Local Risk Management Plan

EUROPEAN UNION (EU) LOCAL RISK MANAGEMENT PLAN

MIRABEGRON (BETMIGA™)

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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: 9.2

Data-lock point for this RMP: 30 Jun 2023

Date of final sign-off: Date of final signature on the electronic signature page

Rationale for submitting an updated RMP: This RMP update includes revisions based on the Committee for Medicinal Products for Human Use (CHMP) day 180 list of outstanding issues received (Procedure No. EMEA/H/C/002388/X/0039) following the EU neurogenic detrusor overactivity (NDO) pediatric indication submission in Nov 2021. Safety concerns were reviewed in accordance with Good Pharmacovigilance Practices (GVP) Module V Rev.2.

Summary of significant changes in this RMP:

- NDO pediatric patients with mild and moderate renal impairment were removed from the list of missing information in accordance with GVP Module V Rev.2 guidance.
- The relevant Sections SIV.3, SVII.1.2, SVII.2, SVII.3.2, SVIII.1, Part 5.1, Part 5.3, and Part 6 were updated to remove NDO pediatric patients with mild and moderate renal impairment from the list of missing information.
- The relevant Sections of the RMP were updated with the most recent data through 30 Jun 2023. Updates to Part 2 of the RMP included updating Module SI to include more recent data for the epidemiology of the indication and target population; Module SII to include information pertaining to nitrosamines from the nonclinical (in vitro and in vivo) studies; Module SIII to include updates in clinical trial exposure from Study 178-MA-2295 and exposure from the clinical trials being carried out in the pediatric population; Module SV to update the post-authorization exposure as per the DLP of 30 Jun 2023.
- Module SIV, Part III and Annex 2: Milestones for pharmacovigilance plans including the implementation of an approved PIP were updated to report the information applicable at the DLP of 30 Jun 2023.
- Annex 4: specific events follow-up forms were updated.

Other RMP versions under evaluation:

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

Details of the currently approved RMP:

Version number:	8.0
Approved with procedure:	EMEA/H/C/002388/II/0033
Date of approval (opinion date)	29 Oct 2020

QPPV approval/oversight:

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

List of Abbreviations

Abbreviation	Definition
ACE	Angiotensin-Converting Enzyme Inhibitor
AE	Adverse Event
APD	Action Potential Duration
APTC	Antiplatelet Trialists' Collaboration
AR	Adrenal Receptor (adrenoceptor)
ARB	Angiotensin Receptor Blocker
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the plasma concentration-time Curve
BOO	Bladder Outlet Obstruction
BPH	Benign Prostatic Hyperplasia
bpm	Beats Per Minute
CG	Cockcroft Gault
CHD	Coronary Heart Disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIC	Clean Intermittent Catheterization
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
C_{max}	Maximum (peak) Serum Concentration
CPRD	Clinical Practice Research Datalink
CSR	Clinical Study Report
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
EAU	European Association of Urology
ECG	Electrocardiogram
EEA	European Economic Area
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
Epi-LUTS	Epidemiology of Lower Urinary Tract Symptoms
ER	Extended Release
EU	European Union
EUROCAT	Epidemiological information on Congenital Anomalies in Europe

FDA	Food and Drug Administration
FDC	Fixed Dose Combination
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Pharmacovigilance Practices
hERG	human Ether-a-go-go-Related Gene
HCM	Hypertrophic Cardiomyopathy
HF	Heart Failure
HIRD	Healthcare Integrated Research Database
ICCS	International Children's Continence Society
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IKs	Outward Currents in Heart Muscle Cells
In	Rapidly Activating Sodium Current
INN	International Nonproprietary Name
IR	Immediate Release
IV	Intravenous
JNC7	Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure seventh report
KPNC	Kaiser Permanente of Northern California
LQTS	Long QT Interval Syndrome
LUTS	Lower Urinary Tract Symptoms
LUTS/BOO	Lower Urinary Tract Symptoms/Bladder Outlet Obstruction
MA	Marketing Authorization
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MI	Myocardial Infarction
MRHD	Maximum Recommended Human Dose
NA	Not Applicable
NBDPN	National Birth Defects Prevention Network
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
PDCO	Pediatric Committee
QTcF	QT interval corrected for heart rate using Fridericia method
PED50	Pediatric Equivalent Dose to mirabegron 50 mg
PIP	Pediatric Investigation Plan
PL	Package Leaflet

p.o.	per os (orally, i.e., by mouth)
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PVR	Post-void Residual
QPPV	Qualified Person for Pharmacovigilance
QT	interval from start of Q to end of T waves on electrocardiogram
QTcI	QT Interval Corrected for Heart Rate Using Individual-Specific Correction Formula
RAS	Randomized Analysis Set
RMP	Risk Management Plan
SAF	Safety Analysis Set
SB	Spina Bifida
SBP	Systolic Blood Pressure
SCD	Sudden Cardiac Death
SET	Single Entity Tablets
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
TEAE	Treatment Emergent Adverse Event
TME	Targeted Medical Event
UDS	Urodynamic Studies
UI	Urinary Incontinence
UK	United Kingdom
US	United States
UTI	Urinary Tract Infection
WPW	Wolff-Parkinson-White syndrome

Table of Contents

1 PRODUCT(S) OVERVIEW

Data-lock point for this Module	30 Jun 2023
Version when Module last updated	9.2

Table Part I.1 Product Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Mirabegron
Pharmacotherapeutic group(s) (ATC Code)	Urologicals, drugs for urinary frequency and incontinence Beta 3-adrenoceptor (AR) agonist ATC code: G04BD12
Marketing Authorization Holder	Astellas Pharma Europe B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Betmiga™ 25mg/50mg prolonged-release tablets (main brand name tablets) Betmiga 8 mg/mL prolonged-release granules for oral suspension (main brand name oral suspension)
Marketing authorization procedure	Centralized 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 refer to the CTD Module 1.3.1

Indication(s) in the EEA	Current (if applicable): **Prolonged-release tablets:** *Overactive bladder in adults* Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.
	Proposed (if applicable): **Prolonged-release tablets:** *Neurogenic detrusor overactivity in the pediatric population* Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 3 to less than 18 years. **Prolonged-release granules for oral suspension:** Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 3 to less than 18 years.
Dosage in the EEA	Current (if applicable): **Prolonged-release tablets:** *Overactive bladder in adults* The recommended dose is 50 mg once daily.
	Proposed (if applicable): **Prolonged-release tablets:** *Neurogenic detrusor overactivity in the pediatric population* Pediatric patients 3 to less than 18 years of age with NDO may be administered Betmiga prolonged-release tablets or Betmiga prolonged-release granules for oral suspension based on the body weight of the patient. The prolonged-release tablets may be administered to patients weighing 35 kg or more; the prolonged-release granules for oral suspension are recommended for patients below 35 kg. The recommended starting dose of Betmiga prolonged-release tablets is 25 mg once daily with food. If needed, the dose may be increased to a maximum dose of 50 mg once daily with food after 4 to 8 weeks. During long-term therapy, patients should be periodically evaluated for treatment continuation and for potential dose adjustment, at least annually or more frequently if indicated. **Prolonged-release granules for oral suspension:** *Neurogenic detrusor overactivity in the pediatric population (aged 3 to less than 18 years)* Pediatric patients 3 to less than 18 years of age with NDO may be administered Betmiga prolonged-release granules for oral suspension or Betmiga prolonged-release tablets based on the body weight of the patient. The recommended dose of Betmiga prolonged-release granules for oral suspension is determined based on patient weight and should be administered once daily with food. Treatment should be initiated at the recommended starting dose. Thereafter, the dose may be

<table>
<tr><td></td><td>increased to the lowest effective dose. The maximum dose should not be exceeded. Patients who reach 35 kg or more while on treatment may be switched from oral suspension to tablet formulation if they can swallow tablets. During long-term therapy, patients should be periodically evaluated for treatment continuation and for potential dose adjustment, at least annually or more frequently if indicated. The following table provides the doses for oral suspension by body weight range.

Daily oral suspension dosing recommendations for pediatric NDO patients aged 3 to less than 18 years according to patient body weight
<table>
<tr><th>Body weight range (kg)</th><th>Starting dose (mL)</th><th>Maximum dose (mL)</th></tr>
<tr><td>11 to < 22</td><td>3</td><td>6</td></tr>
<tr><td>22 to < 35</td><td>4</td><td>8</td></tr>
<tr><td>≥ 35</td><td>6</td><td>10</td></tr>
</table>
NDO: Neurogenic detrusor overactivity

The granules should be reconstituted with 100 mL water prior to administration. If a measuring cup is provided, it should be used to measure the water volume to use for reconstitution. Instructions on reconstitution of the medicinal product before administration are provided in the package leaflet. After reconstitution, the oral suspension is pale brownish yellow suspension.

The oral syringe and adaptor provided with Betmiga prolonged-release granules for oral suspension should be used to measure and administer the correct dose.</td></tr>
<tr><td rowspan="2">Pharmaceutical form(s) and strengths</td><td>Current (if applicable):
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</td></tr>
<tr><td>Proposed (if applicable):
Prolonged-release granules for oral suspension 8 mg/mL:
Yellowish white granules</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>No</td></tr>
</table>

ATC: Anatomical Therapeutic Chemical; AR: adrenoceptor; CTD: Common Technical Document; EEA: European Economic Area; EU: European Union; INN: International Nonproprietary Name; NDO: Neurogenic Detrusor Overactivity; OAB: Overactive Bladder; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics

2 SAFETY SPECIFICATION

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

Data-lock point for this Module	30 Jun 2023
Version when Module last updated	9.2

Indication(s)

Indication for overactive bladder

Adult population

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

Indication for neurogenic detrusor overactivity

Pediatric population

Mirabegron has been developed for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 3 to less than 18 years.

SI.1 Epidemiology of overactive bladder

Incidence of OAB

Adult population

Overactive bladder (OAB) is a subset of lower urinary tract symptoms (LUTS) 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 International Continence Society to standardize the terminology and definitions for LUTS, including OAB, investigators have used 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].

In a cohort study in the United Kingdom (UK) including a random sample of women ≥ 40 years followed for 1 year (n = 5816) the incidence rate of OAB was 88 per 1000 women per year [Dallosso et al, 2004]. Another UK study using data from the General Practice Research Database identified 68 910 men and women (mean age 46.8) with one or more OAB related symptoms. The incidence rate was estimated to be much lower, i.e., 2.8 per 1000 persons per year, which the authors attributed to underreporting by patients or healthcare practitioners [Odeyemi et al, 2006]. In a 16-year follow-up (1991 to 2007) of 1081 Swedish women (≥ 20 years) randomly selected from the general population, changes in the occurrence of urinary incontinence (UI), OAB, and other LUTS were assessed over time. In this study, a cumulative incidence of 20% was reported for OAB [Wennberg et al, 2009].

Potential biases in the reported frequency of OAB include underreporting of symptoms in some populations [Coyne et al, 2009a; Coyne et al, 2009b; Milsom et al, 2001], and differences across studies in definitions of OAB. Sampling may also account for some differences [Irwin et al, 2006].

Prevalence of OAB

OAB may occur in both men and women and have a substantial 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 on quality of life with various results [Eapen and Radomski, 2016]. LUTS and OAB are commonly observed in the adult population, and the prevalence of OAB increases with age with approximately 30% to 40% of the population over 75 years being affected [Warren et al, 2016]. By the year 2020, 25.5 million individuals were projected to be affected by OAB in 5 European countries (Germany, Italy, Spain, Sweden, and the United Kingdom) [Reeves et al, 2006].

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 United States (US), the UK, and Sweden. Overall, 72.3% of men and 76.3% of women reported at least one LUTS occurring at least “sometimes” [Eapen and Radomski, 2016; Coyne et al, 2009a; Coyne et al, 2009b]. The prevalence of OAB depended on how OAB was defined. When OAB was defined by patients “sometimes” having symptoms, the overall prevalence was 35.6%. When OAB was defined by patients “often” having symptoms, the overall prevalence decreased to 24.7% [Eapen and Radomski, 2016]. A population-based cross-sectional study was conducted to provide prevalence estimates of LUTS and OAB in Poland. The study included 6005 participants aged ≥ 40 years. Overall, the prevalence of LUTS was 69.8%; 66.2% in men and 72.6% in women. The overall prevalence of OAB was estimated at 33.9%. The authors reported a lower prevalence of OAB in men (26.8%) than in women (39.5%), and OAB increased with age [Przydacz et al, 2020].

