection

Table continued on next page

	Phase 2, 12-weeks		Phase 3, 12-weeks				Phase 3, 12-weeks			Phase 3, 12-weeks
Study number	**178-CL-044**	**178-CL-045**	**178-CL-046**	**178-CL-047**	**178-CL-074**	**178-CL-048**	**178-CL-049**	**178-CL-051**	**178-EC-001**	**178-CL-090**
Uncontrolled narrow angle glaucoma, urinary or gastric retention, colitis ulcerosa, toxic megacolon, myasthenia gravis	X‡	None	X‡	None	None	X‡	X‡	None	X‡	None
Known or suspected hypersensitivity	Tolterodine, other anti-cholinergics, beta-AR agonists or lactose or other inactive ingredients	Beta-receptor agonists	Tolterodine, other anti-cholinergics, beta-AR agonists or any inactive ingredients	Mirabegron, other beta-AR agonists or any inactive ingredients	Mirabegron, other beta-AR agonists or any inactive ingredients	Beta-receptor agonists or anticholinergics	Tolterodine, other anti-cholinergics, beta-AR agonists or any inactive ingredients	Beta-receptor agonists	Solifenacin, mirabegron, or any of the inactive ingredients	Beta-AR agonist or anticholinergic agent

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	Phase 2, 12-weeks		Phase 3, 12-weeks				Phase 3, 12-weeks			Phase 3, 12-weeks
Study number	**178-CL-044**	**178-CL-045**	**178-CL-046**	**178-CL-047**	**178-CL-074**	**178-CL-048**	**178-CL-049**	**178-CL-051**	**178-EC-001**	**178-CL-090**
Significant cardiac diagnoses	Clinically significant cardio-vascular (CV) or cerebro-vascular disease within 6 months prior to screening, including MI, uncontrolled angina, significant ventricular arrhythmias, sinus tachycardia, HF (NYHA class II/IV), orthostatic hypotension, stroke	History of acute cerebro-vascular disorder, serious CV disorder (MI, HF, uncontrolled angina, serious arrhythmia) or clinically significant orthostatic hypotension within 24 weeks before start of run-in period	None	None	None	Acute cerebro-vascular disease, serious CV disorder (MI, cardiac insufficiency uncontrolled angina pectoris or serious arrhythmias) or clinically significant orthostatic hypotension within 24 weeks before start of run-in period	None	Acute cerebro-vascular disease, serious CV disease (MI, cardiac insufficiency uncontrolled angina pectoris or serious arrhythmias) or clinically significant orthostatic hypotension within 24 weeks before start of run-in period	None	Acute cerebrovascular disorder, serious cardiovascular disorder (myocardial infarction (MI), cardiac failure, uncontrolled angina, serious arrhythmia, etc.), or clinically significant orthostatic hypotension within 24 weeks before initiating the run-in period

Table continued on next page

	Phase 2, 12-weeks		Phase 3, 12-weeks				Phase 3, 12-weeks			Phase 3, 12-weeks
Study number	**178-CL-044**	**178-CL-045**	**178-CL-046**	**178-CL-047**	**178-CL-074**	**178-CL-048**	**178-CL-049**	**178-CL-051**	**178-EC-001**	**178-CL-090**
Severe/ uncontrolled hypertension	SBP ≥160 mmHg and/or DBP ≥100 mmHg	SBP ≥180 mmHg or DBP ≥110 mmHg	SBP ≥180 mmHg and/or DBP ≥110 mmHg	SBP ≥180 mmHg and/or DBP ≥110 mmHg	SBP ≥180 mmHg and/or DBP ≥110 mmHg	SBP ≥180 mmHg or DBP ≥110 mmHg	SBP ≥180 mmHg and/or DBP ≥110 mmHg	SBP ≥180 mmHg or DBP ≥110 mmHg	SBP ≥180 mmHg and/or DBP ≥110 mmHg	SBP ≥180 mmHg or DBP ≥110 mmHg
Heart rate	<45 or >100 beats per minute (bpm)	<50 or >110 bpm	None	None	None	<50 or ≥110 bpm	None	<50 or ≥110 bpm	None	<50 or ≥110 bpm
ECG/QT	ECG with QTc >470 msec, patients with risk factors for torsades de pointes and patients receiving co-medication with QT-prolonging drugs	Risk of torsades de pointes (familial long QT syndrome); QTcF >470 msec	Abnormal ECG, which in the opinion of the investigator made the subject unsuitable for the study.	Abnormal ECG, which in the opinion of the investigator made the subject unsuitable for the study.	Abnormal ECG, which in the opinion of the investigator made the subject unsuitable for the study.	Abnormal ECG, which made the subject unsuitable for the study.	Abnormal ECG, which in the opinion of the investigator made the subject unsuitable for the study.	Abnormal ECG, which made the subject unsuitable for the study.	abnormal ECG or has a known history of QT prolongation or currently taking medication known to prolong the QT interval.	None

Table continued on next page

	Phase 2, 12-weeks		Phase 3, 12-weeks				Phase 3, 12-weeks			Phase 3, 12-weeks
Study number	**178-CL-044**	**178-CL-045**	**178-CL-046**	**178-CL-047**	**178-CL-074**	**178-CL-048**	**178-CL-049**	**178-CL-051**	**178-EC-001**	**178-CL-090**
Clinically significant/ serious diseases	Any other criteria making patient unsuitable for study	Cardiac, hepatic, renal, immuno-logical, pulmonary, or malignant tumors (except for those who have not received treatment for malignant tumors for at least 5 years with no recurrence)	Any other criteria making patient unsuitable for study	Any other criteria making patient unsuitable for study	Any other criteria making patient unsuitable for study	Cardiac, hepatic, renal, immunological, pulmonary, or malignant tumors (except for those who have not received treatment for malignant tumors for at least 5 years with no recurrence); deemed unsuitable	Any other criteria making patient unsuitable for study	Cardiac, hepatic, renal, immunological, pulmonary, or malignant tumors (except for those who have not received treatment for malignant tumors for at least 5 years with no recurrence); deemed unsuitable	Concurrent malignancy or history of cancer (except noninvasive skin cancer) within the last 5 years prior to screening.	Cardiac, hepatic, renal, immuno-logical, pulmonary, or malignant tumors (except for those who have not received treatment for malignant tumors for at least 5 years with no recurrence)

X = Excluded from study.

AR: adrenoceptor; bpm: beats per minute; BPH: benign prostatic hyperplasia; CV: cardiovascular; DBP: diastolic blood pressure; ECG: electrocardiography; HF: heart failure; MI: myocardial infarction; NYHA: New York Heart Association; PVR: post-void residual (volume); QTcF: QT interval corrected for heart rate using Fridericia method; SBP: systolic blood pressure; UTI: urinary tract infection.

† Including 731 patients on mirabegron who also took mirabegron in studies 178-CL-046 or 178-CL-047.

‡ Criteria were added to accommodate precautions with the use of tolterodine (anticholinergic) as an active comparator.

Table 31 Comparison of other exclusion criteria for phase 2/3 studies

	Phase 2, 12-weeks		Phase 3, 12-weeks				Phase 3, 12-weeks			Phase 3, 12-weeks
Study number	**178-CL-044**	**178-CL-045**	**178-CL-046**	**178-CL-047**	**178-CL-074**	**178-CL-048**	**178-CL-049**	**178-CL-051**	**178-EC-001**	**178-CL-090**
Exclusion criteria theme to ensure appropriate target disease										
Patients without experience of urge incontinence before informed consent	None	X	None	None	None	X	None	X	None	None
Significant stress incontinence or mixed stress/urge incontinence where stress is the predominant factor	X	None	X	X	X	None	X	None	X	X
Patients clearly diagnosed as having stress incontinence (only the symptoms of stress incontinence)	None	X	None	None	None	X	None	X	None	X
Patients with transient symptoms suspected of OAB (drug-induced, psychogenic, etc.)	None	X	None	None	None	X	None	None	None	X
Average total daily urine volume > 3000 mL as recorded in the micturition diary	X	X	X	X	X	X	X	X	X	X
Exclusion criteria theme to avoid confounding of efficacy evaluation										
Patients with indwelling catheters or practicing intermittent self-catheterization	X	X	X	X	X	X	X	X	X	X
Nondrug treatment including electrostimulation therapy (a bladder training program or pelvic floor exercises which started more than 1 month prior to entry into the study can be continued)	X	X	X	X	X	X	X	None	X	X

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	Phase 2, 12-weeks		Phase 3, 12-weeks				Phase 3, 12-weeks			Phase 3, 12-weeks
Study number	**178-CL-044**	**178-CL-045**	**178-CL-046**	**178-CL-047**	**178-CL-074**	**178-CL-048**	**178-CL-049**	**178-CL-051**	**178-EC-001**	**178-CL-090**
Patients given radiotherapy/ thermotherapy/surgical therapy affecting urethral function	None	X	None	None	None	X	None	X	X	X
Patient was using medications intended to treat OAB or prohibited medications listed in the protocol	X	X	X	X	X	X	X	None	X	None
Patient who did not complete the micturition diary according to the instructions	X	None	None	None	None	None	None	None	None	None

OAB: overactive bladder.

X = The stated exclusion criterion or one that addressed a similar subpopulation but included some variation in wording was used.

SIV.2 Limitations to detect adverse reactions in clinical trial development program

The clinical development program for mirabegron is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or adverse reactions caused by prolonged or cumulative exposure.

From the "rule of threes" [Higgins et al, 2008], consideration can be given to the statistical power of the available clinical trials experience for the occurrence of AEs that were not observed, as a measure of detectability. The rule of threes provides a 95% upper bound, or probability, of observing at least 1 event if the sample is 3 times the reciprocal of the frequency of the event. For the overall mirabegron monotherapy phase 2 to 4 program and the mirabegron and solifenacin succinate combination therapy program including patients who have received mirabegron only in studies 178-CL-100 and 178-CL-101, where 9043 patients have received at least 1 dose of mirabegron monotherapy, this upper bound for detecting no events would be 3/9043 = 0.00033. Therefore, with over 9000 patients, there is a 95% probability that at least 1 case could be detected if the event frequency is 0.00033, or 3.3 events in 10000 patients (not taking into account the background incidence rate of the event).