In Europe, OAB prevalence has been estimated in population-based cross-sectional studies [Irwin et al, 2006; Milsom et al, 2001]. Milsom et al, included 16 776 randomly selected men and women ≥40 years old from France, Germany, Italy, Spain, Sweden, and the UK and estimated the prevalence of OAB at 16.6% (15.6% in men and 17.4% in women) [Milsom et al, 2001]. In the EPIC Study[1], including 19 165 men and women aged ≥ 18 years from Canada, Germany, Italy, Sweden, and the United Kingdom, the prevalence of OAB was estimated at 11.8% (10.8% in men and 12.8% in women) [Irwin et al, 2006]. A more recent extension of the EPIC Study conducted among subjects in the Czech Republic, Russia, and Turkey found an overall OAB prevalence of 18% in men and 28% in women, with those aged 60+ years having a notably higher prevalence [Kogan et al, 2014].

[1] Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries

One Finnish Study (n = 3517) in men and women aged 18-79 years reported prevalence of OAB at 8% overall (6.5% in men; 9.3% in women) [Tikkinen et al, 2007].

As with incidence rates, prevalence estimates may also be biased by patients' underreporting of symptoms and the use of non-standard definitions of OAB in different studies [Irwin et al, 2006].

Demographics of the OAB population and risk factors for OAB

The prevalence of OAB increases with age. In a population-based survey conducted in France, Germany, Italy, Spain, Sweden, and the United Kingdom, the prevalence of OAB symptoms was estimated among men and women aged ≥ 40 years [Milsom et al, 2001]. In this study, prevalence in both men and women generally increased with age (Table 1). [Milsom et al, 2001]. Similar results were reported in a recent Polish study where the prevalence of OAB was lower in men than women and increased with age [Przydacz et al, 2020].

Table 1 Prevalence of overactive bladder by age and gender in Europe

Age (years)	Men (%)	Women (%)
40-44	3.4	8.7
45-49	6.0	10.6
50-54	9.8	11.9
55-59	13.2	16.9
60-64	18.9	16.9
65-69	23.7	17.5
70-74	22.3	22.1
≥ 75	41.9	31.3

Source: [Milsom et al, 2001]

Previously, the difference in overall prevalence between men and women has been reported to be small (less than 2%) [Irwin et al, 2006; Stewart et al, 2003; Milsom et al, 2001]. More recently, studies in Europe and the US have reported symptoms of OAB to occur with a 4% to 16% greater prevalence in women than in men [Przydacz et al, 2020; Coyne et al, 2011; Coyne et al, 2009a; Coyne et al, 2009b]. Overall, 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 [Coyne et al, 2011; Stewart et al, 2003]. The overall prevalence of OAB increased from 17% to 26% in a cohort of Swedish women during a16-year observational period, between 1991 and 2007 [Wennberg et al, 2009]. In women, OAB prevalence with and without urge incontinence has been reported to be similar at 9.3% and 7.6%, respectively. In men, the prevalence of OAB without urge incontinence has been reported to be higher than that of OAB with urge incontinence (13.4% and 2.6%, respectively) [Stewart et al, 2003]. In a US study including 10 000 men and women aged 18-70 years, the prevalence of OAB was higher in African American (20.2%) and Hispanic (18.1%) men compared to white (14.6%) men, while African American women (32.6%) had a slightly higher prevalence than Hispanic (29.0%) and white (29.4%) women [Coyne et al, 2013a; Coyne et al, 2013b].

Risk factors for OAB

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 [Wen et al, 2014; Jo et al, 2012; Teleman et al, 2004]. Pregnancy and menopause may also increase the risk of developing OAB symptoms in women [Lugo Salcedo et al, 2013; Brown, 2002]. Metabolic syndrome and its related factors have also been associated with higher prevalence rates of OAB [Heo et al, 2023]. In a meta-analysis including data from over 28 studies, age and body mass index were associated with increased risks for OAB, whereas employment status was associated with a decreased risk of OAB [Zhu et al, 2019].

Main existing treatment options

The treatment options are aimed at reducing symptoms of OAB and include conservative management (e.g., simple clinical interventions and containment treatment), lifestyle interventions (e.g., caffeine reduction, physical exercise, fluid intake modification, and weight reduction), behavioral and physical therapies (e.g., prompted voiding, bladder training, and pelvic floor muscle training), pharmacological treatment and in more severe cases surgical management [EAU guidelines on urinary incontinence, 2020; Nambiar et al, 2018]. The Fourth International Consultation on Incontinence and the European Association of Urology classify the management of UI into initial treatment and specialized therapy. Initial management strategies for OAB should be offered to symptomatic patients who are bothered by the condition [EAU guidelines on urinary incontinence, 2020; Gulur and Drake, 2010]. Behavioral and physical therapy have been shown to be effective in the treatment of OAB, however, long-term benefits may be short-lived outside the clinical trial setting due to non-compliance [EAU guidelines on urinary incontinence, 2020; Nambiar et al, 2018].

Pharmacotherapy for OAB consists mainly of antimuscarinics including darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine and trospium [EAU guidelines on urinary incontinence, 2020; Nambiar & Lucas, 2014]. Several systematic reviews of individual antimuscarinic drugs versus placebo with cure of UI as an outcome measure showed superiority of antimuscarinics compared to placebo, although the absolute effect sizes were sometimes small [Nambiar et al, 2018]. In controlled clinical studies, UI is reduced by between 30% and 80% and urgency episodes are reduced by 20% to 55% [Novara et al, 2008].

A study that 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 but that persistence with antimuscarinic drugs was low in the study cohort [Margulis et al, 2018].

Botulinum toxin type A is approved for the treatment of OAB in some European countries and the UK [Nambiar and Lucas, 2014]. The first-in-class β_3-adrenoceptor agonist mirabegron is indicated in the European Union (EU), US, Japan, and several other countries for the management of OAB syndrome [Deeks, 2018].

The European Association of Urology (EAU) guidelines recommend the use of antimuscarinic drugs for adults with urgency UI who failed conservative treatment. Whenever possible, extended-release formulations of antimuscarinic drugs should be considered for these patients. If an antimuscarinic treatment proves ineffective, dose escalation or offering an alternative antimuscarinic formulation, or mirabegron, or a combination should be considered [EAU guidelines on urinary incontinence, 2020].

According to the EAU guidelines, surgical treatment options should be considered for women with uncomplicated and complicated stress UI, patients with genitourinary prolapse, men with stress UI and patients with refractory detrusor overactivity and low compliance bladders [EAU guidelines on urinary incontinence, 2020].

Natural history of OAB in the untreated population, including mortality and morbidity

OAB is generally not associated with mortality [Bhosle et al, 2005]. A systematic review and meta-analysis investigating the impact of nocturia on mortality included 11 studies (19 590 men and 14 241 women) and suggested that the risk of mortality may be higher in individuals with nocturia. However, in this study, the estimates did not differ substantially by gender, age group, follow up or nocturia case definition, and the association between nocturia and mortality likely reflected the underlying chronic illness as a cause of nocturia [Pesonen et al, 2020].

OAB has an impact on health-related quality of life, particularly emotional symptoms, sexual health, and overall well-being [Warren et al, 2016; Rogers et al, 2009]. 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 Canada, Germany, Italy, Sweden, 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 experience 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 tend to exhibit relatively poor health, impaired quality of life, social isolation, and depression [Holroyd-Leduc et al, 2004].

Important comorbidities

Commonly observed comorbidities associated with OAB include hypertension, diabetes mellitus, depression, dementia, dyslipidemia, stroke, and cardiovascular diseases [Arana et al, 2018; Durden et al, 2018; Hallas et al, 2018; Lua et al, 2017].

A systematic review investigating comorbidities of urgency UI (a symptom of OAB) reported that falls in elderly individuals, depression, urinary tract infections, increased body mass index, diabetes and death were associated with urinary UI [Coyne et al, 2013a; Coyne et al, 2013b]. In a follow-up cohort involving 12 570 females ≥ 40 years, bowel urgency, osteoporosis, imbalance, ankle swelling and cystitis, were associated with OAB [McGrother et al, 2006].

OAB and urinary incontinence have been associated with multiple comorbid conditions including cardiac failure, chronic renal failure, diabetes, chronic obstructive pulmonary disease, neurological disease including stroke and multiple sclerosis, general cognitive impairment, sleep disturbances, depression, and metabolic syndrome [EAU guidelines on urinary incontinence, 2020].

SI.2 Epidemiology of neurogenic detrusor overactivity

Incidence of NDO

Pediatric population

Neurogenic Detrusor Overactivity (NDO) is a condition characterized by involuntary detrusor contractions during the bladder filling phase that can result in UI. Any neurological condition that impacts the brain or spinal cord, resulting in the interruption of the signaling pathways that control bladder function, for example, spinal cord injury, multiple sclerosis, or spinal dysraphism, may lead to NDO. Myelomeningocele, a common and severe form of spina bifida (SB), is the most common neurological disorder responsible for bladder dysfunction (including NDO) in pediatric patients [Austin et al, 2021].

Data on the epidemiology of NDO in the pediatric general population are scarce. One multi-center national study of 47 Urodynamic Units across Spain, representing approximately 35% of the Spanish population, estimated the NDO incidence in children at 2.3 per 100 000 inhabitants per year [Prieto et al, 2012].

Prevalence of NDO

The occurrence of conditions underlying NDO may be considered as a proxy of the NDO prevalence in the pediatric population.

The most common neurological disorder responsible for bladder dysfunction in pediatric patients is myelomeningocele, with traumatic and neoplastic spinal cord lesions being less frequent [Austin et al, 2021]. Myelomeningocele is the most common subtype of SB. In 2 large registry-based US studies involving 1046 and 2172 SB cases, 85.6% and 81.2% of cases were classified as myelomeningocele [Sawin et al 2015; Agopian et al, 2012].

Prevalence of Spina bifida

In a systematic review and meta-analysis including 123 studies, the prevalence of SB per 10 000 live births was reported to range between 3.8 in Australia and 8.1 in Asia [Atta et al, 2016].

Based on National Birth Defects Prevention Network (NBDPN) data (2010–2014) from 14 US state-conducted active case-finding programs, the national prevalence of SB in the US was estimated at 3.6 per 10 000 live births [Mai et al, 2019].

EUROCAT is a network of population-based congenital anomaly registries providing standardized epidemiologic information on congenital anomalies in Europe [EUROCAT, 2020]. According to EUROCAT, the estimated mean (95% confidence interval) prevalence

of SB in Europe overall (1980 - 2018) was 2.3 (2.2 - 2.3) cases per 10 000 live births [EUROCAT, 2020].

Two small studies of pediatric myelomeningocele patients reported concurrent diagnosis of NDO in 34% to 39% of patients [Thorup et al, 2011; Ulsenheimer et al, 2004].

Based on the estimated prevalence of SB in Europe, the proportion of patients with myelomeningocele and the proportion of pediatric patients with NDO, we can estimate the prevalence of children with myelomeningocele and NDO to range between 0.6 and 0.8 per 10 000 live births in Europe (as calculated below).

Prevalence = 2.3 per 10 000 live births x (0.81 to 0.86) x (0.34 to 0.39) = 0.6 to 0.8 per 10 000 live births.

Prevalence of Cerebral palsy

From 2 US nationally representative surveys, the estimated prevalence of cerebral palsy was 26 (95% Confidence interval [CI]: 21 – 32) per 10 000 children from the 2011 - 2012 National Survey of Children's Health, and 29 (95% CI: 23 – 37) per 10 000 children from the 2011-2013 National Health Interview Survey [Maenner et al, 2016].