The program evaluated safety based upon duration of use up to 12 months and therefore, it is recognized that events with latent onset beyond this exposure period would not be detected. Routine surveillance is implemented in the post-marketing phase to identify potential delayed adverse reactions Section 3.

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare	Number of patients included in the development program is > 4000 for 3 months and > 900 for 12 months	This allows detection of short term adverse events with an approximate frequency of 1:1300 and longer term approximate frequency of 1:300 with 90% confidence if there were no background incidence (frequency categories rare ≥ 1/10000 to < 1/1000, and uncommon ≥ 1/1000 to < 1/100).
Due to prolonged exposure	Maximum exposure > 1 year	No implications, as no specific events due to prolonged exposure have been observed. During the clinical development of mirabegron, > 900 adult patients have received mirabegron for at least 1 year.
Due to cumulative effect	Maximum exposure > 1 year	No implications, as no specific events due to prolonged exposure have been observed. During the clinical development of mirabegron, > 900 adult patients have received mirabegron for at least 1 year.
Which have long latency	Maximum exposure > 1 year	No implications; events with latent onset beyond an exposure period of > 1 year would not be detected during clinical development. Routine surveillance is implemented in the post-marketing phase to identify potential delayed adverse reactions.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

Children

No subjects under the age of 18 were included in the original clinical development program for adults. The Marketing authorization holder (MAH) is currently evaluating the safety and efficacy of mirabegron in an EMA PDCO agreed pediatric program with Pediatric Investigation Plans (PIP) for OAB P/0350/2019 dated 30-Sep-2019, and for NDO P/0056/2017 dated 17-Mar-2017. The Summary of Product Characteristics (SmPC) Section 4.2, Posology and Method of Administration) describes that the safety and efficacy of mirabegron in children below 18 years of age have not yet been established. No approved pediatric data are available. Further, the PL provides instruction not to 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.

Pregnant or breastfeeding women

Embryo-fetal development studies in rabbits showed that mirabegron induced cardiomegaly and dilated aorta in rabbit fetuses at systemic exposure levels 15.7-fold higher than the non-protein bound human clinical exposure at the 50 mg dose (35.7-fold higher than the total human systemic AUC (area under the plasma concentration-time curve) at the maximum recommended human dose (MRHD). Cardiomegaly and dilated aorta were absent from rat fetuses following the administration of mirabegron to pregnant rats during organogenesis at doses resulting in systemic exposures 73.5-fold higher than the non-protein bound human AUC (95.6-fold higher than the total AUC at MRHD).

There have been 9 pregnancies during the clinical development program (7 in mirabegron-treated patients, 1 in a female partner of a mirabegron-treated volunteer, and 1 in a placebo-treated volunteer). Of the 8 mirabegron-exposed cases, 3 pregnancies were completed with outcome of full-term live born males, 1 of these males was born with cryptorchidism which resolved within his first 6 months of life with no intervention; 2 pregnancies resulted in spontaneous abortion; 2 pregnancies resulted in elective abortions; and there was 1 completed suicide in which pregnancy was discovered on autopsy. A spontaneous complete abortion of 1 of 2 gestational sacs was reported in the placebo-treated healthy volunteer. Five pregnancies occurred during treatment with combination therapy. All pregnancies in the combination therapy groups were terminated except for 2 pregnancies in patients treated with combination 5 + 50 mg. Both patients discontinued study drug and underwent normal pregnancy, labor and delivery of a healthy baby.

Section 4.6 (Fertility, pregnancy and lactation) of the SmPC indicates there is limited amount of data from the use of mirabegron in pregnant women. Studies in animals have shown reproductive toxicity (further described in SmPC Section 5.3 Pre-clinical Safety Data). As a precautionary measure, and as stated in SmPC Section 4.6, mirabegron is not recommended during pregnancy and in women of childbearing potential not using contraception.

Patients who are breastfeeding are commonly excluded from clinical trials. Available pharmacokinetic data in animals have shown excretion of mirabegron/metabolites in milk (for further details see SmPC Section 5.3). As stated in SmPC Section 4.6, mirabegron is excreted in the milk of rodents and therefore is predicted to be present in human milk. No studies have been conducted to assess the impact of mirabegron on milk production in humans, its presence in human breast milk, or its effects on the breastfed child. Mirabegron should not be administered during breastfeeding.

Patients with other relevant co-morbidity

Cardiovascular

The population studied in the mirabegron OAB trials is representative of the general OAB population with regards to cardiovascular risk factors and concomitant therapies. Publications have described the cardiovascular co-morbidities in OAB patients that are age and gender matched to a non-OAB population from the EPIC study and the HealthCore Integrated Research Database (HIRD) [Andersson et al, 2010; Coyne et al, 2008]. Diabetes and hypertension were the 2 most common cardiovascular co-morbidities in the OAB population with prevalence rates significantly higher than the non-OAB age and gender matched group [Andersson et al, 2010 and Coyne et al, 2008].

Baseline demographics and co-morbidities for OAB patients in the mirabegron program and OAB and non-OAB patients from the HIRD database and EPIC study are presented in [Table 32]. The mean patient age was higher in the mirabegron studies compared with the typical OAB population from the HIRD database and EPIC study. There were a higher percentage of male patients in mirabegron studies compared with the HIRD database and EPIC study. The percentage of patients with hypertension at baseline was higher in the mirabegron studies compared with OAB populations from the HIRD database and EPIC study. The percentage of patients with diabetes at baseline in the mirabegron OAB studies was similar to that reported in the OAB populations. Additionally, patients in the mirabegron OAB studies received many of the common concomitant medications/classes of medications used to manage these cardiovascular co-morbidities [Table 33]. Therefore, the safety of mirabegron has been assessed in a study population that is representative of the OAB population and includes similar or greater prevalence of the 2 most common cardiovascular co-morbidities.

Table 32 Cardiovascular risk factors in the mirabegron OAB population compared with populations evaluated in other OAB programs

	Europe/North America OAB 12-week Phase 3 (n=4611)	Europe/North America Long-Term Controlled (n=2444)	HIRD OAB (n=6607)	HIRD No OAB (n=6607)	EPIC OAB (n=1434)	EPIC No OAB (n=1434)
Male gender	1298 (28.2%)	634 (25.9%)	1102 (16.7%)	1102 (16.7%)	502 (35.0%)	502 (35.0%)
Mean age (years)	59.4	59.6	50.8	50.8	53.8	53.7
Heart failure	21 (0.5%)	9 (0.4%)	85 (1.3%)	38 (0.6%)	NR	NR
Hypertension	1776 (38.5%)	969 (39.6%)	1790 (27.1%)	983 (14.9%)	418 (29.3%)	325 (22.7%)
Diabetes	377 (8.2%)	187 (7.7%)	538 (8.1%)	303 (4.6%)	128 (8.9%)	87 (6.1%)

HIRD: Health Core Integrated Database; OAB: overactive bladder; n= number (of patients); NR: not reported.
Source: Andersson et al, 2010; Coyne et al, 2008.

Table 33 Concomitant medications during the double-blind period in mirabegron OAB studies

	Europe/North America OAB 12-week Phase 3 Population (n=4611)	Europe/North America Long-Term Controlled Population (n=2444)
ACE/ARB	1311 (28.4%)	714 (29.2%)
Beta Blockers	778 (16.9%)	451 (18.5%)
Calcium Channel Blockers	552 (12.0%)	317 (13.0%)
Diuretics	477 (10.3%)	289 (11.8%)
Lipid Lowering Agents	1317 (28.6%)	631 (25.8%)
Antithrombotics	963 (20.9%)	501 (20.5%)
Antidiabetics	409 (8.9%)	217 (8.9%)

OAB: overactive bladder; ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blockers.

Data pertaining to patients with pre-existing cardiovascular disease who may be at particular risk of developing heart failure if they experience increased blood pressure, tachycardia, and/or arrhythmia secondary to QT prolongation are considered missing information. Data are limited in patients with stage 2 hypertension (SBP $\geq$ 160 mmHg or DBP $\geq$ 100 mmHg), and this is reflected in the SmPC.

Immuno-compromised patients

Immuno-compromised patients, including transplant patients have not been included in the study population, in order to obtain a picture of the safety and tolerability of the mirabegron that is not confounded by the underlying disease, transplantation and medication required to prevent rejection and to treat complications. There is no reason that mirabegron would be less tolerated or less effective in this population.

Patients with a disease severity different from the inclusion criteria in the clinical trial population

No upper limit of disease severity was applied for inclusion in the trials. The lower limit of disease severity applied in the trial, reflects the common definition and symptoms of OAB. The OAB phase 2/3 trials included patients who:

- had symptoms of OAB (urinary frequency and urgency with or without incontinence for ≥ 3 months);
- experienced frequency of micturition on average ≥8 times per 24-hour period during the 3-day micturition diary period;
- experienced 3 episodes of urgency (grade 3 or 4) with or without incontinence, during the 3-day micturition diary period (Europe/North America studies);
- had utilized prior OAB antimuscarinic therapy and patients who were antimuscarinic treatment naive.

The disease severity of patients in the clinical trials is similar to the target population.

Subpopulations carrying known and relevant polymorphisms

In healthy subjects who are genotypically poor metabolizers of cytochrome P450 (CYP) 2D6 isoenzymes (CYP2D6) substrates, mean C_{max} and AUC_{inf} of a single 160-mg dose of a mirabegron IR formulation were 14% and 19% higher than in extensive metabolizers, indicating that CYP2D6 genetic polymorphism has minimal impact on the mean plasma exposure to mirabegron (study 178-CL-005). As stated in SmPC Section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction, CYP2D6 genetic polymorphism has minimal impact on the mean plasma exposure to mirabegron. Interaction of mirabegron with a known CYP2D6 inhibitor is not expected and was not studied. No dose adjustment is needed for mirabegron when administered with CYP2D6 inhibitors or in patients who are CYP2D6 poor metabolizers.

Non-clinical studies performed to date do not indicate any potential for altered responsiveness for mirabegron in patients that exhibit genetic $beta_3$-AR polymorphism.

Patients of different racial and/or ethnic origin

In the Global phase 2 through 4 population, the majority of patients (6247/8566, 72.9%) were White [Table 11]. A large number of Asian patients (1983/8566, 23.1%), a significant number of Black or African American patients (284/8566, 3.4%) and patients of other race (45/8566, 0.5%) were also included in this population. No apparent differences by race were observed; however, due to small numbers of non-White patients in phase 3 through 4 studies and non-White, non-Asian patients in phase 3 through 4 studies, conclusions regarding TEAEs and other safety assessments according to race cannot be drawn. No dosage adjustment is necessary based upon race, as the pharmacokinetics of mirabegron are not influenced by race.

Module SV. Post-authorization experience

Data-lock point for this Module	30-Jun-2020
Version when Module last updated	8.0

SV.1 Post-authorization exposure

SV.1.1 Method used to calculate exposure

Mirabegron was first approved for marketing in Japan on 01-Jul-2011 for the indication of OAB. It was subsequently approved for the indication of OAB in the US on 28-Jun-2012 and in the Europe on 20-Dec-2012.

The worldwide estimated patient exposure from marketing experience is based on internal company sales data and/or audited pharmacy or wholesale sales of Mirabegron received from IQVIA Medical Database or similar syndicated sources with an estimated daily regimen of one unit (tablet) for either strengths of Mirabegron. The number of patients reported does not represent unique patients. This estimate is based on standard units sold during 01-Jan-2018 to 30-Jun-2020.

Calculation:

Number of Patients = Number of units sold in Interval Period / Number of Treatment days in Interval Period

Patient years= Number of units sold in Interval Period / Duration (365 days)

SV.1.2 Exposure

[Table 34] shows the cumulative and interval exposure. It is estimated the worldwide cumulative exposure until the DLP of 30-Jun-2020 is 18519232 patients since launch, and in the interval period (01- Jan-2018 to 30-Jun-2020) it is 9905608 patients.

Table 34 Cumulative and interval exposure table by region, gender, age group, and dose

		Sex		Age (years)				Dose	
	Region	***Male***	***Female***	***2 to ≤16***	***>16 to 65***	***>65***	***Unknown***	***25mg***	***50mg***
Cumulative	**Overall**	**7126258**	**11392974**	**18416**	**5626571**	**12710060**	**164185**	**4498852**	**14020380**
	EU	1655511	3538829	4162	2250531	2939647	-	549775	4644566
	Non-EU Total	5470747	7854145	14254	3376040	9770413	164185	3949077	9375814
	Japan	3530010	3281944	-	1068632	5713331	29992	1807503	5004451
	Asia	914711	898704	-	266405	1539329	7681	154541	1658874
	Canada	172691	623085	2683	345001	429940	18152	326037	469739
	US and Brazil	853335	3050412	11571	1696002	2087813	108360	1660996	2242750

Note: Values were calculated from estimated patient exposure and rounded to the nearest whole number. Of note, IMS (Intercontinental Medical Statistics) data is updated quarterly and historical data is refreshed taking into account new information. This may on rare occasions result in exposure cumulative estimates showing some relative variances to previous estimates.

Post-marketing exposure by sex and age (interval and cumulative)

In order to provide a reliable estimate of market exposure to mirabegron, the volume of tablets captured in the IQVIA Medical Database is used as the data source. IQVIA Medical Database includes direct and indirect sales (units [pack] data) on registered products collected primarily from wholesalers and pharmacies. After projection, IQVIA Medical Database takes the number of packs sold in that time period and multiplies it by the pack price to obtain the total sales value. Although IQVIA Medical Database data does not reflect the direct distribution to patient, the shipments to pharmacies should closely reflect patient demand.

The daily dose for both strengths of mirabegron is 1 tablet. To estimate the number of patients treated with mirabegron, the conservative assumption was made that patients who started with mirabegron therapy remained on mirabegron for the entire interval with 100% compliance. To estimate the number of patients, the amount of tablets sold was divided by the number of assumed treatment days per month. This approach does not take into account inventory levels of distributors or pharmacies.

To allocate the estimated number of patients treated globally with mirabegron, IQVIA Medical data was used as the source to derive the sex and age factors. IQVIA Medical data is a syndicated survey completed by physicians based on their treated patient population. The survey is available for only the US, Japan, and EU5 countries (France, Germany, Italy, Spain and United Kingdom [UK]). The factors generated for Japan were applied to the Asia patient estimates.

Table 35 Post-authorization exposure by age group and gender

Age group	Cumulative (01-Jul-2011 to 30-Jun-2020)				Interval (01-Jan-2018 – 30-Jun-2020)			
	Persons		*Person-time (Years)*		*Persons*		*Person-time (Years)*	
	M	F	M	F	M	F	M	F
Mirabegron	**6841486**	**11677746**	**3370457**	**5750680**	**3829975**	**6075633**	**1888755**	**2996202**
2 to ≤16	1571	16846	775	8307	1205	16329	595	8052
>16 to 65	1213837	4412734	597918	2174407	637077	2170987	314175	1070624
>65	5595249	7114810	2756561	3502201	3181438	3881472	1568928	1914151
Unknown	30829	133356	15203	65765	10255	6845	5057	3375

F: female; M: male.

Table 36 Post-authorization exposure by dose

Dose level	Cumulative (01-Jul-2011 to 30-Jun-2020)		Interval (01-Jan-2018 – 30-Jun-2020)	
	Persons	*Person-time (Years)*	*Persons*	*Person-time (Years)*
Overall	**18519232**	**9121137**	**9905608**	**4884957**
25 mg	4498850	2214148	2232718	1101066
50 mg	14020382	6906989	7672890	3783891

Table 37 Post-authorization exposure by territory

	Cumulative (01-Jul-2011 to 30- Jun-2020)		Interval (01-Jan-2018 to 30-Jun-2020)	
Territory	***Persons***	***Person-time (Years)***	***Persons***	***Person-time (Years)***
Overall	**18519232**	**9121137**	**9905608**	**4884957**
EU	5194340	2560775	2928095	1443992
Non-EU	13324892	6560362	6977513	3440965

Module SVI. Additional EU requirements for the safety specification

Data-lock point for this Module	30-Jun-2020
Version when Module last updated	8.0

Potential for misuse for illegal purposes

Based upon pharmacology, beta3-receptors are not amongst the CNS receptors known to mediate abuse related effects. Evaluation of the clinical data in the mirabegron program shows that mirabegron is unlikely to demonstrate abuse potential. Among the 7487 patients who received at least one dose of mirabegron in phase 2/3 studies, there were no reported AEs suggesting a risk of abuse liability.

Module SVII. Identified and potential risks

Data-lock point for this Module	30-Jun-2020
Version when Module last updated	8.0

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable.

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2 Risk considered important for inclusion in the list of safety concerns in the RMP

Safety Concerns for Inclusion in RMP	Risk-benefit Impact
Important identified risks – none	
Important potential risks	
QT prolongation	The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart which can be detected by an ECG. Torsade de Points is a variant of a fast heartbeat that can be a result of long QT interval. Some patients have in their medical history a long QT syndrome or low amounts of potassium (hypokalemia) in their blood. A long QT syndrome is a heart rhythm disorder that can potentially cause fast, chaotic heartbeats. These rapid heartbeats may trigger a sudden fainting spell or seizure. Mirabegron, at normal doses, has not shown relevant QT prolongation in clinical studies. However, since patients with a known history of QT prolongation or patients who are taking medicinal products which are known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients.
Table continued on next page	

Safety Concerns for Inclusion in RMP	Risk-benefit Impact
Fetal disorders after exposure during pregnancy	There is limited amount of data from the use of mirabegron in pregnant women. To date, 1 report of fetal disorder due to exposure during pregnancy has been received from post-marketing experience, concerning a full-term live born male with so-called cryptorchidism, which is undescended testicles. Studies in animals have shown embryofetal toxicity (see SmPC Section 5.3). Mirabegron is not recommended during pregnancy and in women of childbearing potential not using contraception.
Cardiac failure, particularly in patients with pre-existing cardiovascular diseases or cardiovascular risk factors	Added as potential important risk per EMA Pharmacovigilance Risk Assessment Committee (PRAC) request with the PRAC's rationale that "it is difficult to conclude a relationship between mirabegron and cardiac failure, it cannot be ruled out that patients with pre-existing risk factors developed cardiac failure after the use of mirabegron." The EMA PRAC considered this risk better managed as an important potential risk. In the mirabegron clinical program, adverse events related to cardiac failure were infrequent with no discernable imbalances between mirabegron and tolterodine. In patients that reported a history of heart failure, there did not appear to be any evidence that mirabegron treatment exacerbated the condition.
Missing information	
Pediatric use	The safety and efficacy of mirabegron in adolescents and children below 18 years of age is being investigated and mirabegron should therefore not be used in these patients.

AUC: are under dose concentration curve; ECG: electrocardiogram; EMA: European Medicine Agency; OAB: overactive bladder; PRAC: Pharmacovigilance Risk Assessment Committee; QT: interval from start of Q to end of T waves on electrocardiogram.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

There are no new safety concerns in this updated RMP.