The surveillance of cerebral palsy in a European network of 20 population-based registries reported that a prevalence of cerebral palsy of about 19 per 10 000 in 1980 and 18 per 10 000 live births in 2003 [Sellier et al, 2016].

In a systematic review of LUTS and urodynamic findings in cerebral palsy patients, the prevalence of NDO in pediatric population with cerebral palsy ranged between 17% and 78% [Samijn et al, 2017].

Based on the estimated prevalence of cerebral palsy in Europe and the proportion of pediatric patients with NDO, it is possible to estimate the prevalence of children with cerebral palsy and NDO to range between 3.1 and 14.0 per 10 000 live births in Europe (as calculated below).

Prevalence: 18 per 10 000 live births x (0.17 to 0.78) = 3.1 to 14.0 per 10 000 live births.

Demographics of the target population - age, gender, racial/ethnic origin, and risk factors for NDO

The demographics of conditions underlying NDO may be used to review the demographic variability in the NDO population.

In the US NBDPN study including 1046 SB cases, myelomeningocele tended to be slightly more prevalent among Hispanics (2.7 per 10 000 live births) as compared to non-Hispanic whites (2.2 per 10 000 live births) or non-Hispanic blacks (2.0 per 10 000 live births) [Agopian et al, 2012]. Another NBDPN US study has estimated the prevalence of spina bifida to be the highest in Hispanic and American Indian/Alaska natives (4.5 per 10 000 live births) and lowest in Asian/Pacific Islanders (1.6 per 10 000 live births) [Mai et al, 2019].

In a study that investigated gender differences in neural tube defects among 1467 patients in the US, the neural tube defects were more common among females than males, however,

similar prevalence was observed of myelomeningocele for females and males [Deak et al, 2008]. Among 1046 cases of SB in a US study, myelomeningocele was more prevalent among white females than white males (55.8% versus 44.2%), while the condition was more prevalent in Hispanic males than Hispanic females (57.5% versus 42.5%) and black males than black females (61.4% versus 38.6%) [Agopian et al, 2012].

In a Swedish study including 590 children with cerebral palsy, 58% were boys and 42% were girls [Chounti et al, 2013]. In a US study investigating trends in birth prevalence of cerebral palsy, the prevalence was similar for males and females (1.9 versus 1.7 per 1000 one-year survivors) [Van Naarden Braun et al, 2016]. In a population-based Danish study, investigating the prevalence of cerebral palsy among 17 580 live births, 27 were male (62.8%) and 16 were female (37.2%) [Frøslev-Friis et al, 2015].

Risk factors for NDO

Any neurological condition that impacts the brain or spinal cord, resulting in the interruption of the signaling pathways that control bladder function may lead to NDO, while the most common neurological disorder responsible for bladder dysfunction in pediatric patients is myelomeningocele [Austin et al, 2021]. Other congenital malformations or acquired diseases that may cause neurogenic bladder include total or partial sacral agenesis, which can be part of the caudal regression syndrome, traumatic or neoplastic spinal lesions, and anorectal or cloacal malformations [Stein et al, 2020].

Main existing treatment options

A qualitative literature review evaluated current treatment strategies for children with neurogenic bladder dysfunction. According to the review, the approaches vary across a spectrum, with a proactive strategy on one end of the spectrum and an expectant strategy at the other end. The proactive management strategy is characterized by early and frequent labs, imaging, and urodynamic (UDS) evaluation, with early initiation of clean intermittent catheterization (CIC) and proceeding with pharmacotherapy, or surgery if indicated. The expectant management strategy prioritizes surveillance labs and imaging prior to proceeding with invasive assessments and interventions such as UDS or pharmacotherapy. Both treatment strategies are utilized, and data have historically been inconclusive in demonstrating efficacy of one regimen over the other [Hobbs et al, 2021].

The goal of treatment of neurogenic bladder in children is to optimize bladder emptying, protect the urinary tract from complications and improve continence. Urodynamic tests are normally performed in a newborn, and based on the findings, CIC with or without pharmacotherapy is generally started early before the development of upper tract changes. Pharmacotherapy is based on treatment with anticholinergics that act against the muscarinic receptors on the detrusor muscle wall with the aim to decrease intravesical pressures and overactive contractions and indirectly increase functional bladder capacity. Approved antimuscarinics for the treatment of detrusor overactivity include oxybutynin, tolterodine, propiverine, trospium, solifenacin, darifenacin, and fesoterodine [Kroll, 2017]. Oxybutynin is the most frequently used antimuscarinic in children, however, its use is limited by

dose-dependent side effects (including dry mouth, facial flushing, blurred vision, and heat intolerance). Tolterodine, solifenacin, trospium chloride, and propiverine and their combinations have been used safely in children [Stein et al, 2020]. Treatments with Botulinum Toxin-A and alpha-blockers are under investigation for the treatment of neurogenic bladder [Kroll, 2017].

Mirabegron, a β3-adrenoreceptor agonist, is an alternative treatment option to antimuscarinics and has been found effective and safe for the treatment of NDO in pediatric patients 3 to <18 years [Baka-Ostrowska et al, 2021]. On 25 Mar 2021, the Food and Drug Administration (FDA) approved mirabegron for the treatment of NDO in children aged 3 years and older.

Overall, the EAU guideline panel advocates a proactive approach. In newborns with SB, CIC should be started as soon as possible after birth. In those with intrauterine closure of the defect, urodynamic studies should be performed before the patient leaves the hospital. In those with closure after birth, urodynamics should be done within the next 3 months. Anticholinergic medications are recommended when detrusor overactivity is confirmed through urodynamic testing. Close follow-up including ultrasound, bladder diary, urinalysis, and urodynamics are necessary within the first 6 years and after that the time intervals can be prolonged, depending on the individual risk and clinical course. In all other children with the suspicion of a neurogenic bladder due to various reasons such as tethered cord, inflammation, tumors, trauma, or other reasons as well as those with anorectal malformations, urodynamics, and preferably video-urodynamics, should be carried out as soon as there is suspicion of a neurogenic bladder, and conservative treatment should be started soon after confirmation of the diagnosis of neurogenic bladder [Stein et al, 2020].

Natural history of NDO in the untreated population, including mortality and morbidity

If left untreated, NDO may lead to decreased bladder compliance and deterioration of the upper urinary tract [Baka-Ostrowska et al, 2021]. NDO can lead to elevated bladder pressures and, if not adequately managed with standard treatment, may require augmentation cystoplasty to prevent renal damage [Austin et al, 2021]. A detrusor pressure of 40 cm H_2O has been proposed as a critical threshold above which patients may be at increased risk for upper urinary tract dysfunction potentially resulting in renal damage [Austin et al, 2021].

Comorbidities in patients with NDO

UI in children is associated with comorbidities such as constipation and/or fecal incontinence, psychiatric disorders, sleep disorders, developmental disorders, and urinary tract infections [Schultz-Lampel et al, 2011].

Module SII. Nonclinical part of the safety specification

Data-lock point for this Module	30 Jun 2023
Version when Module last updated	9.2

A comprehensive safety evaluation of mirabegron was performed including safety pharmacology, genotoxicity, carcinogenicity, local tolerance, single - (adult only) and repeat (adult and juvenile) 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
- Embryo-fetal 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, IKto, 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 animals 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. *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.	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.

Key safety findings (from non-clinical studies)	Relevance to human usage
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.
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.
Hepatic effects	
Distribution studies using radiolabeled mirabegron showed higher levels of radioactivity in the liver than in plasma in rodents and non-rodents. *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	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.

Key safety findings (from non-clinical studies)	Relevance to human usage
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 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. *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.	Non-clinical data suggest that mirabegron is unlikely to have significant CNS effects in humans at the recommended therapeutic dose.

Key safety findings (from non-clinical studies)	Relevance to human usage
Nitrosamines	
The in vitro bacterial reverse mutation assay demonstrated that the N-nitroso-mirabegron impurity had no discernible mutagenic potential. The absence of mutagenic potential for this same impurity was confirmed in the mouse lymphoma L5178Y cell assay. However, in the in vivo[2] MutaMouse gene mutation assay, repeat dose administration of N-nitroso-mirabegron resulted in a significant, dose-related increase in mutation frequency in the liver. There was no increase in mutation rate in either the stomach or bone marrow.	The in vitro non-clinical studies suggest that the N-nitroso-mirabegron impurity identified in the pediatric formulation was not mutagenic while the in vivo results indicate a mutagenic potential. Based on these results, it is concluded that a mutagenic potential for nitroso-mirabegron impurity cannot be ruled out. Risk of exposure to N-nitroso-mirabegron is mitigated by release specification limits such that the exposure to this nitrosamine impurity is below an acceptable intake level.

AUC: area under the plasma concentration-time curve; AR: adrenoceptor; C_{max}: maximum (or peak) serum concentration; CNS: central nervous system; CYP3A4: Cytochrome P450 3A4; 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; NOAEL: no-observed-adverse-effect level; p.o.: By mouth/ oral administration; QT: QT interval is defined from the beginning of the QRS complex to the end of the T wave; QTc: QT interval corrected for heart rate; QTcB: QT interval corrected for heart rate using Bazett's formula.

[2] The results of the in vivo MutaMouse gene mutation assay were received post DLP of this RMP and have been added as a late-breaking information, thereby bearing no impact on the DLP of this Module.

Module SIII. Clinical trial exposure

Data-lock point for this Module	30 Jun 2023
Version when Module last updated	9.2

SIII.1 Brief overview of development

SIII.1.1 Mirabegron monotherapy adult clinical development program

As of the data-lock point (DLP) of this Module, the mirabegron monotherapy clinical development program had consisted of 54 completed studies in healthy subjects, patients with OAB, patients with lower urinary tract symptoms/bladder outlet obstruction (LUTS/BOO) or patients with type 2 diabetes mellitus. There are a total of 35 phase 1 studies and 1 phase 4 study in healthy subjects, 14 phase 2 and phase 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, US, Canada, Japan, Australia/New Zealand, South Africa, China, India, Korea, and Taiwan.

Of the 54 completed studies in the mirabegron monotherapy clinical development program, 4 phase 1 studies, 1 phase 4 study in healthy subjects 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 54 completed studies. Additional information and analyses in this risk management plan (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 and phase 3 studies: This population consists of the 6-placebo-controlled, double-blind, 12-week phase 2 and phase 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 and phase 3 study 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 and phase 3 clinical trial populations (including open extension)

- Global phase 2 and phase 3: This population includes all patients who received at least 1 dose of mirabegron in a phase 2 and phase 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 and Phase 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 and phase 3	Global OAB 12-week phase 2 and phase 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 this Module, 1 postmarketing phase 1 study (178-CL-111) in healthy subjects in Japan, 1 postmarketing phase 4 study (178-MA-2294) in healthy subjects in China, 1 post marketing phase 3 study (178-CL-090), 1 postmarketing phase 3b study (178-EC-001) and 5 phase 4 studies (178-MA-1001, 178-MA-1005, 178-MA-1008, 178-MA-3016 and 178-MA-2295) have been conducted.

Table 4 Overview of Mirabegron Monotherapy Post-Marketing Studies

Study	Phase	Randomized	Treatment groups	Population	Treatment duration	Countries	Status
178-CL-111	1	N/A	Mirabegron as add-on to Tolterodine	Healthy volunteers	2 weeks	Japan	Completed
178-CL-090	3	X	Placebo, Mirabegron, Tolterodine	OAB	12 weeks	China, India, Korea, Taiwan	Completed
178-EC-001	3b	X	Mirabegron, Solifenacin succinate	OAB	12 weeks	Australia, Canada, Europe, Latin America, Middle East	Completed
178-MA-1001	4	X	Mirabegron, Tolterodine	OAB	14 weeks	Canada, USA	Completed
178-MA-1005	4	X	Mirabegron, Placebo	OAB	20 weeks	Canada, USA	Completed
178-MA-1008	4	X	Mirabegron, Placebo	BPH	20 weeks	North America and Europe	Completed
178-MA-3016	4	X	Mirabegron, Placebo	BPH	16 weeks	Japan, Korea	Completed
178-MA-2294	4	X	Mirabegron	OAB	Single dose	China	Completed
178-MA-2295	4	X	Mirabegron	OAB	12 weeks	China	Completed

BPH: Benign Prostatic Hyperplasia; N/A: Not Applicable, OAB: Overactive Bladder; USA: United States of America

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. As of the DLP of this Module 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 subjects 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 postmarketing 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 [ongoing 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 < 3 years]).