Considering the guidance provided in GVP Module V Revision 2 and based on feedback received via the Pharmacovigilance Risk Assessment Committee (PRAC) assessment report (procedure EMEA/H/C/002388/II/0033), the following risks were removed from the list of safety concerns:

- Increased heart rate and tachycardia and Increased blood pressure were removed from the list of important identified risks.
- UTI and Concomitant treatment with CYP2D6 substrates with narrow therapeutic indices or individually dose-titrated were removed from the list of important potential risks.
- End-stage renal disease and severe hepatic impairment were removed from missing information.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

There are currently no ongoing important identified risks for mirabegron.

Important potential risk: QT prolongation

The important potential risk of QT prolongation is described further in [Table 38].

Table 38 Details for the important potential risk of QT prolongation

Potential risk	QT prolongation
Potential mechanisms	Non-clinical data suggest no discernable mechanism for QT prolongation by mirabegron. *In vitro* data showed that neither mirabegron nor the 5 most abundant metabolites significantly altered the I_{Kr} (hERG), I_{Ks} (hKvLQT1/mink), I_{to} (hKv4.3/Kchip2.2), I_{Na} (hNav1.5) and I_{Ca} (hCav1.2) conductance. In addition, there was no indication that mirabegron or its metabolites significantly altered APD in guinea pig papillary muscle. Moreover, in the dog ventricular wedge model, mirabegron did not prolong the QT interval, did not alter transmural dispersion of repolarization, did not induce premature ventricular contractions and did not induce ventricular tachycardia
Evidence source(s) and strength of evidence	CTD Module 5.3.5.3, Research Report: Mirabegron and Cardiovascular Safety, Appendix 5. Following a review of mirabegron safety data, QT prolongation was categorized as an important potential risk. Mirabegron, at normal doses, has not shown relevant QT prolongation in clinical studies. However, since patients with a known history of QT prolongation or patients who are taking medicinal products which are known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown.
Characterization of the risk	In an Italian prospective ECG study where genetic screening was conducted among 44596 infants, the prevalence of long QT syndrome was estimated at 1:2534 (95% CI, 1:1583 to 1:4350) or 0.039% (95% CI, 0.023%-0.063%) [Schwartz et al, 2009]. While congenital long QT syndrome can result in cardiac arrest or sudden death in approximately 13% of untreated patients before the age of 40 [Priori et al, 2003], the prevalence in an older population could be lower. Schouten and other researchers have noted that patients with congenital long QT syndrome have a high incidence of ventricular fibrillation and sudden cardiac death; however, the exact risks were not quantified [Schouten et al, 1991; Zareba et al, 1998]. A prospective study of 328 long QT syndrome patients found that 47% had a history of ventricular tachyarrhythmia prior to study enrollment and during the 10-year follow-up period, the following event rates were reported: syncope at 5.3% per year (5.5% and 2.6% with and without a cardiac event history before study enrollment, respectively), and probable long QT syndrome-related death before age 50 at 0.9% per year (0.8% and 1.3%, respectively) [Moss et al, 1991]. Among patients from genotyped families with long QT syndrome followed for a mean of 28 years, 13% (87/647) suffered either cardiac arrest or sudden death prior to age 40 and before receiving therapy for long QT syndrome [Priori et al, 2003]. The risk of these cardiac events was influenced by QTc and the locus of the genetic mutation (e.g., LQT1, LQT2, LQT3). In a representative sample of the US population over age 40, approximately 6.7% of males and 6.0% of females had prolonged QT intervals [Benoit et al, 2005]. In a review of 7 prospective cohort studies (n=36,031 subjects) from the Netherlands (n=4), Denmark (n=1), Finland (n=1), and the US (n=1), an estimated 8.7% of the general population was identified with QT prolongation [Montanez et al, 2004]. Other studies have noted that women are more susceptible to QT prolongation with drug exposure [Drici, 2001; Reinoehl et al, 1996]. While the risk of ventricular arrhythmia was not found in the literature, an increase risk of sudden death among patients with QT prolongation has been observed with the RR ranging from 1.7 (95% CI, 1.0 to 2.9) to 2.3 (95% CI, 1.4 to 3.9) when compared to patients with QTc < 440 msec [Algra et al, 1991].

Table continued on next page

Potential risk	QT prolongation
Risk groups or risk factors	Potential risk groups are those receiving the therapeutic dose of mirabegron 50 mg once daily who concurrently have a known history of QT prolongation or who are concurrently taking medications known to prolong QT interval.
Preventability	Special warning for patients with a known history of QT prolongation or patients who are concurrently taking medications known to prolong QT interval (SmPC Section 4.4).
Impact on the risk-benefit balance of the product	As specifically determined by a thorough QT study (178-CL-077): According to International council for harmonization of technical requirements for pharmaceuticals for human use (ICH) E14 (2005) criteria, mirabegron did not cause a QT interval corrected for heart rate using individual-specific correction formula (QTcI) prolongation at the therapeutic dose of 50 mg in female and male volunteers. According to ICH E14 (2005) criteria, mirabegron did not cause a QTcI interval prolongation at the supratherapeutic dose of 100 mg in female and male volunteers. The supratherapeutic dose of mirabegron 100 mg is associated with an approximately 2.9 and 2.6-fold increase in C_{max} and AUC_{tau} relative to mirabegron 50 mg. According to ICH E14 (2005) criteria, mirabegron prolonged the QTc interval at the supratherapeutic dose of 200 mg in female volunteers. 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% confidence interval [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 supratherapeutic dose of 200 mg is associated with an approximately 8.4- and 6.5-fold increase in C_{max} and AUC_{tau} relative to mirabegron 50 mg. The absence of QTc prolongation at the therapeutic dose of mirabegron 50 mg and the supratherapeutic dose of mirabegron 100 mg was supported by the following findings: • In the Global OAB 12-week Phase 2/3 Population, a similar and low frequency of QTc-related TEAE (retrieved by the Torsade de pointes (TdP)/QT prolongation SMQ in placebo-, mirabegron 50 mg-, mirabegron 100 mg- and tolterodine-treated patients. • In the Europe/North America OAB 12-week Phase 3 Population, a similar frequency of maximum QTcF values > 450, 480 and 500 msec or maximum change from baseline QTcF values of 30 msec to < 60 msec and 60 msec in placebo-, mirabegron 50 mg-, mirabegron 100 mg- and tolterodine-treated patients. In patients with no underlying cardiac disease risk and who are taking the therapeutic dose (50 mg), the risk of QTc prolongation is low. Therefore, the primary safety concern arising from these findings is considered a potential risk of QT prolongation in only the following patient subpopulations: • 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.
Potential public health impact of safety concern	Given that mirabegron prolonged the QTc interval only at the supratherapeutic dose of 200 mg, a dose which increased C_{max} and AUC_{tau} by approximately 8.4- and 6.5-fold relative to mirabegron 50 mg, the potential public health impact of the safety concern is in theory limited to those patients with a known history of QT prolongation, those concurrently taking medications known to prolong QT interval, or those receiving exposure that is equivalent to the supratherapeutic dose of mirabegron 200 mg. A prolonged QT interval in these patients may predispose them to serious ventricular arrhythmias.

AUC: area under the plasma concentration-time curve; AE: adverse event; APTC: antiplatelet trialists' collaboration; CI: confidence interval; C_{max}: maximum (peak) serum concentration; CTD: common technical document; ECG: electrocardiogram; ICH: International council for harmonization of technical requirements for pharmaceuticals for human use; LAD: left anterior descending artery; NA: North America; OAB: overactive bladder; QT: QT interval; QTc: QT interval corrected for heart rate; QTcI: QT interval corrected for heart rate using individual-specific correction formula; QTcF: QT interval corrected using Fridericia's formula; RR: relative risk; SAE: serious adverse event; TdP: torsade de pointes; TEAE: treatment-emergent adverse event US: United States.

Important potential risk: Fetal disorders after exposure during pregnancy

The important potential risk of fetal disorders after exposure during pregnancy is summarized in [Table 39].

Table 39 Details for the important potential risk of fetal disorders after exposure during pregnancy

Potential risk	Fetal disorders after exposure during pregnancy
Potential mechanisms	Findings of cardiomegaly and dilated aorta were noted in the rabbit embryo-fetal development study at doses that were lethal to the mothers (9% mortality rate) and which negatively affected the health of the remaining animals (decrease in body weight or decrease in body weight gain). Based on a series of investigational studies, it was concluded that mirabegron, at high systemic exposures (15.7-fold higher than the non-protein bound human systemic exposure at MRHD; 35.7-fold higher than the total human systemic exposure at MRHD) was associated with these fetal findings and that these findings were the result of cross activation of beta 1-AR by mirabegron. These conclusions were based on the observation that the fetal findings of cardiomegaly and dilated aorta were present in animals administered mirabegron at doses which increased the maternal heart rate by 33 to 39% for a period of 8 hours per day and that these findings could be significantly attenuated by co-administration of the $beta_1$-AR antagonist, metoprolol, at doses that blocked the increases in heart rate. Smaller increases in heart rate (20 to 22%) for shorter durations (i.e., 4 hours) failed to show similar fetal findings. Further evidence that the fetal findings of cardiomegaly and dilated aorta were $beta_1$-AR mediated comes from investigational studies that demonstrated similar findings with the non-specific beta AR agonist, isoproterenol. These fetal findings were observed only at doses of isoproterenol that increased maternal heart rates and were also blocked by the $beta_1$-AR antagonist, metoprolol.
Evidence source(s) and strength of evidence	CTD Module 5.3.5.3, Integrated Summary of Safety; CTD Module 5.3.5.3, 120-day Safety Update. There is limited amount of data from the use of mirabegron in pregnant women.
Characterization of the Risk	The incidence of congenital heart disease has been estimated to vary from 4 to 10 per 1,000 live births, but it can be as high as 50 to75 per 1,000 in some samples depending upon the relative frequency of ventricular septal defects and how early diagnoses are made [Hoffman & Kaplan, 2002; Acharya et al, 2004]. No information specific to the OAB population was available. However, the mean age of this population (50 to 60 years of age) tends to be higher than the traditional age range of women of child-bearing potential (15 to 44 years of age), therefore, the pregnancy rate and fetal exposure would potentially be lower.