Until the DLP of this Module, 4 phase 1 studies have been completed: studies 178-CL-201 and 178-CL-208 in young healthy adult subjects 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 adult clinical development program

Overall, until the DLP of this Module, 1957 healthy subjects and 14 266 patients have been enrolled into the mirabegron monotherapy program, of which approximately 1619 healthy subjects and 8566 patients have received mirabegron.

In the mirabegron monotherapy clinical development program, patients and healthy subjects 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 2 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 healthy subjects 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; OAB: overactive bladder

† Includes subjects from completed studies until 30 Jun 2023.

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 Good Clinical Practice (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		**1619**
Mirabegron IR/OCAS single dose	< 25	29
	≥ 25 to < 50	59
	≥ 50 to < 100	199
	≥ 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, 178-CL-208 and 178-MA-2294*.

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

† Includes subjects from completed studies until 30 Jun 2023.

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

* 178-MA-2294 was a phase 4 study, but in healthy subjects.

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**.

OAB: overactive bladder

† Includes subjects from completed studies until 30 Jun 2023.

§ 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	753	459
	≥ 45 to < 65	206	131
	≥ 65 to < 75	34	28
	≥ 75	3	5
	Total	**996**	**623**
Mirabegron IR/OCAS single dose	< 45	348	147
	≥ 45 to < 65	58	41
	≥ 65 to < 75	10	4
	≥ 75	2	3
	Total	**418**	**195**
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, 178-CL-208, and 178-MA-2294*

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

† Includes subjects from completed studies until 30 Jun 2023.

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

* 178-MA-2294 was a phase 4 study, but in healthy subjects.

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
≥ 85	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**

OAB: overactive bladder

† Includes subjects from completed studies until 30 Jun 2023.

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	286
	Other	61
	Total	**1619**
Mirabegron IR/OCAS single dose	Caucasian	345
	Black	57
	Asian	185
	Other	26
	Total	**613**
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, 178-CL-208, and 178-MA-2294*.

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

† Includes subjects from completed studies until 30 Jun 2023.

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

* 178-MA-2294 was a phase 4 study, but in healthy subjects.

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 2023. 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 and phase 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 baseline creatinine clearance, mirabegron monotherapy Global Overactive Bladder 12-week phase 2 and phase 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.

† 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 baseline creatinine clearance and baseline hypertension status, mirabegron monotherapy Europe/North America Overactive Bladder 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; 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 baseline creatinine clearance and baseline hypertension status, 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.

Study 178-MA-2295 was a Phase 4, Open-label, Randomized, Prospective, Interventional Post-authorization Efficacy and Safety Study of Mirabegron 50 mg and 25 mg for the Treatment of Overactive Bladder in Chinese Subjects. The clinical study report (CSR) was completed in Aug 2022; however, the data are not yet integrated. Therefore, a summary of the exposure data are presented below:

- 231 subjects (92.8%) completed treatment (78/84 subjects [92.9%] in the mirabegron 25 mg group and 153/165 subjects (92.7%) in the mirabegron 50 mg group). One subject in the mirabegron 25 mg group discontinued from the study before receiving any treatment and was therefore excluded from the SAF.
- In the SAF, 64/83 subjects (77.1%) in the mirabegron 25 mg (total) group and 120/165 subjects (72.7%) in the mirabegron 50 mg (as randomized) group were female. The majority of subjects were Han (243/248 [98.0%] subjects). The median age (range) was 48 (18-75) years in the mirabegron 25 mg (total) group and 53 (18-83) years in the mirabegron 50 mg (as randomized) group.
- In the SAF, the median duration of exposure was 58 days in the mirabegron 25 mg (total) group and 85 days in the mirabegron 50 mg (as randomized) group.

- At week 4, 35/81 subjects (43.2%) from the mirabegron 25 mg (total) group, had their dose of 25 mg up-titrated to 50 mg. At week 8, 4/45 subjects (8.9%) in the mirabegron 25 mg (total) group had their dose increased.

SIII.2.2 Mirabegron and solifenacin combination therapy clinical development program

Overall, until the DLP of this Module, 166 healthy subjects 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 subjects 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 safety analysis set (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 15.

Table 15 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

Treatment group	Duration of exposure (days)	Persons	Person time (year)‡
	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††**
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††**
	≥ 1	159	NA

Treatment group	Duration of exposure (days)	Persons	Person time (year)‡
Mirabegron + Tolterodine	≥ 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 2023.

‡ 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.

††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 15 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 e-Diary 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 randomized analysis set (RAS) patients (including patients from site 10 153) 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 16 and for phase 2 through phase 4 clinical studies in Table 17.

Table 16 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 2023.

‡ 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 17 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[a]**	**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††**
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.

[a] 1 patient can be in multiple groups and is counted once

† Includes subjects from completed studies until 30 Jun 2023.

‡ 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 18 and for the phase 2 and 3 clinical studies in Table 19.

Table 18 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**

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 2023.

‡ 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 19 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**	**3246**	**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**	**1928**	**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 2023.

‡Person time (year) is the sum of exposure to study drug expressed in years for all patients within an age and gender 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 gender 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 20 and for phase 2 through phase 4 clinical studies in Table 21.

Table 20 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	Caucasian	46

Treatment group and formulation	Racial group	Person‡
Coadministration of SET multiple dose	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 2023.

‡ 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 21 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 2023.

‡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 15).

SIII.2.3 Mirabegron pediatric clinical development program

Overall, until the DLP of this Module, 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 80-130 mg (40-65 mL) suspension (Study 178-CL-203) or with multiple doses of 25 mg, titrated up to 50 mg, or with multiple mirabegron suspension doses dependent on body weight, ranging from 24-28 mg (3-6 mL), titrated up to 48-88 mg (6-11 mL) (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 healthy subjects 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 22 (phase 1) and Table 23 (phase 3) based upon exposure data from completed clinical trials.

Table 22 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 2023.

Table 23 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 2023.

The exposure by age group and gender for the mirabegron monotherapy program in the pediatric population is provided in Table 24 (phase 1) and Table 25 (phase 3).

Table 24 Exposure by age group and gender, 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 single 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 2023.

‡ 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 25 Exposure by age group and gender, 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 2023.

‡ 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 26 (phase 1) and Table 27 (phase 3).

Table 26 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 2023.

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

Table 27 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 2023.

‡ 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 28.

Table 28 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	26
178-CL-207	3	0

† Includes subjects randomized until 30 Jun 2023.

Module SIV. Populations not studied in clinical trials

Data-lock point for this Module	30 Jun 2023
Version when Module last updated	9.2

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 ≥ 10 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 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 and phase 3 OAB studies. The majority of patients exposed to mirabegron were enrolled in 10 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.

Severe renal impairment (Estimated glomerular filtration rate according to Larsson equation < 30 mL/min)

Reason for exclusion:

Patients with severe renal impairment (defined as estimated glomerular filtration rate [eGFR] < 30 mL/min according to Larsson calculation) 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 renal impairment which can be expected to lead to AEs not related to mirabegron.

Table 29 Comparison of key safety exclusion criteria for phase 2 and phase 3 studies

	Phase 2, 12-weeks		Phase 3, 12-weeks					Phase 3b, 12 weeks	Phase 3, 52-weeks	
Study number	**178-CL-044**	**178-CL-045**	**178-CL-046**	**178-CL-047**	**178-CL-074**	**178-CL-048**	**178-CL-090**	**178-EC-001**	**178-CL-049**	**178-CL-051**
Number of patients exposed to mirabegron	673	626	989	875	872	379	369	936	1632†	203
Age range	≥ 18 years	20-80 years	≥ 18 years	≥ 18 years	≥ 18 years	≥ 20 years	Legal minimum age requirement (country-specific) at the time of informed consent	≥ 18	≥ 18 years	≥ 20 years
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)	None	Clinically significant	Clinically significant, at risk for urinary retention	Clinically significant lower urinary tract obstructive disease (BPH)
PVR volume	> 200 mL	≥ 100 mL	None	None	None	≥ 100 mL	≥ 100 mL	> 200 mL	None	≥ 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	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	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

	Phase 2, 12-weeks		Phase 3, 12-weeks					Phase 3b, 12 weeks	Phase 3, 52-weeks	
Study number	**178-CL-044**	**178-CL-045**	**178-CL-046**	**178-CL-047**	**178-CL-074**	**178-CL-048**	**178-CL-090**	**178-EC-001**	**178-CL-049**	**178-CL-051**
Uncontrolled narrow angle glaucoma, urinary or gastric retention, colitis ulcerosa, toxic megacolon, myasthenia gravis	X‡	None	X‡	None	None	X‡	None	X‡	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	Beta-AR agonist or anticholinergic agent	Solifenacin, mirabegron, or any of the inactive ingredients	Tolterodine, other anti-cholinergics, beta-AR agonists or any inactive ingredients	Beta-receptor agonists

	Phase 2, 12-weeks		Phase 3, 12-weeks					Phase 3b, 12 weeks	Phase 3, 52-weeks	
Study number	**178-CL-044**	**178-CL-045**	**178-CL-046**	**178-CL-047**	**178-CL-074**	**178-CL-048**	**178-CL-090**	**178-EC-001**	**178-CL-049**	**178-CL-051**
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	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	None	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
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 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
Heart rate	<45 or >100 beats per minute (bpm)	<50 or >110 bpm	None	None	None	<50 or ≥110 bpm	<50 or ≥110 bpm	None	None	<50 or ≥110 bpm

	Phase 2, 12-weeks		Phase 3, 12-weeks					Phase 3b, 12 weeks	Phase 3, 52-weeks	
Study number	**178-CL-044**	**178-CL-045**	**178-CL-046**	**178-CL-047**	**178-CL-074**	**178-CL-048**	**178-CL-090**	**178-EC-001**	**178-CL-049**	**178-CL-051**
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.	None	Abnormal ECG or has a known history of QT prolongation or currently taking medication known to prolong the QT interval.	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.
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	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	Concurrent malignancy or history of cancer (except noninvasive skin cancer) within the last 5 years prior to screening.	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

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 30 Comparison of other exclusion criteria for phase 2 and phase 3 studies

	Phase 2, 12-weeks		Phase 3, 12-weeks					Phase 3b, 12-weeks	Phase 3, 52-weeks	
Study number	**178-CL-044**	**178-CL-045**	**178-CL-046**	**178-CL-047**	**178-CL-074**	**178-CL-048**	**178-CL-090**	**178-EC-001**	**178-CL-049**	**178-CL-051**
Exclusion criteria theme to ensure appropriate target disease										
Patients without experience of urge incontinence before informed consent	None	X	None	None	None	X	None	None	None	X
Significant stress incontinence or mixed stress/urge incontinence where stress is the predominant factor	X	None	X	X	X	None	X	X	X	None
Patients clearly diagnosed as having stress incontinence (only the symptoms of stress incontinence)	None	X	None	None	None	X	X	None	None	X
Patients with transient symptoms suspected of OAB (drug-induced, psychogenic, etc.)	None	X	None	None	None	X	X	None	None	None
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	X	X	X	X	X	X	X	X	X	None

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)										
Patients given radiotherapy/ thermotherapy/surgical therapy affecting urethral function	None	X	None	None	None	X	X	X	None	X
Patient was using medications intended to treat OAB or prohibited medications listed in the protocol	X	X	X	X	X	X	None	X	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 limited in the ability 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% confidence interval, 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 9831 patients have received at least 1 dose of mirabegron monotherapy, this confidence interval for detecting 0 events would be 3/9831 = 0.000305. Therefore, with over 9000 patients, there is a 95% probability that at least 1 event could be detected if the event frequency is 0.000305, or 3.05 events in 10 000 patients (not considering 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 postmarketing phase to identify potential delayed adverse reactions (see 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 > 6600 for 12 weeks and > 1100 for 12 months	This allows detection of short-term adverse events with an approximate frequency of 1:2200 and longer-term approximate frequency of 1:366 with 95% 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, > 1100 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, > 1100 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 Pediatric Committee (PDCO) agreed pediatric program with Pediatric Investigation Plans (PIP) for NDO EMEA-000597-PIP-03-15-M05 P/0187/2022 dated 25 May 2022 and OAB EMEA-000597-PIP-02-10-M09 Decision P/0550/2022 dated 04 Jan 2023. A clinical development program for use of mirabegron in pediatric patients with NDO and OAB is currently ongoing (project code ED178). The completed pivotal pediatric study (178-CL-206A) conducted as part of the agreed PIP, showed that mirabegron was efficacious, safe, and well tolerated by all 86 NDO patients from 3 to less than 18 years of age involved. The safety and efficacy information of the mirabegron prolonged-release tablets and prolonged-release granules for oral suspension has been updated for the pediatric population NDO indication in the Summary of Product Characteristics (SmPC). The safety and efficacy of mirabegron in children below 3 years of age have not yet been established, as per updated EU SmPC. Further, the package leaflet (PL) provides instruction not to give this medicine to children under 3 years of age for the treatment of NDO.