Table continued on next page

Potential risk	Fetal disorders after exposure during pregnancy
Risk groups or risk factors	Fetal disorders may be relevant during pregnancy.
Preventability	Precautionary text in Section 4.6 of the SmPC that mirabegron is not recommended during pregnancy and in women of childbearing potential not using contraception.
Impact on the risk-benefit balance of the product	The important potential risk of fetal disorders after exposure during pregnancy is included due to fetal findings of cardiomegaly and dilated aorta reported in rabbits at high systemic exposures (15.7-fold the non-protein bound human exposure at MRHD; 35.7 fold the total systemic human exposure at MRHD). Similar findings were not reported in rat fetuses from dams with systemic exposure 73.5-fold higher than the non-protein bound human exposure at MRHD (95.6-fold the total systemic human exposure at MRHD
Potential public health impact of safety concern	The occurrence of cardiomegaly and dilated aorta in fetuses from only rabbits and only at high concentrations of mirabegron indicates that the risk to the human fetus from this OAB therapeutic, when taken chronically at doses up to the MHRD, is small. Fetuses from pregnant humans may potentially be at risk; however, pregnant women represent a small proportion of the target OAB population. The impact of cardiomegaly and dilated aorta if it were to occur in the human fetus are unknown but it could be potentially serious. Mirabegron is excreted in the milk of rodents and therefore is predicted to be present in human milk. Women who are nursing should not be administered mirabegron.

AR: adrenoceptor; CTD: Common Technical Document; MRHD: maximum recommended human dose; OAB: overactive bladder: SmPC: Summary of Product Characteristics.

Important potential risk: Cardiac failure, particularly in patients with pre-existing cardiovascular diseases or cardiovascular risk factors

In the Final PRAC assessment report to the Periodic Safety Update Report (PSUR) 7 dated 14-Jan-2016, Astellas was requested to modify the wording of the safety concern regarding 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. The previous statement *"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"* was modified to *"Cardiac failure, particularly in patients with pre-existing cardiovascular diseases or cardiovascular risk factors."*

Astellas was also requested to include this modified wording as an important potential risk from the previous category of missing information based on the rationale that "*it is difficult to conclude a relationship between mirabegron and cardiac failure, it cannot be ruled out that patients with pre-existing risk factors developed cardiac failure after the use of mirabegron."* The EMA PRAC considered this risk better managed as an important potential risk based on this rationale.

SVII.3.2 Presentation of the missing information

Missing information: Pediatric use
Evidence source: A clinical development program for use of mirabegron in pediatric patients with OAB and NDO is currently ongoing (project code ED178).
Anticipated risk/consequence of the missing information: The safety and efficacy of mirabegron in adolescents and children below 18 years of age is being investigated and mirabegron should therefore not be used in these patients. There is no current indication for use of mirabegron in the pediatric population although there is evidence that mirabegron is used in this population. This risk is mitigated by clearly stated indications in Section 4.2, "Posology and method of administration" of the SmPC: "The safety and efficacy of mirabegron in children below 18 years of age have not been established. No data are available." and Section 2, "What you need to know before you use Betmiga" of the PL "Do not give this medication 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".

OAB: overactive bladder; NDO: neurogenic detrusor overactivity.

Module SVIII. Summary of the safety concerns

Data-lock point for this Module	30-Jun-2020
Version when Module last updated	8.0

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important potential risks	• QT prolongation • Fetal disorders after exposure during pregnancy • Cardiac failure, particularly in patients with pre-existing cardiovascular diseases or cardiovascular risk factors
Missing information	• Pediatric use

QT: QT interval.

3 PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

Data-lock point for this Module	30-Jun-2020
Version when Module last updated	8.0

3.1 Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection

Specific adverse reaction follow-up questionnaires

The use of standardized questionnaires are designed to gather all the necessary information for accurate case assessment and early detection of any changes in the risk benefit ratio of the product. Procedures for distribution and use of Follow-up Questionnaires within the Pharmacovigilance department are similar for all medicinal products. In general, the regional Drug Safety Officer contacts the reporter (by phone or by letter) to collect additional information for specific reported adverse events and completes the questionnaire. The questionnaire is also sent to the reporter to ask for confirmation by signing the document. The information is forwarded to the Pharmacovigilance department within pre-established timelines. The Pharmacovigilance department processes and reports all safety related information in accordance with local regulation.

Table 40 Specific adverse reaction follow-up questionnaires

Description	Purpose	Safety concern(s) addressed
Follow-up Questionnaire for QT prolongation /Torsade de pointes	To ensure continuous monitoring of potential adverse events of QT prolongation	QT prolongation
Pregnancy reporting form and Follow- up Questionnaire for Pregnancy outcome	To ensure continuous monitoring of potential events of pregnancy	Fetal disorders after exposure during pregnancy

The adverse event Follow-up Questionnaires are provided in [Annex 4].

3.2 Additional pharmacovigilance activities

Table 41 Additional Pharmacovigilance Activities

Activity	Objective(s)/Description	Milestone(s)
Implementation of an approved PIP	To ensure continuous monitoring to identify potential adverse events reported in pediatric patients	PIPs were approved by EMA for the conditions "Treatment of idiopathic overactive bladder" (OAB P/0350/2019 dated 30-Sep-2019) and for the condition "Treatment of neurogenic detrusor overactivity" (NDO P/0056/2017 dated 17-Mar- 2017). The PIPs contain the development plans for these 2 conditions in the pediatric population. Each PIP contains 2 non-clinical studies in juvenile animals (completed), 2 phase 1 studies in children (1 pharmacokinetic study with mirabegron tablets and 1 pharmacokinetic study with mirabegron suspension, both are completed), 1 bio-availability and food effect study in young healthy adults (completed), 2 phase 2/3 studies in patients with NDO (1 completed, 1 planned), and 1 planned phase 2/3 study in patients with OAB.

EMA: European Medicines Agency; NDO: neurogenic detrusor overactivity; OAB: overactive bladder; PIP: pediatric investigation plan.

Table 42 Additional Pharmacovigilance Activities completed

Study short name and title	Study 178-PV-002 (Drug utilization study [DUS] of mirabegron (Betmiga) using real-world healthcare databases from the Netherlands, Spain, United Kingdom and Finland)
Rationale and study objectives	The objectives of the study are to assess the effectiveness of the Direct Healthcare Professional Communication (DHPC) letter as a risk minimization measure in the participating countries by quantifying the proportions of mirabegron initiators with documented severe uncontrolled hypertension (primary objective) and the frequency of blood pressure recordings at baseline and during mirabegron treatment, especially in hypertensive patients (secondary objective) before and after DHPC dissemination.
Study design	An observational retrospective cohort study among patients initiating mirabegron (Betmiga) treatment using real-world data from the Netherlands, Spain, the UK and Finland will be performed. The study will compare the time periods relative to the DHPC letter dissemination.
Study population	Mirabegron initiators during the years 2012 to 2016 will be selected from the databases by prescriptions of mirabegron since first authorization (20-Dec2012) and until end of data availability (31-Dec-2016). The date of the first mirabegron prescription will be the index date. A baseline period of 12 months preceding the index date will be defined to capture information on blood pressure and hypertension before the index date. Users with less than 12 months recorded history in the database prior to the index date will be excluded. No other exclusion criteria apply.
Milestones	These assessments will be performed during and/or shortly before start of mirabegron use, and pre- and post-DHPC dissemination 07-Sep- 2015 on a quarterly basis in multiple countries in Europe. On 11 Jul 2018, the final study report for this post-authorization safety study (PASS) was submitted to EMA as a type II variation. An updated study report was submitted to EMA on 16 Apr 2019 as per request of PRAC Rapporteur. On 14 Jun 2019, the CHMP endorsed the PRAC assessment report and approved the type II variation.

CHMP: Committee for Medicinal Products for Human Use; DHPC: direct healthcare professional communication; DUS: Drug Utilization Study; EMA: European Medicine Agency; PASS: post-authorization safety study; PRAC: Pharmacovigilance Risk Assessment Committee; UK: United Kingdom.

Study short name and title	178-CL-114 (Post-authorization Safety Program—Evaluation of Cardiovascular Events in Users of Mirabegron and Other Treatments for Overactive Bladder)
Rationale and study objectives	To estimate and compare the risk of CV events among new users of mirabegron and comparator antimuscarinic drugs used in the treatment of OAB. Additional analytic focus will be on the population aged more than 65 years and individuals with high CV risk.
Study design	In the proposed program, cohorts of patients who receive drugs used in the treatment of OAB will be drawn from the US and European populations. The new-user design for the individual medications will be adopted.
Study population	A new user of any drug of interest will be a patient who receives a first prescription or dispensing for a given drug during the study period without a prescription or dispensing for the same medication in the previous 6 months (US) or 12 months (Europe). As the study is focusing on the evaluation of the CV safety of antimuscarinic medications, not the description of CV morbidity among patients with a diagnosis of OAB, the study population will include all new antimuscarinic medication users and a claim indicative of an OAB diagnosis will not be required. Special subpopulations will be those aged 65 years and older and subjects with high CV risk.
Milestones	An interim report was completed and submitted to EMA on 25-Jun-2018 and the final report was completed and submitted to EMA on 27-Nov-2019. The study found no higher risk for MACE (major adverse cardiovascular event), AMI (acute myocardial infarction), stroke, CV mortality, or all-cause mortality among current users of mirabegron as compared to current users of antimuscarinic medications. Given the diverse nature of the study population, these study findings may be generalizable to mirabegron users in healthcare systems beyond those included in this study.

AMI: acute myocardial infarction; CV: cardiovascular; EMA: European Medicines Agency; MACE: major adverse cardiovascular event; OAB: overactive bladder; US: United States.

3.3 Summary table of additional pharmacovigilance activities

Table Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Not applicable				

4 PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Data-lock point for this Module	30-Jun-2020
Version when Module last updated	8.0

There are currently no ongoing or planned post-authorization efficacy studies.

5 RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

Data-lock point for this Module	30-Jun-2020
Version when Module last updated	8.0

5.1 Routine Risk Minimization Measures

Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
QT prolongation	Routine risk communication: • SmPC Section 4.4 • PL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Specific recommendation to exercise caution when administering mirabegron in patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval, are provided in SmPC Section 4.4 and PL Section 4.
Fetal disorders after exposure during pregnancy	Routine risk communication: • SmPC Section 4.6 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Specific recommendation not to use Mirabegron during pregnancy; in women of childbearing potential not using contraception; as well as discussing with the doctor or pharmacist first before breast feeding, are provided in SmPC Section 4.6 and PL Section 2.
Cardiac failure, particularly in patients with pre-existing cardiovascular diseases or cardiovascular risk factors	There are no risk minimization measures specific to cardiac failure. Cardiac failure is not included in the EU SmPC however it was added to the EU-RMP as a potential important risk per EMA PRAC request with the PRAC's rationale that "it is difficult to conclude a relationship between mirabegron and cardiac failure, it cannot be ruled out that patients with pre-existing risk factors developed cardiac failure after the use of mirabegron." The EMA PRAC considered this risk better managed as an important potential risk based on this rationale.
Table continued on next page	

Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Pediatric use	Routine risk communication: • SmPC Section 4.2 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Specific recommendation not to give this medicine to children and adolescents under the age of 18 years is given in SmPC Section 4.2 and PL Section 2.

CYP: cytochrome P450; DBP: diastolic blood pressure; EMA: European Medicines Agency; GFR: glomerular filtration rate; IR: immediate release; OAB: overactive bladder; PL: Package Leaflet; PSUR: periodic safety update report; PRAC: Pharmacovigilance Risk Assessment Committee; RMP: risk management plan; SBP: systolic blood pressure; SmPC: Summary of Product Characteristics; TME: targeted medical event.

5.2 Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

5.2.1 Removal of additional risk minimization activities

Table Part V.2: Removal of additional risk minimization activities

Activity	Safety concern(s) addressed	Rationale for the removal of additional risk minimization activity
Not applicable		

5.3 Summary of Risk Minimization Measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
QT prolongation	Routine risk communication: • SmPC Section 4.4 • PL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Specific recommendation to exercise caution when administering mirabegron in patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval, are provided in SmPC Section 4.4 and PL Section 4.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Use of a Targeted Data Questionnaire
Table continued on next page		

Table Part V.3: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Fetal disorders after exposure during pregnancy	Routine risk communication: • SmPC Section 4.6 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: Specific recommendation not to use Mirabegron during pregnancy in women of childbearing potential not using contraception, as well as discussing with the doctor or pharmacist first before breastfeeding, are provided in SmPC Section 4.6 and PL Section 2.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Use of a Targeted Data Questionnaire.
Cardiac failure, particularly in patients with pre-existing cardiovascular diseases or cardiovascular risk factors	There are no risk minimization measures specific to cardiac failure. Cardiac failure is not included in the EU SmPC however it was added to the EU-RMP as a potential important risk per EMA PRAC request with the PRAC's rationale that "it is difficult to conclude a relationship between mirabegron and cardiac failure, it cannot be ruled out that patients with pre-existing risk factors developed cardiac failure after the use of mirabegron." The EMA PRAC considered this risk better managed as an important potential risk based on this rationale.	Routine pharmacovigilance signal detection activities via monitoring of cardiac failure events within the cardiac events TME.
Pediatric use	Routine risk communication: • SmPC Section 4.2 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: Specific recommendation not to give this medicine to children and adolescents under the age of 18 years is given in SmPC Section 4.2 and PL Section 2.	Additional pharmacovigilance activities: • Implementation of an approved Pediatric Investigational Plan • Post marketing use in pediatric population is considered a special situation and are routinely monitored via Pharmacovigilance signal detection activities.

EMA: European Medicines Agency; GFR: glomerular filtration rate; OAB: overactive bladder; PL Package Leaflet; PSUR: periodic safety update report; PRAC: Pharmacovigilance Risk Assessment Committee; RMP: risk management plan; SmPC: Summary of Product Characteristics; TME: targeted medical event.

6 SUMMARY OF THE RISK MANAGEMENT PLAN

Data-lock point for this Module	30-Jun-2020
Version when Module last updated	8.0

Summary of risk management plan for Betmiga (mirabegron)

This is a summary of the risk management plan (RMP) for Betmiga. The RMP details important risks of Betmiga, how these risks can be minimized, and how more information will be obtained about Betmiga's risks and uncertainties (missing information).

Betmiga's SmPC and its PL give essential information to healthcare professionals and patients on how Betmiga should be used.

This summary of the RMP for Betmiga should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Betmiga's RMP.

I. The medicine and what it is used for

Betmiga is authorized for the indication of overactive bladder with symptoms of urinary incontinence, urgency and urinary frequency in adult patients (see SmPC for the full indication). It contains mirabegron as the active substance and it is given by the oral route of administration.

Further information about the evaluation of Betmiga's benefits can be found in Betmiga's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage post-authorization RMP.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Betmiga, together with measures to minimize such risks and the proposed studies for learning more about Betmiga's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Betmiga is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Betmiga are risks that need special risk management activities to further investigate or minimize the risk. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Betmiga. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important potential risks	• QT prolongation • Fetal disorders after exposure during pregnancy • Cardiac failure, particularly in patients with pre-existing cardiovascular diseases or cardiovascular risk factors
Missing information	• Pediatric use

QT: interval from start of Q to end of T waves on electrocardiogram;

II.B Summary of important risks

There are no ongoing important identified risks for mirabegron.

Important potential risk: QT prolongation	
Evidence for linking the risk to the medicine	CTD Module 5.3.5.3, Research Report: Mirabegron and Cardiovascular Safety, Appendix 5. Following a review of mirabegron safety data, QT prolongation was categorized as an important potential risk. Mirabegron, at normal doses, has not shown relevant QT prolongation in clinical studies. However, since patients with a known history of QT prolongation or patients who are taking medicinal products which are known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown.
Risk factors and risk groups	Potential risk groups are those receiving the therapeutic dose of mirabegron 50 mg once daily who concurrently have a known history of QT prolongation or who are concurrently taking medications known to prolong QT interval.
Risk minimization measures	Routine risk communication: • SmPC Section 4.4 • PL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Specific recommendation to exercise caution when administering mirabegron in patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval, are provided in SmPC Section 4.4 and PL Section 4.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Use of a Targeted Data Questionnaire

CTD: common technical document; QT: interval between the start of the Q wave to the end of the T wave on electrocardiogram; QTc: QT interval corrected for heart rate; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Important potential risk: Fetal disorders after exposure during pregnancy	
Evidence for linking the risk to the medicine	CTD Module 5.3.5.3, Integrated Summary of Safety; CTD Module 5.3.5.3, 120-day Safety Update. Following a review of mirabegron safety data, fetal disorders after exposure during pregnancy was categorized as an important potential risk. There are limited amount of data from the use of mirabegron in pregnant women.
Risk factors and risk groups	Fetal disorders may be relevant during pregnancy.
Risk minimization measures	Routine risk communication: • SmPC Section 4.6 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: Specific recommendation not to use mirabegron during pregnancy; in women of childbearing potential not using contraception; as well as discussing with the doctor or pharmacist first before breast feeding, are provided in SmPC Section 4.6 and PL Section 2.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Use of a Targeted Data Questionnaire

CTD: common technical document; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Important potential risk: Cardiac failure, particularly in patients with pre-existing cardiovascular diseases or cardiovascular risk factors	
Evidence for linking the risk to the medicine	Added as potential important risk per EMA PRAC request with the PRAC's rationale that "*it is difficult to conclude a relationship between mirabegron and cardiac failure, it cannot be ruled out that patients with pre-existing risk factors developed cardiac failure after the use of mirabegron.*" The EMA PRAC considered this risk better managed as an important potential risk based on this rationale.
Risk factors and risk groups	Patients with pre-existing cardiovascular disease or risk factors.
Risk minimization measures	There are no risk minimization measures specific to cardiac failure. Cardiac failure is not included in the EU SmPC however it was added to the EU-RMP as a potential important risk per EMA PRAC request with the PRAC's rationale that "it is difficult to conclude a relationship between mirabegron and cardiac failure, it cannot be ruled out that patients with pre-existing risk factors developed cardiac failure after the use of mirabegron." The EMA PRAC considered this risk better managed as an important potential risk based on this rationale.
Additional pharmacovigilance activities	None, only routine pharmacovigilance activities.

EMA: European Medicines Agency; EU: European Union; PRAC: Pharmacovigilance Risk Assessment Committee.

Missing information: Pediatric use	
Evidence for linking the risk to the medicine	The safety and efficacy of mirabegron in children below 18 years of age have not yet been established. No data are available.
Risk factors and risk groups	The safety and efficacy of mirabegron in adolescents and children below 18 years of age have not yet been investigated and mirabegron should therefore not be used in these patients. There is no current indication for use of mirabegron in the pediatric population although there is evidence that mirabegron is used in this population (cumulative exposure in all age groups until 31-Oct-2016 is 5702480 patients).
Risk minimization measures	Routine risk communication: • SmPC Section 4.2 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: Specific recommendation not to give this medicine to children and adolescents under the age of 18 years is given in SmPC Section 4.2 and PL Section 2.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Implementation of an approved Pediatric Investigational Plan

PL: Package Leaflet; SmPC: Summary of Product Characteristics.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies that are conditions of the marketing authorization or specific obligation of Betmiga.