The clinical development program for use of mirabegron in pediatric patients with OAB is not completed. The SmPC Section 4.2, (Posology and Method of Administration) describes that the safety and efficacy of mirabegron in children below 18 years of age for the treatment with OAB 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 for the treatment with OAB because the safety and efficacy of mirabegron in this age group has not been established.

The planned pediatric Study 178-CL-207 will evaluate safety and tolerability of mirabegron in children with NDO from 6 months to less than 3 years old, and the ongoing pediatric Study 178-CL-204 will evaluate safety and tolerability of mirabegron in children with OAB from 5 to less than 18 years old. Due to the limited number of children from 3 to 5 years-old included in the clinical trials, the safety in patients from 3 to less than 5 years-old is considered missing information.

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 area under the plasma concentration-time curve [AUC] 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 OAB clinical development program in adults (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. With regard to these 5 pregnancies in the combination therapy group of mirabegron 50 mg plus solifenacin 5 mg, 3 of the 5 pregnancies were terminated. With regard to the two remaining pregnancies in patients in the combination therapy group, both patients discontinued study drug and carried out normal pregnancies with normal labor and delivery. Within the NDO pediatric clinical development program for mirabegron, no cases of pregnancy have been reported. Pregnant and breastfeeding patients were excluded from the pediatric clinical development program. Females of childbearing potential needed to agree to try not to become pregnant and to use a highly effective method of birth control if sexually active.

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.

NDO pediatric patients with mild and moderate renal impairment

Within the NDO pediatric clinical development program for mirabegron, patients with mild or moderate renal impairment were included. In 178-CL-206A study, there have been only 3 patients with renal impairment (1 child and 2 adolescents, all from a single site), and in the single pharmacokinetic dose studies (Study 178-CL-202 and Study 178-CL-203), there have been only 1 child (Study 178-CL-202) and 1 adolescent (Study 178-CL-203) with renal impairment included. Patients with mild or moderate renal impairment were given the same dose as those without any renal impairment. Data are limited in NDO pediatric patients with mild and moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2). No additional scientific rationale to suspect a different safety profile for NDO pediatric patients with mild

and moderate renal impairment from those without any renal impairment with respect to mirabegron therapy is available. The SmPC reflects the appropriate dosage in pediatric NDO patients aged from 3 to less than 18 years of age with renal impairment weighing 35 kg or more, the recommended dose is no more than the starting dose (for further details see SmPC Section 4.2).

NDO pediatric patients without clean intermittent catheterization (CIC)

For enrollment of patients in the NDO pediatric studies, the patients had to be willing to perform regular CIC. This was for both safety and assessment purposes. CIC is imperative for treatment for conditions involving neurogenic lower urinary tract dysfunction in order to prevent urinary tract infections due to incomplete bladder emptying [Blok et al, 2022]. This consideration is consistently reflected also for Study 178-CL-207, which is being conducted for NDO pediatrics from 6 months to less than 3 years. In addition, the SmPC clarifies that patients with NDO who received mirabegron in clinical studies needed to have been performing CIC to be eligible for those studies (for further details see SmPC Section 5.1). Because the MAH did not enroll patients not using CIC, there is no safety data for children taking mirabegron while not performing CIC; therefore, this population would be considered missing information due to different safety profile and potentially differing clinical needs.

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 comorbidities 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 comorbidities 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 comorbidities for OAB patients in the mirabegron program and OAB and non-OAB patients from the HIRD database and EPIC Study are presented in Table 31. The mean patient age was higher in the mirabegron studies compared with the typical OAB population from the HIRD database and EPIC Study. The percentage of male patients in mirabegron studies was higher compared with the HIRD database and lower compared with the 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 comorbidities [Table 32]. 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 comorbidities.

Table 31 Cardiovascular risk factors in the mirabegron Overactive Bladder population compared with populations evaluated in other Overactive Bladder 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: HealthCore Integrated Database; n = number (of patients); NR: not reported.

Source : Andersson et al, 2010 ; Coyne et al, 2008.

Table 32 Concomitant medications during the double-blind period in mirabegron Overactive Bladder 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%)

ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blockers; OAB: Overactive Bladder.

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 ≥ 160 mmHg or DBP ≥ 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, 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 and phase 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, most patients (6247/8566, 72.9%) were White Table 11. Many Asian patients (1983/8566, 23.1%), a significant number of Black or African American patients (284/8566, 3.3%) 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 2023
Version when Module last updated	9.2

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. Mirabegron tablets and mirabegron for oral suspension were approved in the US on 25 Mar 2021 for the NDO indication in pediatric patients from 3 and older.

The worldwide estimated patient exposure from marketing experience is based on the calculation wherein the number of patients exposed to mirabegron is estimated from the volume of units as reported in IQVIA databases with an estimated daily regimen of 1 unit (tablet) for either strength of mirabegron. It is assumed that a patient remained on treatment during the entire reporting period and was 100% compliant. . The number of patients reported does not represent unique patients. This estimate is based on standard units sold during 01 Jan 2022 to 30 Jun 2023.

Calculation:

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

SV.1.2 Exposure

Table 33 and Table 34 show the cumulative and interval exposure respectively by region, gender, age group, and dose. It is estimated that the worldwide cumulative exposure until the DLP of 30 Jun 2023 is approximately 34 million patients since launch and the interval period (01 Jan 2022 to 30 Jun 2023), it is 7 912 503 patients.

Note: Values were calculated from estimated patient exposure and rounded to the nearest whole number. Of note, IQVIA data are updated quarterly, and historical data are refreshed considering new information. This may on rare occasions result in exposure cumulative estimates showing some relative variances to previous estimates.

Source: IQVIA MIDAS® sales volume data for mirabegron for the period Q1-2022 to Q2-2023, reflecting estimates of real-world activity Copyright IQVIA. All rights reserved. IQVIA Medical data for mirabegron for the period year 2023.

Table 33 Cumulative exposure table by region, gender, age group, and dose

		Gender		Age (years)				Dose	
	Region	***Male***	***Female***	***2 to ≤16***	***>16 to 65***	***>65***	***Unknown***	***25mg***	***50 mg***
Cumulative	**Overall**	**13 015 346**	**20 760 457**	**27 042**	**9 328 328**	**24 254 605**	**165 828**	**7 831 289**	**25 944 513**
	EU	3 123 169	6 712 457	7887	3 992 840	5 834 900	-	1 050 896	8 784 731
	Non-EU Total	**9 892 177**	**14 047 999**	**19 155**	**5 335 488**	**18 419 705**	**165 828**	**6 780 393**	**17 159 783**
	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Asia	1 919 188	1 905 657	402	503 997	3 312 228	8218	255 827	3 569 018
	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EU: European Union.

Note: Values were calculated from estimated patient exposure and rounded to the nearest whole number. Of note, IMS data are updated quarterly, and historical data are refreshed considering new information. This may on rare occasions result in exposure cumulative estimates showing some relative variances to previous estimates.

Source: IQVIA MIDAS® sales volume data for mirabegron for the period Q1-2022 to Q2-2023, reflecting estimates of real-world activity Copyright IQVIA. All rights reserved. IQVIA Medical data for mirabegron for the period year 2023.

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

		Gender		Age (years)				Dose	
	Region	***Male***	***Female***	***2 to ≤16***	***>16 to 65***	***>65***	***Unknown***	***25mg***	***50mg***
Interval	**Overall**	**3 135 609**	**4 776 893**	**7731**	**1 952 263**	**5 952 509**	**0**	**1 733 715**	**6 178 787**
	EU	837 409	1 734 707	1891	937 905	1 632 320	0	281 093	2 291 024
	Non-EU Total	**2 298 200**	**3 042 186**	**5841**	**1 014 357**	**4 320 189**	**0**	**1 452 623**	**3 887 764**
	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Asia	468 656	444 881	402	114 696	798 439	0	39 296	874 241
	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EU: European Union

Note: Values were calculated from estimated patient exposure and rounded to the nearest whole number. Of note, IQVIA data are updated quarterly, and historical data are refreshed considering new information. This may on rare occasions result in exposure cumulative estimates showing some relative variances to previous estimates

Post-marketing exposure by gender and age (cumulative)

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 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 one 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 number of tablets sold was divided by the number of assumed treatment days per month. This approach does not consider inventory levels of distributors or pharmacies.

To allocate the estimated number of patients treated globally with mirabegron, IQVIA Medical data were used as the source to derive the gender 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

	Cumulative (01 Jul 2011 to 30 Jun 2023)				Interval (01 Jan 2022 to 30 Jun 2023)			
Age group	Persons		Person-time (Years)		Persons		Person-time (Years)	
	M	F	M	F	M	F	M	F
Mirabegron	**13 015 346**	**20 760 457**	**6 415 100**	**10 229 825**	**3 135 609**	**4 776 893**	**1 546 328**	**2 355 728**
2 to ≤16	6492	20 550	3201	10 134	2788	4943	1375	2438
>16 to 65	2 262 535	7 065 794	1 115 084	3 482 765	544 705	1 407 558	268 622	694 138
>65	10 714 342	13 540 262	5 281 045	6 670 917	2 588 116	3 364 393	1 276 331	1 659 153
Unknown	31 977	133 851	15 770	66 009	0	0	0	0

F: female; M: male.

Source: IQVIA MIDAS® sales volume data for Mirabegron for the period Q1-2022 to Q2-2023, reflecting estimates of real-world activity Copyright IQVIA. All rights reserved. IQVIA Medical data for Mirabegron for the period year 2023.

Table 36 Post-authorization exposure by dose

	Cumulative (01 Jul 2011 to 30 Jun 2023)		Interval (01 Jan 2022 to 30 Jun 2023)	
Dose level	**Persons**	**Person-time (Years)**	**Persons**	**Person-time (Years)**
Overall	**33 775 802**	**16 644 925**	**7 912 503**	**3 902 056**
25 mg	7 831 289	3 857 543	1 733 715	854 983
50 mg	25 944 513	12 787 383	6 178 787	3 047 073

Note: Values were calculated from estimated patient exposure and rounded to the nearest whole number. Of note, IQVIA data are updated quarterly, and historical data are refreshed considering new information. This may on rare occasions result in exposure cumulative estimates showing some relative variances to previous estimates.

Source: IQVIA MIDAS® sales volume data for mirabegron for the period Q1-2022 to Q3-2023, reflecting estimates of real-world activity Copyright IQVIA. All rights reserved. IQVIA Medical data for mirabegron for the period year 2023.

Table 37 Post-authorization exposure by territory

	Cumulative (01 Jul 2011 to 30 Jun 2023)		Interval (01 Jan 2022 to 30 Jun 2023)	
Territory	**Persons**	**Person-time (Years)**	**Persons**	**Person-time (Years)**
Overall	**33 775 802**	**16 644 925**	**7 912 503**	**3 902 056**
EU	7 831 289	3 857 543	1 733 715	854 983
Non-EU	25 944 513	12 787 383	6 178 787	3 047 073

EU: European Union

Note: Values were calculated from estimated patient exposure and rounded to the nearest whole number. Of note, IQVIA data are updated quarterly, and historical data are refreshed considering new information. This may on rare occasions result in exposure cumulative estimates showing some relative variances to previous estimates.

Source: IQVIA MIDAS® sales volume data for mirabegron for the period Q1-2022 to Q2 -2023, reflecting estimates of real-world activity Copyright IQVIA. All rights reserved. IQVIA Medical data for mirabegron for the period year 2023.

Module SVI. Additional EU requirements for the safety specification

Data-lock point for this Module	30 Jun 2023
Version when Module last updated	9.2

Potential for misuse for illegal purposes

Based upon pharmacology, beta 3-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 1 dose of mirabegron in phase 2 and phase 3 studies, there were no reported AEs suggesting a risk of abuse liability. The postmarketing data are consistent with these findings and do not provide evidence for mirabegron being abused or misused for illegal purposes.

Module SVII. Identified and potential risks

Data-lock point for this Module	30 Jun 2023
Version when Module last updated	9.2

SVII.1 Identification of safety concerns in the initial risk management plan submission

Not applicable as this RMP is not an initial RMP submission.

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the risk management plan

Not applicable.

SVII.1.2 Risk considered important for inclusion in the list of safety concerns in the risk management plan

Safety Concerns for Inclusion in RMP	Risk-benefit Impact
Important identified risks	
None	N/A
Important potential risks	
QT prolongation	OAB and NDO indication 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. Mirabegron as shown in clinical trials, 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. 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.

Safety Concerns for Inclusion in RMP	Risk-benefit Impact
Fetal disorders after exposure during pregnancy	OAB and NDO indication 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	
Safety in patients from 3 to less than 5 years old	The safety and efficacy of mirabegron in patients between 3 and 5 years- old have not been established. Insufficient numbers of patients between the ages of 3 and 5 years were studied and thus no conclusions can be drawn about safety in this population. Due to the limited number of children from 3 to 5 years old included in the clinical trials, the safety in patients from 3 to less than 5 years old is considered missing information.
NDO pediatric patients without clean intermittent catheterization (CIC)	In the pediatric NDO studies, only patients willing to perform regular clean intermittent catheterization (CIC) were included. There is no safety data for NDO pediatric patients taking mirabegron while not performing CIC, therefore this would be considered missing information and mirabegron should therefore be used with caution in this patient population.

AUC: Area Under Dose Concentration Curve; CIC: Clean Intermittent Catheterization; ECG: Electrocardiogram; EMA: European Medicines Agency; NDO: Neurogenic Detrusor Overactivity; OAB: Overactive Bladder; PRAC: Pharmacovigilance Risk Assessment Committee; QT: Interval from start of Q to end of T waves on electrocardiogram; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

SVII.2 New safety concerns and reclassification with a submission of an updated risk management plan

In accordance with the Committee for Medicinal Products for Human Use (CHMP) day 180 list of outstanding issues received (Procedure No. EMEA/H/C/002388/X/0039) in which the MAH was asked to describe in detail the rationale to include patients with mild and moderate renal impairment as missing information as well as the pharmacovigilance activities that should be implemented to address this missing information, and considering the guidance provided in good pharmacovigilance practices (GVP) Module V Rev 2, the MAH proposed to remove "NDO pediatric patients with mild and moderate renal impairment" from the missing information list:

- The MAH has stated in Section SIV.3 that small numbers of patients with mild and moderate renal impairment were enrolled in the NDO pediatric clinical development program for mirabegron and thus no conclusions can be drawn regarding whether pediatric patients with normal renal function have a different safety profile than those with mild or moderate renal impairment. Those included received the same dose as those without renal impairment.
- There is however, no scientific rationale to suspect a different safety profile for NDO pediatric patients with mild and moderate renal impairment from those without any renal impairment with respect to mirabegron therapy. According to GVP Module V Rev 2 guidance regarding missing information, it "refers to gaps in knowledge about the safety of a medicinal product for certain anticipated utilization (e.g., long term use) or for use in particular patient populations, for which there is insufficient knowledge to determine whether the safety profile differs from that characterized so far. The absence of data itself (e.g., exclusion of a population from clinical studies) does not automatically constitute a safety concern". Therefore, after further analysis of the definition provided in the GVP Module V Rev 2, the MAH is of the position that the information regarding patients with mild and moderate renal impairment do not constitute the missing information because it does not fall into knowledge gap. Thus, NDO pediatric patients with mild and moderate renal impairment was removed from the list of 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 IKr (hERG), IKs (hKvLQT1/mink), Ito (hKv4.3/Kchip2.2), INa (hNav1.5) and ICa (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	OAB in adults 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. Therefore, the effects of mirabegron in these patients is unknown. NDO in pediatrics There have been no clinically relevant cases of QT prolongation from the completed NDO study in pediatric patients (178-CL-206A).
Characterization of the risk	<u>Long QT syndrome in adults</u> 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]. A study using data from the Kaiser Permanente of Northern California (KPNC) health care system including 1.7 million individuals found that 5.8% of cohort members had ECG readings indicating long QT syndrome; the majority were male (63.1%) or aged ≥65 years (58.3%). Commonly observed comorbidities in this cohort included hypertension (58.2%), cancer (45.5%), COPD (42.4%), hyperlipidemia (32.6%), obesity (23.2%), heart failure (18.9%), and acute coronary syndrome (13.4%) [Iribarren et al, 2014]. The prevalence of long QT syndrome among 7,764 young individuals aged 14-35 years who underwent ECG screening in the UK was 6.5% [Chandra et al, 2014]. There are no studies available from the literature reporting on the epidemiology of long QT syndrome among adults with OAB. <u>Long QT syndrome in children</u> The study using KPNC data mentioned above included 78,808 children aged 0-17 years, 2715 (3.4%) of whom had ECG readings indicative of long QT syndrome [Iribarren et al, 2014]. In an Italian hospital-based ECG screening study among 44,596 infants 15 to 25 days old, the prevalence of congenital long QT syndrome was estimated at 1:2534 (95% CI, 1:4350 to 1:1583) or 0.04% (95% CI, 0.02%-0.06%) [Schwartz et al, 2009]. In a systematic review and meta-analysis of the literature of hypertrophic cardiomyopathy (HCM), long QT syndrome (LQTS), and Wolff-Parkinson-White syndrome (WPW) that potentially cause sudden cardiac death (SCD), 30 articles were selected meeting eligibility criteria. ECG-based prevalence rates of the 3 studies reporting on LQTS in children and young adults ranged from 1 to 12 per 100,000, with a summary phenotypic prevalence rate of 7 per

Potential risk	**QT prolongation**
	100,000 and substantial heterogeneity [Rodday et al, 2021]. There are no studies available from the literature reporting on the epidemiology of long QT syndrome among children with NDO.
Risk groups or risk factors	OAB in adults 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. NDO in pediatrics This would also apply to children taking the maximum pediatric dose, which is the pediatric equivalent of the adult 50 mg dose. For children above 35 kg, the formulation would be the PED50 tablet. Children who weigh more than 11 kg but less than 35 kg or who are more than 35 kg but cannot take tablet would take mirabegron oral suspension (8 mg/mL). For children taking suspension, the therapeutic dose (equivalent to adult 50 mg dose) would be 6 mL (for children 11 to < 22 kg), 8 mL (for children 22 to <35 kg), and 11 mL (for children > 35 kg).
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 healthy subjects. 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 healthy subjects. 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 healthy subjects. 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 healthy subjects, 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 and phase 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	OAB in adults 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. NDO in pediatrics

Potential risk	QT prolongation
	The expected effects and safety concerns in the NDO pediatric population taking the therapeutic dose are not expected to differ from those of the adult population.

AE: adverse event; APD: action potential duration; APTC: antiplatelet trialists' collaboration; AUC: area under the plasma concentration-time curve; CI: confidence interval; Cmax: maximum (peak) serum concentration; COPD: Chronic obstructive pulmonary disease; CTD: common technical document; ECG: electrocardiogram; HCM: hypertrophic cardiomyopathy; hERG: human ether-a-go-go-related gene; ICH: International council for harmonization of technical requirements for pharmaceuticals for human use; ICa: ionized calcium; IKr: delayed rectifier potassium current; IKs: outward currents in heart muscle cells; INa: rapidly activating sodium current; Ito: transient outward potassium current; KPNC: Kaiser Permanente of Northern California; LQTS: long QT interval syndrome; NDO: Neurogenic detrusor overactivity; OAB: overactive bladder; PED50: pediatric equivalent dose to mirabegron 50 mg; 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; SCD: Sudden cardiac death; SmPC: Summary of Product Characteristics; SMQ: Standardized MedDRA Query;; TdP: torsade de pointes; TEAE: treatment-emergent adverse event US: United States; WPW: Wolff-Parkinson-White syndrome

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	In a systematic analysis of the global epidemiology of congenital heart disease in the year 2017 for 195 countries from the Global Burden of Disease Study, the overall prevalence (95% uncertainty interval) of congenital heart disease was estimated at 1788 (1587 to 1999) per 100,000 babies at birth, 1233 (1092 to 1393) per 100,000 children younger than 1 year, and 157 (143 to 172) per 100,000 individuals (all ages); the age-standardized prevalence rate was estimated at 171 (156 to 187) per 100,000. The same study estimated 261,247 (216,567 to 308,159) CHD related deaths to have occurred

Potential risk	Fetal disorders after exposure during pregnancy
	globally in 2017, with a mortality rate of 131 (107 to 155) per 100,000 children younger than 1 year, and an age-standardized mortality rate of 3.9 (3.2 to 4.6) per 100,000 individuals [Zimmerman et al, 2020]. A literature-based meta-analysis including 42 studies and 2.6 million children estimated prevalence of unrepaired congenital heart disease at 381 (308 to 462) per 100,000 overall, with the prevalence being lower in males (338 [279 to 397]) than in females (408 [344 to 473] per 100,000 [Liu et al, 2020]. There are no studies available from the literature reporting on the occurrence of congenital heart disease in infants, e.g., as a proportion per live births, of women with OAB symptoms or NDO 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	OAB and NDO indication 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 MRHD, 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. Based on available data, there are not expected to be differences between the OAB and NDO populations with respect to potential public health impact.

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

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

In the Final Pharmacovigilance Risk Assessment Committee (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: Safety in patients from 3 to less than 5 years old
Evidence source: A clinical development program for use of mirabegron in pediatric patients with OAB and NDO is currently ongoing (project code ED178). One pivotal pediatric NDO study was completed and showed that mirabegron was efficacious, safe, and well tolerated by the NDO patients from 3 to less than 18 years of age involved. The clinical development program for use of mirabegron in pediatric patients with OAB is not completed.
Anticipated risk/consequence of the missing information: The safety and efficacy of mirabegron in children from 3 and less than 5 years old with NDO and OAB have not yet been established and mirabegron should therefore not be used in these patients. This risk is mitigated by the clearly stated pediatric NDO indication in SmPC Section 4.2, Posology and Method of Administration of the mirabegron prolonged-release tablets and prolonged-release granules for oral suspension: "The safety and efficacy of mirabegron in children below 3 years of age have not yet been established". For the OAB indication, the mirabegron prolonged-release tablets SmPC Section 4.2 states: "The safety and efficacy of mirabegron in children below 18 years of age for the treatment with OAB have not yet been established. No data are available". Section 2, "What you need to know before you use Betmiga" of PL states "Do not give this medicine to children and adolescents under 18 years of age for the treatment of overactive bladder because the safety and efficacy of Betmiga in this population has not been established. Betmiga is not to be used in children under 3 years of age for the treatment of neurogenic detrusor overactivity."
Missing information: NDO pediatric patients without clean intermittent catheterization (CIC)
Evidence source: In the pediatrics NDO studies, only patients willing to perform regular CIC were included. There is no safety data for NDO pediatric patients taking mirabegron while not performing CIC; therefore, this population would be considered missing information due to different safety profile and potentially differing clinical needs. Mirabegron should therefore be used with caution in this patient population.
Population in need of further characterization: Mirabegron has not been studied in pediatric patients without CIC. The SmPC Section 5.1, Pharmacodynamic properties, includes entry criteria regarding patients performing CIC: "Patients had a diagnosis of NDO with involuntary detrusor contractions with detrusor pressure increase greater than 15 cm H_2O and performed CIC."