II.C.2 Other studies in post-authorization development plan

The following 2 required Additional Pharmacovigilance Activities studies (category 3) have been completed:

- **Study short name:** 178-CL-114 Post-authorization Safety Program—Evaluation of Cardiovascular Events in Users of Mirabegron and Other Treatments for Overactive Bladder.

  Purpose of the study: To estimate and compare the risk of CV (cardiovascular) events among new users of mirabegron and comparator antimuscarinic drugs used in the treatment of OAB. Additional analytic focus will be on the population aged more than 65 years and individuals with high CV risk.

  Study results: the study found no higher risk for MACE (major adverse cardiovascular event), AMI (acute myocardial infarction), stroke, CV mortality, or all-cause mortality among current users of mirabegron as compared to current users of antimuscarinic medications. Given the diverse nature of the study population, these

study findings may be generalizable to mirabegron users in healthcare systems beyond those included in this study.

- **Study short name:** 178-PV-002 Drug utilization study (DUS) of mirabegron (Betmiga) using real-world healthcare databases from the Netherlands, Spain, UK and Finland.

  Purpose of the study: To assess the effectiveness of the DHPC (direct healthcare professional communication) letter as a risk minimization measure in the participating countries by quantifying the proportions of mirabegron initiators with documented severe uncontrolled hypertension (primary objective) and the frequency of blood pressure recordings at baseline and during mirabegron treatment, especially in hypertensive patients (secondary objective) before and after DHPC dissemination.

  Study results: the study concluded that the use of mirabegron in patients with severe uncontrolled hypertension is uncommon, reflecting the low prevalence in the population, but also suggesting that current labelling seems to generally work well with respect to minimizing risks in this population.

Annex 4 Specific adverse event follow-up forms

Data-lock point for this annex	30-Jun-2020
Version when annex last updated	8.0

Table of contents

Email to:		**Case Number**	
Fax to:			

Instructions

With this questionnaire, we would like to request specific follow-up information regarding the case you reported for QT Prolongation and/or Torsades de Pointes associated with mirabegron. Please provide as much information as possible, focusing on the information that is relevant for the QT Prolongation and/or Torsades de Pointes case and has not previously been provided. If requested information is not available or applicable (not applicable as assessed by the reporter), please include "N/A" in the specific field. Please consider the applicable data privacy restrictions in your country while completing this form. Please attach any relevant supporting documentation, if available.

Thank you in advance for your cooperation.

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Pregnancy Reporting Form

Case Number:

PATIENT INFORMATION {please consider (local) data privacy restrictions}					
Patient ID/ Initials	**Country of Incidence**	**Date of Birth/Age** (dd-Mmm-yyyy)	**Gender** ☐ Male ☐ Female	**Weight** ☐ Kg ☐ Lbs (US)	**Height** ☐ cm ☐ in

ADVERSE EVENT INFORMATION				
Adverse Event (AE)	**Seriousness Criteria** Select all that apply	**Relationship to Astellas Suspect Drug**	**Start Date:** (dd-Mmm-yyyy) / **End Date:** (dd-Mmm-yyyy)	**Outcome** Select only one
	☐ Death* ☐ Life-Threatening ☐ Hospitalization/Prolonged Hospitalization ☐ Persistent or Significant Disability ☐ Congenital Anomaly ☐ Would have led to one of the above if left untreated (Medically Important) ☐ Non-Serious	☐ Possible ☐ Unassessable ☐ Not related	Day / Month / Year Or ☐ Ongoing	☐ Fatal ☐ Not recovered/Not resolved ☐ Recovered /Resolved ☐ Recovered /Resolved with sequelae ☐ Recovering /Resolving ☐ Unknown (Unk)

Treatment received ☐ YES ☐ NO	Start Date: (dd-Mmm-yyyy)			End Date (dd-Mmm-yyyy) or Treatment Ongoing			
	Day	Month	Year	Day	Month	Year	Or
If yes, please specify							☐ Ongoing

Please provide additional details about the adverse event below:

*Death: Please provide date of death (dd-Mmm-yyyy): Was Autopsy performed? ☐ Yes ☐ No ☐ Unknown (Unk)

CLINICAL SIGNS AND SYMPTOMS OF THE EVENT

	YES	NO	UNK		YES	NO	UNK
Acute blurred vision	☐	☐	☐	Lightheadedness	☐	☐	☐
Acute deafness	☐	☐	☐	Loss of consciousness	☐	☐	☐
Arrhythmia	☐	☐	☐	Palpitations	☐	☐	☐
Bradycardia	☐	☐	☐	Seizures	☐	☐	☐
Chest Discomfort / Pain	☐	☐	☐	Shortness of breath	☐	☐	☐
Disturbance of consciousness	☐	☐	☐	Tachycardia	☐	☐	☐
Gasping noise during sleep	☐	☐	☐	☐ Other (If yes, please specify):	☐	☐	☐

Please provide details, including duration of signs and symptoms below:

UNDERLYING CONDITIONS / POTENTIAL RISK FACTORS FOR THE REPORTED EVENT

	YES	NO	UNK		YES	NO	UNK
Alcohol use	☐	☐	☐	Hypertension	☐	☐	☐
Arrhythmia	☐	☐	☐	Ischemic heart disease (e.g., myocardial infarction)	☐	☐	☐
Congenital heart defects If yes, please specify:	☐	☐	☐	Other cardiac disorder If yes, please specify:	☐	☐	☐
Congenital QT syndrome (long or short)	☐	☐	☐	Similar episode(s) in the past	☐	☐	☐
Electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia) If yes, please specify:	☐	☐	☐	Smoking	☐	☐	☐
Heart failure	☐	☐	☐	Thyroid disease	☐	☐	☐

UNDERLYING CONDITIONS / POTENTIAL RISK FACTORS FOR THE REPORTED EVENT (continued)

Pregnancy Reporting Form

Case Number:

	YES	NO	UNK		YES	NO	UNK
History of hepatic impairment If yes, please specify:	☐	☐	☐	Valvular heart disease If yes, please specify:	☐	☐	☐
History of renal impairment or renal disease If yes, please specify:	☐	☐	☐	Other (If yes, please specify):	☐	☐	☐
Possible drug interaction* (If yes, please specify drugs):					☐	☐	☐

* If yes, add details to suspect drug information and/or relevant concomitant medication or relevant historical drug section

RELEVANT MEDICAL HISTORY

DESCRIPTION	**START DATE** dd-Mmm-yyyy	**STOP DATE** dd-Mmm-yyyy or Ongoing
		☐ Ongoing
		☐ Ongoing
		☐ Ongoing

Please provide additional details below:

SURGICAL HISTORY	YES	NO	UNK	**FAMILY HISTORY**	YES	NO	UNK
Cardioversion	☐	☐	☐	Family history of cardiovascular disease If yes, please specify:	☐	☐	☐
Other (If yes, please specify):	☐	☐	☐	Family history of congenital QT syndrome	☐	☐	☐

SUSPECT DRUG INFORMATION

Drug Name	**Indication**	**Dose per Administration**	**Frequency**	**Start Date** dd-Mmm-yyyy	**Stop Date** dd-Mmm-yyyy or Ongoing
1.					☐ Ongoing
If therapy discontinued/interrupted, did event abate after stopping the drug? ☐ YES If yes, when?					☐ NO ☐ UNK ☐ N/A
If therapy discontinued/interrupted, did event reappear after reintroduction? ☐ YES If yes, when?					☐ NO ☐ UNK ☐ N/A
2.					☐ Ongoing
If therapy discontinued/interrupted, did event abate after stopping the drug? ☐ YES If yes, when?					☐ NO ☐ UNK ☐ N/A
If therapy discontinued/interrupted, did event reappear after reintroduction? ☐ YES If yes, when?					☐ NO ☐ UNK ☐ N/A
3.					☐ Ongoing
If therapy discontinued/interrupted, did event abate after stopping the drug? ☐ YES If yes, when?					☐ NO ☐ UNK ☐ N/A
If therapy discontinued/interrupted, did event reappear after reintroduction? ☐ YES If yes, when?					☐ NO ☐ UNK ☐ N/A

RELEVANT CONCOMITANT MEDICATION (used within 30 days prior to the earliest event onset, including homeopathic, herbal or other therapies)*

Drug Name	**Indication**	**Dose per Administration**	**Frequency**	**Start Date** dd-Mmm-yyyy	**Stop Date** dd-Mmm-yyyy or Ongoing
1.					☐ Ongoing
2.					☐ Ongoing
3.					☐ Ongoing

*Please list all medications used that prolong QT interval. Commonly used drug classes that may prolong the QT interval include antimicrobials (e.g., erythromycin), antiarrhythmics (e.g., amiodarone), antipsychotics (e.g., risperidone), antidepressants (e.g., citalopram) and antiemetics (e.g., domperidone).

RELEVANT HISTORICAL DRUG INFORMATION (having a start and stop date 30 days or more prior to the earliest event onset)

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Pregnancy Reporting Form

Case Number:

Drug Name	**Indication**	**Dose per Administration**	**Frequency**	**Start Date** dd-Mmm-yyyy	**Stop Date** dd-Mmm-yyyy
1.					
2.					
3.					

RELEVANT INVESTIGATIONS PERFORMED (Laboratory / Diagnostic Test Results Available)

Test/ Name	**YES**	**NO**	**Unit** If applic-able	**Result Before Administration**	**Date** dd-Mmm-yyyy	**Result at Time of Event**	**Date** dd-Mmm-yyyy	**Result after discontinuation/ treatment/ resolution of the event**	**Date** dd-Mmm-yyyy
Cardiac monitoring studies	☐	☐							
(e.g., Holter monitor, event monitor) If yes, please specify:									
Electrocardiogram or Rhythm Strips	☐	☐							
If yes, please specify:									
Bicarbonate	☐	☐							
Echocardiography	☐	☐							
QT/QTc Intervals	☐	☐							
Serum Calcium	☐	☐							
Serum Chloride	☐	☐							
Serum Magnesium	☐	☐							
Serum Potassium	☐	☐							
Serum Sodium	☐	☐							
Specify other:	☐	☐							

Please provide details of additional investigations (including the reason for the investigation) below:

GENERAL INFORMATION Please add any other information you consider relevant to provide.