CIC: clean intermittent catheterization; NDO: Neurogenic detrusor overactivity

Module SVIII. Summary of the safety concerns

Data-lock point for this Module	30 Jun 2023
Version when Module last updated	9.2

Table 40 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
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	• Safety in patients from 3 to less than 5 years old • NDO pediatric patients without clean intermittent catheterization (CIC)

CIC: clean intermittent catheterization; NDO: Neurogenic detrusor overactivity; QT: QT interval.

3 PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

Data-lock point for this Module	30 Jun 2023
Version when Module last updated	9.2

3.1 Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection

Specific adverse reaction follow-up questionnaires

The use of standardized questionnaires is 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 41 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].		

Table 42 Other forms of routine 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 EMEA-000597-PIP-02-10-M09 Decision P/0550/2022 dated 04 Jan 2023) and for the condition “Treatment of neurogenic detrusor overactivity” (NDO EMEA-000597-PIP-03-15-M05 P/0187/2022 dated 25 May 2022). 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), two phase 1 studies in children (1 pharmacokinetic study with mirabegron tablets and 1 pharmacokinetic study with mirabegron suspension, both are completed), 1 bioavailability and food effect study in young healthy adults (completed), one phase 2 study (completed) and one phase 3 study (planned) with NDO, and 1 ongoing phase 3 study in patients with OAB.

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

3.2 Additional pharmacovigilance activities

Table 43 Additional Pharmacovigilance Activities

Study short name and title	178-CL-204 – A phase 3, double-blind, randomized, multicenter, parallel group, placebo controlled sequential dose titration study to evaluate efficacy, safety, and pharmacokinetics of mirabegron in pediatric subjects from 5 to < 18 years of age with overactive bladder
Rationale and study objectives	Primary objective: -To evaluate the efficacy of mirabegron in children (5 to < 12 years of age) with OAB Secondary objective: -To evaluate the efficacy of mirabegron in children (5 to < 12 years of age) with OAB -To evaluate the safety and tolerability of mirabegron in pediatric subjects with OAB -To evaluate the pharmacokinetics after multiple dose administration of mirabegron in pediatric subjects with OAB Exploratory objective: -To evaluate the efficacy of mirabegron in pediatric subjects (5 to < 18 years) with OAB
Study design	Phase 3, double-blind, randomized, multicenter, parallel group, placebo-controlled sequential dose titration study to evaluate efficacy, safety, and pharmacokinetics of mirabegron in pediatric subjects with OAB.
Study population	Male and female pediatric subjects 5 to < 18 years of age with overactive bladder (OAB as defined according to the International Children's Continence Society [ICCS]) who have had received 4 weeks of urotherapy prior to randomization.
Milestones	Final CSR submission: estimated Jan 2024.

CSR: Clinical study report OAB: Overactive Bladder; ICCS: International Children's Continence Society

Study short name and title	178-CL-207-A phase 3, open-label, multicenter, baseline-controlled sequential dose titration study followed by a fixed dose observation period to evaluate pharmacokinetics, efficacy, and safety of mirabegron prolonged-release microgranula-based suspension in children from 6 months to less than 3 years of age with neurogenic detrusor overactivity
Rationale and study objectives	Primary objective: -To evaluate the efficacy of mirabegron prolonged-release microgranula-based suspension after multiple dose administration in the pediatric population Secondary objective: -To evaluate the additional efficacy of mirabegron prolonged-release microgranula-based suspension

	-To evaluate the safety and tolerability of mirabegron prolonged-release microgranula-based suspension after multiple-dose administration -To evaluate the pharmacokinetics of mirabegron prolonged-release microgranula-based suspension after multiple-dose administration Exploratory objective: -To evaluate other efficacy parameters of mirabegron prolonged-release microgranula-based suspension -To evaluate additional safety parameters of mirabegron prolonged-release microgranula-based suspension
Study design	Phase 3, open-label, multicenter, baseline-controlled sequential dose titration study followed by a fixed dose observation period to evaluate PK, efficacy, and safety of mirabegron prolonged-release microgranula-based suspension in children from 6 months to less than 3 years of age with NDO.
Study population	Male and female participants aged 6 months to less than 3 years of age with NDO.
Milestones	Protocol submission, final CSR completion, final CSR submission (estimated Jan 2026).

CSR: Clinical Study Report; NDO: Neurogenic detrusor overactivity; PK: Pharmacokinetics

3.3 Summary table of additional pharmacovigilance activities

Table 44 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				
A phase 3, Double-blind, randomized, multicenter, parallel group, placebo controlled sequential dose titration study to evaluate efficacy, safety, and		Safety in patients from 3 to less than 5 years old[3]	Final CSR	Estimated Jan 2024

[3] As explained in Annex 8 (RMP v 9.1.), it was requested in the CHMP day 120 list of outstanding issues to add pediatric use to the safety specification again and to rename it to “safety in patients between 3 and 5 years-old” due to limited number of patients included in clinical trials and to include both ongoing/planned PIP studies 178-CL-204 & 178-CL-207 in the pharmacovigilance plan as category 3. Neither study includes children from 3 to less than 5 years old but may contribute to the overall safety profile in pediatric patients.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
pharmacokinetics of mirabegron in pediatric subjects from 5 to < 18 years of age with overactive bladder (178-CL-204). Ongoing				
Open-label, multicenter, baseline-controlled sequential dose titration study followed by a fixed dose observation period to evaluate pharmacokinetics, efficacy, and safety of mirabegron prolonged-release microgranula-based suspension in children from 6 months to less than 3 years of age with neurogenic detrusor overactivity (178-CL-207) Planned		Safety in patients from 3 to less than 5 years old[3]	Protocol submission	Finalized 16 Nov 2021
			Final CSR	Estimated Jan 2026

4 PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Data-lock point for this Module	30 Jun 2023
Version when Module last updated	9.2

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 2023
Version when Module last updated	9.2

5.1 Routine Risk Minimization Measures

Table 45 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 2 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 2.
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 are provided in SmPC Section 4.6 and PL Section 2; as well as discussing with the doctor or pharmacist first before breast feeding in 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.
Safety in patients from 3 to less than 5 years old	Routine risk communication: • SmPC Section 4.2 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Specific recommendation that the safety and efficacy of mirabegron in children below 18 years of age for the treatment with OAB have not yet been established is given in SmPC Section 4.2, and not to give this medicine to children and adolescents under the age of 18 years for the treatment of OAB is given in PL Section 2.
NDO pediatric patients without clean	Routine risk communication: • SmPC Section 5.1

Safety concern	Routine risk minimization activities
intermittent catheterization (CIC)	• PL Section 2

CIC: Clean Intermittent Catheterization; EMA: European Medicines Agency; EU-RMP: European Union risk management plan; NDO: Neurogenic detrusor overactivity; PL: Package Leaflet; PRAC: Pharmacovigilance Risk Assessment Committee; QT: Interval between the start of the Q wave to the end of the T wave on electrocardiogram; SmPC: Summary of Product Characteristics

5.2 Additional Risk Minimization Measures

Routine risk minimization activities as described in Table 45 are sufficient to manage the safety concerns of the medicinal product.

5.2.1 Removal of additional risk minimization activities

Table 46 Removal of additional risk minimization activities

Activity	Safety concern(s) addressed	Rationale for the removal of additional risk minimization activity
None	N/A	N/A

5.3 Summary of Risk Minimization Measures

Table 47 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 2 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 2.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Use of a Follow-up Questionnaire
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 Follow-up Questionnaire

Safety concern	Risk minimization measures	Pharmacovigilance activities
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.
Safety in patients from 3 to less than 5 years old	Routine risk communication: • SmPC Section 4.2 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Specific recommendation that the safety and efficacy of mirabegron children below 18 years of age for the treatment with OAB have not yet been established (detailed in SmPC Section 4.2) and not to give this medicine to children and adolescents under the age of 18 years for the treatment of OAB (detailed in PL Section 2).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Implementation of an approved Pediatric Investigational Plan • Post marketing use in pediatric population is considered a special situation and is routinely monitored via PV signal detection activities. Additional pharmacovigilance activities: • Study 178-CL-204 • Study 178-CL-207
NDO pediatric patients without clean intermittent catheterization (CIC)	Routine risk communication: • SmPC Section 5.1 • PL Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Implementation of an approved Pediatric Investigational Plan • Post marketing use in pediatric population is considered a special situation and is routinely monitored via PV signal detection activities Additional pharmacovigilance activities: • None

CIC: clean intermittent catheterization; EMA: European Medicines Agency; EU-RMP: European Union risk management plan; NDO: Neurogenic detrusor overactivity; PL Package Leaflet; PRAC: Pharmacovigilance Risk Assessment Committee; PV: Pharmacovigilance; QT: interval between the start of the Q wave to the end of the T wave on electrocardiogram; SmPC: Summary of Product Characteristics; TME: targeted medical event.

6 SUMMARY OF THE RISK MANAGEMENT PLAN

Data-lock point for this Module	30 Jun 2023
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Summary of risk management plan for Betmiga (mirabegron)

This is a summary of the 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 OAB with symptoms of urinary incontinence, urgency, and urinary frequency in adult patients and for the treatment of NDO in pediatric patients, from 3 to less than 18 years of age (see SmPC for the full indication). It contains mirabegron as the active substance and it is given by the oral route of administrations dosage form mentioned below:

- Prolonged-release tablets (25 mg, 50 mg)
- Prolonged-release granules for oral suspension (8 mg/mL mirabegron)

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 European Medicine Agency (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 risks for which there is causal association with the use of Betmiga. Potential risks are risks 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 identified risks	• None
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	• Safety in patients from 3 to less than 5 years old • NDO pediatric patients without clean intermittent catheterization (CIC)

CIC: Clean Intermittent Catheterization; NDO: Neurogenic detrusor overactivity; 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	OAB in adults 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.

Important potential risk: QT prolongation	
	NDO in pediatrics There have been no clinically relevant cases of QT prolongation from the completed NDO study in pediatric patients (178-CL-206A).
Risk factors and risk groups	OAB in adults 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. NDO in pediatrics This would also apply to children taking the maximum pediatric dose, which is the pediatric equivalent of the adult 50 mg dose. For children above 35 kg, the formulation would be the PED50 tablet. Children who weigh more than 11 kg but less than 35 kg or who are more than 35 kg but cannot take tablet would take mirabegron oral suspension (8 mg/mL). For children taking suspension, the therapeutic dose (equivalent to adult 50 mg dose) would be 6 mL (for children 11 to < 22 kg), 8 mL (for children 22 to <35 kg), and 11 mL (for children > 35 kg).
Risk minimization measures	Routine risk communication: • SmPC Section 4.4 • PL Section 2 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 2. Additional risk minimization measures: • None

CTD: common technical document; PED50: pediatric equivalent dose to mirabegron 50 mg; PL: Package Leaflet; 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; 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 is limited amount of data from the use of mirabegron in pregnant women.

Important potential risk: Fetal disorders after exposure during pregnancy	
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 breastfeeding, are provided in SmPC Section 4.6 and in PL Section 2. Additional risk minimization measures: • None

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 risk minimization measures: • None.

EMA: European Medicines Agency; EU: European Union; PRAC: Pharmacovigilance Risk Assessment Committee; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics

Missing information: Safety in patients from 3 to less than 5 years old	
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 that the safety and efficacy of mirabegron in children below 18 years of age for the treatment with OAB have not yet been established is given in SmPC Section 4.2, and not to give this medicine to children and adolescents under the age of 18 years for the treatment of OAB is given in PL Section 2.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 178-CL-204[4] • Study 178-CL-207[4] See [Section II.C] of this summary for an overview of the post-authorization development plan.
Missing information: NDO pediatric patients without CIC	
Risk minimization measures	Routine risk communication: • SmPC Section 5.1 • PL Section 2
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

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 category 3 studies are additional pharmacovigilance activities planned or ongoing to address safety in pediatric patients.

178-CL-204: A phase 3, double blind, randomized, multicenter, parallel group, placebo-controlled sequential dose titration study to evaluate efficacy, safety, and pharmacokinetics of mirabegron in pediatric subjects from 5 to < 18 years of age with overactive bladder.

[4] It was requested in the CHMP day 120 list of outstanding issues to add pediatric use to the safety specification again and to rename it to “safety in patients between 3 and 5 years-old” due to limited number of patients included in clinical trials to include both ongoing/planned PIP studies 178-CL-204 & 178-CL-207 in the pharmacovigilance plan as category 3. Neither study includes children from 3 to less than 5 years old but may contribute to the overall safety profile in pediatric patients.

Purpose of the study:

Primary objective:

-To evaluate the efficacy of mirabegron in children (5 to < 12 years of age) with OAB.

Secondary objective:

-To evaluate the safety and tolerability of mirabegron in pediatric subjects with OAB.

-To evaluate the pharmacokinetics after multiple dose administration of mirabegron in pediatric subjects with OAB.

-To evaluate the efficacy of mirabegron in children (5 to < 12 years of age) with OAB

178-CL-207: A phase 3, open-label, multicenter, baseline-controlled sequential dose titration study followed by a fixed dose observation period to evaluate pharmacokinetics, efficacy, and safety of mirabegron prolonged-release microgranula-based suspension in children from 6 months to less than 3 years of age with neurogenic detrusor overactivity

Purpose of the study:

Primary objective:

-To evaluate the efficacy of mirabegron prolonged-release microgranula-based suspension after multiple dose administration in the pediatric population.

Secondary objective:

-To evaluate the additional efficacy of mirabegron prolonged-release microgranula-based suspension.

-To evaluate the safety and tolerability of mirabegron prolonged-release microgranula-based suspension after multiple-dose administration.

-To evaluate the pharmacokinetics of mirabegron prolonged-release microgranula-based suspension after multiple-dose administration.

7 ANNEXES

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Annex 4 Specific adverse event follow-up forms

Data-lock point for this annex	30 Jun 2023
Version when annex last updated	9.2

Table of contents

Follow-up Questionnaire for QT Prolongation and/or Torsades de Pointes

Case Number:			
Reported Event:		**Patient Details:**	Age/Age group ☐ Male ☐ Female

Thank you for reporting the initial report related to QT Prolongation and/or Torsades de Pointes during the use of <Astellas product>.
With this questionnaire, we would like to request specific follow-up information, in order to perform a better scientific evaluation of the case.

SIGNS AND SYMPTOMS OF THE EVENT

☐ Acute blurred vision	☐ Loss/ disturbance of consciousness
☐ Acute deafness	☐ Palpitations
☐ Arrhythmia	☐ Seizures
☐ Bradycardia	☐ Shortness of breath
☐ Chest Discomfort / Pain	☐ Tachycardia
☐ Gasping noise during sleep	☐ Other:
☐ Lightheadedness	

UNDERLYING CONDITIONS / RISK FACTORS

☐ Alcohol use (units per week):	☐ History of renal impairment or renal disease:
☐ Arrhythmia	☐ Hypertension
☐ Congenital heart defects:	☐ Ischemic heart disease (e.g., myocardial infarction)
☐ Congenital QT syndrome (long or short)	☐ Other cardiac disorder:
☐ Electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia):	☐ Similar episode(s) in the past
	☐ Thyroid disease
☐ Family history of cardiovascular disease:	☐ Valvular heart disease:
☐ Family history of congenital QT syndrome:	☐ Possible drug interaction
☐ Heart failure	☐ Smoking (packs per week):
☐ History of hepatic impairment:	☐ Other:

TREATMENT HISTORY

☐ Ablation	☐ Cardioversion
☐ Angioplasty	☐ Medicinal Product(s):
☐ Cardiac Resynchronization Therapy (CRT)	☐ Valve Replacement/Repair

MEDICATION

Drug Name	Suspect Product (S) Concomitant (C) AE Treatment (T)	Indication	Dose/Frequency/ Route of Administration	Start Date dd-Mmm-yyyy	Stop Date *dd-Mmm-yyyy* or *Ongoing*
☐					
☐					
☐					

RELEVANT INVESTIGATIONS *Provide results at time of the event. Provide other results (baseline, peak of event and resolution) in Additional Details field or attach as copy.*

Investigation	Date dd-Mmm-yyyy	Result/Unit
☐ Bicarbonate		
☐ Serum Chloride		
☐ Serum Magnesium		
☐ Serum Potassium		
☐ Serum Sodium		

RELEVANT INVESTIGATIONS *Provide results at time of the event. Provide other results (baseline, peak of event and resolution) in Additional Details field or attach as copy.*		
INVESTIGATION	**DATE** dd-Mmm-yyyy	**RESULT/UNIT**
☐ Cardiac monitoring studies (e.g., Holter monitor, event monitor):		
☐ Electrocardiogram or ☐ Rhythm Strips		
☐ QT interval uncorrected: (HR) /		
☐ QTc Bazett : (HR) /		
☐ QTc Fridericia : (HR) /		
☐ Other:		

ADDITIONAL DETAILS / OTHER RELEVANT INFORMATION

REPORTER INFORMATION		
REPORTER NAME / CREDENTIALS	**DATE** (dd-Mmm-yyyy)	**SIGNATURE** (to confirm the accuracy of the data)

Pregnancy Reporting Form

Case Number:		Reported Event:		Patient Details:	Age/Age group

Thank you for reporting the initial report related to Pregnancy during the use of <Astellas product>.
With this questionnaire, we would like to request specific follow-up information, in order to perform a better scientific evaluation of the case.

Complete the fields below when case is coming from an Astellas study

Protocol #	Study ARM	Country	Site #	Subject ID	Subject Randomization #

DEMOGRAPHICS {MOTHER (M) AND/OR FATHER (F)}

PATIENT INITIALS	HOW WAS THE MOTHER EXPOSED TO ASTELLAS DRUG	DATE OF BIRTH/AGE (dd-Mmm-yyyy)	WEIGHT	HEIGHT
	☐ Mother ☐ Exposed via Father	M: F:	☐ Kg ☐ Lbs M:	☐ cm ☐ in M:

CURRENT PREGNANCY DETAILS

Last Menstrual Period (LMP)	Gestational age weeks days	Gestational age at time of exposure weeks days	Specify method of determining gestational age
Number of foetuses	Contraception method	☐ Treatment for infertility	Reason for contraception failure

OBSTETRIC / PREGNANCY HISTORY

☐ Abnormal menstrual cycles	☐ Previous pregnancy complications	☐ Gravida Specify number	☐ Para Specify number
☐ Previous fetal/neonatal abnormalities	☐ History of subfertility		

UNDERLYING CONDITIONS / RISK FACTORS {MOTHER (M) AND/OR FATHER (F)}

Allergies	☐ M ☐ F	Hypertension	☐ M ☐ F	Sexually transmitted disorder	☐ M ☐ F
Asthma	☐ M ☐ F	Immune disorder	☐ M ☐ F	Thyroid disorder	☐ M ☐ F
Diabetes	☐ M ☐ F	Infection	☐ M ☐ F	Recreational drug use (e.g. smoking, alcohol, illicit drug use, specify amount and if stopped during pregnancy)	☐ M ☐ F
Epilepsy	☐ M ☐ F	Psychiatric or mental health disorder	☐ M ☐ F		
Heart disease	☐ M ☐ F	Seizure disorder	☐ M ☐ F	Other	☐ M ☐ F

FAMILY HISTORY {MOTHER (M) AND/OR FATHER (F)}

☐ Consanguinity between parents (specify degree)	☐ Congenital anomalies ☐ M ☐ F	☐ Mental illness	☐ M ☐ F
	☐ Hereditary disease ☐ M ☐ F	☐ Other	☐ M ☐ F

ADVERSE EVENT INFORMATION (MOTHER) ☐ Not Applicable

ADVERSE EVENT	START DATE dd-Mmm-yyyy	STOP DATE dd-Mmm-yyyy or Ongoing	SERIOUSNESS[1]	OUTCOME[2]	RELATIONSHIP TO ASTELLAS SUSPECT DRUG[3]

[1]SERIOUSNESS CRITERIA: *1. Death*, 2. Requires/Prolongs Hospitalization, 3. Congenital Anomaly, 4. Life Threatening, 5. Persistent or Significant Disability, 6. Important Medical Event, 7. Non-serious*

[2]OUTCOME: *1-Recovered 2-Recovering 3-Not Recovered 4-Recovered with Sequelae 5-Death* 6-Unknown*

[3]RELATIONSHIP TO ASTELLAS SUSPECT DRUG (TAKEN BY THE MOTHER OR FATHER): 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:

Other pregnancy complications:

MEDICATION						
DRUG NAME (SPECIFY IF VIA FATHER (F))	SUSPECT PRODUCT (S) CONCOMITANT (C) AE TREATMENT (T)		INDICATION	DOSE/FREQUENCY/ ROUTE OF ADMINISTRATION	START DATE dd-Mmm-yyyy	STOP DATE dd-Mmm-yyyy or Ongoing
F ☐						
F ☐						
F ☐						

RELEVANT INVESTIGATIONS *Provide results at time of the event. Provide other results (baseline, peak of event and resolution) in Additional Details field or attach as copy.*

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

ADDITIONAL DETAILS / OTHER RELEVANT INFORMATION

REPORTER INFORMATION		
REPORTER NAME / CREDENTIALS	DATE (dd-Mmm-yyyy)	SIGNATURE (to confirm the accuracy of the data)

Follow-up Questionnaire for Pregnancy Outcome

Case Number:		Reported Event:		Patient Details:	Age/Age group

Thank you for reporting the initial report related to Pregnancy during the use of <Astellas product>.
With this questionnaire, we would like to request specific follow-up information related to the outcome of the Pregnancy, in order to perform a better scientific evaluation of the case. Complete a separate form for each neonate.

OUTCOME OF CURRENT PREGNANCY

☐ Vaginal delivery	☐ Elective caesarean	☐ Emergency caesarean
☐ Live birth	☐ Miscarriage	☐ Late foetal death
☐ Ectopic pregnancy	☐ Molar pregnancy	☐ Elective termination
☐ Abnormal placenta	☐ Premature delivery (< 37 weeks)	☐ 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	BREAST FEEDING	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?

ADVERSE EVENT INFORMATION OF THE NEONATE (including complications) ☐ Not Applicable

(If more than one adverse event, provide details in Additional Details / Other Relevant Information section)

ADVERSE EVENT	START DATE dd-Mmm-yyyy	STOP DATE dd-Mmm-yyyy or Ongoing	SERIOUSNESS[1]	OUTCOME[2]	RELATIONSHIP TO ASTELLAS SUSPECT DRUG[3]

[1] SERIOUSNESS CRITERIA: *1. Death*, 2. Requires/Prolongs Hospitalization, 3. Congenital Anomaly, 4. Life Threatening, 5. Persistent or Significant Disability, 6. Important Medical Event, 7. Non-serious*

[2] OUTCOME: *1-Recovered 2-Recovering 3-Not Recovered 4-Recovered with Sequelae 5-Death* 6-Unknown*

[3] RELATIONSHIP TO ASTELLAS SUSPECT DRUG (TAKEN BY THE MOTHER OR FATHER): 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 / OTHER RELEVANT INFORMATION

REPORTER INFORMATION

REPORTER NAME / CREDENTIALS	DATE (dd-Mmm-yyyy)	SIGNATURE (to confirm the accuracy of the data)

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

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Not applicable

Electronic Signature Page

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