REPORTER CONTACT INFORMATION

Date of this report (dd-Mmm-yyyy)	**Please specify your affiliation/function:**		
	☐ Physician ☐ Pharmacist ☐ Other (If other, please specify):		
Name	Address	Telephone /Fax	Email

HEALTH CARE PRACTITIONER CONTACT INFORMATION (if different than the Reporter Contact Information above)

Name	Address	Telephone /Fax	Email

PERSON COMPLETING FORM (if different than the Reporter Contact Information above)

Name	Address (including function/department)	Telephone /Fax	Email

MEDICALLY QUALIFIED (SUB) INVESTIGATOR FOR ASTELLAS SPONSORED STUDIES

Signature (to confirm the accuracy of the data and the causal relationship)	Name	Date (dd-Mmm-yyyy)

Case Number:

ASTELLAS ONLY		
AE in Native Language (EEA Only) as Reported (Mandatory field if available)	Specify Language	

Email to:			**Case Number:**		
Fax to:			**Patient Details:**	Patient Initials	
Protocol #	**Study ARM**	**Country**	**Site #**	**Subject ID**	**Subject Randomization #**

Instructions

With this questionnaire we would like to request specific follow-up information regarding the pregnancy you reported. Provide as much information as possible, focusing on information that is relevant for the case that has not previously been provided. Consider the applicable data privacy restrictions in your country while completing this form. Attach any relevant supporting documentation, if available.

Thank you in advance for your cooperation.

astellas

Pregnancy Reporting Form

Case Number:

DEMOGRAPHICS (MOTHER)				
PATIENT INITIALS	**WHO WAS EXPOSED TO ASTELLAS DRUG**	**DATE OF BIRTH/AGE** (dd-Mmm-yyyy)	**WEIGHT** ☐ Kg ☐ Lbs	**HEIGHT** ☐ cm ☐ in
	☐ Mother ☐ Father (enter additional details of mother/father below)			

CURRENT PREGNANCY DETAILS						
Last Menstrual Period (LMP)		Gestational age:		weeks		days
Expected date of delivery		Gestational age at time of exposure		weeks		days
Number of foetuses		☐ Treatment for infertility				
Contraception method:		Reason for contraception failure:				

OBSTETRIC / PREGNANCY HISTORY			
☐ Abnormal menstrual cycles			☐ Previous pregnancy complications
☐ Para	Specify number:		☐ Previous fetal/neonatal abnormalities
☐ Gravida	Specify number:		☐ History of subfertility
Additional information/comments:			

UNDERLYING CONDITIONS / POTENTIAL RISK FACTORS (MOTHER AND/OR FATHER)	
☐ Infection	☐ Immune disorder
☐ Diabetes	☐ Allergies
☐ Epilepsy	☐ Psychiatric illness
☐ Hypertension	☐ Recreational drug use (e.g. smoking, alcohol, illicit drug use)

FAMILY HISTORY (MOTHER AND/OR FATHER)	
☐ Congenital anomalies	☐ Mental illness
☐ Hereditary disease	☐ Other
Additional information/comments:	

ADVERSE EVENT INFORMATION (MOTHER) ☐ **Not Applicable**

ADVERSE EVENT	**START DATE** dd-Mmm-yyyy	**STOP DATE** dd-Mmm-yyyy or Ongoing	**SERIOUSNESS[1]**	**RELATIONSHIP TO ASTELLAS SUSPECT DRUG[2]**
		☐ Ongoing		
		☐ Ongoing		

[1]**SERIOUSNESS CRITERIA:** *1. Death*, 2. Requires/Prolongs Hospitalization, 3. Congenital Anomaly, 4. Life Threatening, 5. Persistent or Significant Disability, 6. Would have led to one of the above if left untreated (Medically Important), 7. Non-serious*

[2]**RELATIONSHIP TO ASTELLAS SUSPECT DRUG:** Do you consider that there is a reasonable possibility that the event may have been caused by the Astellas suspect drug? *1. Yes, 2. No, 3. Unassessable*

*Date of death (dd-Mmm-yyyy):	Autopsy details:
Additional details about the adverse event:	
Other pregnancy complications:	

Pregnancy Reporting Form

Case Number:

RELEVANT MEDICATION (including pregnancy supplements) (**MOTHER,** including the any medication exposed to via Father)

DRUG NAME	BATCH/ LOT#	INDICATION	DOSE / ROUTE OF ADMINISTRATION	FREQUENCY	START DATE dd-Mmm-yyyy	STOP DATE dd-Mmm-yyyy
1.						☐ Ongoing
2.						☐ Ongoing
3.						☐ Ongoing

RELEVANT INVESTIGATIONS (MOTHER)

INVESTIGATION	RESULT	DATE dd-Mmm-yyyy	INVESTIGATION	RESULT	DATE dd-Mmm-yyyy
☐ Alpha fetoprotein			☐ Ultrasound scan		
☐ Amniocentesis			☐ Urine glucose		
☐ Beta human chorionic gonadotrophin			☐ Urine protein		
☐ Blood pressure	/		☐ Serology (e.g. rubella, toxoplasmosis)		
☐ Chorionic villus sampling			☐ Other:		

Details of additional investigations (including reason for the investigation):

GENERAL INFORMATION (MOTHER AND/OR FATHER)

REPORTER CONTACT INFORMATION

DATE OF THIS REPORT (dd-Mmm-yyyy)	SPECIFY YOUR AFFILIATION/FUNCTION:		
	☐ Physician ☐ Pharmacist ☐ Other:		
NAME	ADDRESS	TELEPHONE /FAX	EMAIL

MEDICALLY QUALIFIED INVESTIGATOR/SUB-INVESTIGTOR FOR ASTELLAS SPONSORED STUDIES

SIGNATURE (to confirm the accuracy of the data and the causal relationship)	NAME	DATE (dd-Mmm-yyyy)

Email to:		**Case Number:**	
Fax to:		**Patient Details:**	Patient Initials Patient Gender ☐ Male ☐ Female

Instructions

With this questionnaire we would like to request specific follow-up information regarding the outcome of the pregnancy you reported. Provide as much information as possible, focusing on information that is relevant to the pregnancy that has not previously been provided. Complete a separate form for each neonate. Consider the applicable data privacy restrictions in your country while completing this form. Attach any relevant supporting documentation, if available.

Thank you in advance for your cooperation.

Follow-Up Questionnaire for Pregnancy Outcome

Case Number:

OUTCOME OF CURRENT PREGNANCY		
☐ Vaginal delivery	☐ Elective C-section	☐ Emergency C-section
☐ Live birth	☐ Miscarriage	☐ Late foetal death
☐ Ectopic pregnancy	☐ Molar pregnancy	☐ Elective termination
☐ Abnormal placenta	☐ Complications for neonate	☐ Complications for mother
Provide any additional details of delivery, including complications:		

NEONATAL INFORMATION AT BIRTH								
GENDER	**DATE OF BIRTH** dd-Mmm-yyyy	**WEIGHT**	**LENGTH**	**HEAD CIRCUMFERENCE**	**BREASTFEEDING**	**GESTATIONAL AGE AT BIRTH**		
☐ Boy ☐ Girl		☐ Kg ☐ Lbs	☐ cm ☐ in	☐ cm ☐ in	☐	Weeks		Days
☐ Apgar Score	After 1 minute:		After 5 minutes:			After 10 minutes:		
☐ Uneventful (healthy baby)			☐ Admission to high dependency or intensive care unit					
☐ Need for resuscitation			☐ Drug therapies					
☐ Malformation / anomaly diagnosed at birth			☐ Dysmaturity					
☐ Malformation / anomaly diagnosed later after birth			☐ Neonatal illness					
☐ Hospitalization			☐ If outcome above is anything other than uneventful, is this outcome related to Astellas drug?					
Additional details								

ADVERSE EVENT INFORMATION OF THE NEONATE (including complications) ☐ **Not Applicable**
(If more than one adverse event, provide details in General Information section)

ADVERSE EVENT	**START DATE** dd-Mmm-yyyy	**STOP DATE** dd-Mmm-yyyy or ongoing	**SERIOUSNESS**[1]	**RELATIONSHIP TO ASTELLAS SUSPECT DRUG**[2]
		☐ Ongoing		

[1]**SERIOUSNESS CRITERIA:** *1. Death*, 2. Requires/Prolongs Hospitalization, 3. Congenital Anomaly, 4. Life Threatening, 5. Persistent or Significant Disability, 6. Would have led to one of the above if left untreated (Medically Important), 7. Non-serious*

[2]**RELATIONSHIP TO ASTELLAS SUSPECT DRUG:** Do you consider that there is a reasonable possibility that the event may have been caused by the Astellas suspect drug?

1. Yes, 2. No, 3. Unassessable

*Date of death (dd-Mmm-yyyy):	Autopsy details:
Additional details about the adverse event:	

GENERAL INFORMATION

REPORTER CONTACT INFORMATION

DATE OF THIS REPORT (dd-Mmm-yyyy)	**SPECIFY YOUR AFFILIATION/FUNCTION**		
	☐ Physician ☐ Pharmacist ☐ Other:		
NAME	**ADDRESS**	**TELEPHONE /FAX**	**EMAIL**

MEDICALLY QUALIFIED INVESTIGATOR/SUB-INVESTIGATOR FOR ASTELLAS SPONSORED STUDIES

SIGNATURE (to confirm the accuracy of the data and the causal relationship)	**NAME**	**DATE** (dd-Mmm-yyyy)

Annex 6 Details of proposed additional risk minimization activities (if applicable)

Data-lock point for this annex	30-Jun-2020
Version when annex last updated	8.0

Not applicable